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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

SARS-CoV-2 Infection During Pregnancy and Increased Risk of Preeclampsia

By Maria F. Gallo, PhD

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SYNOPSIS: A meta-analysis of 28 observational studies found that having SARS-CoV-2 infection during pregnancy was associated with a 58% increase in the adjusted odds of having preeclampsia compared to those without SARS-CoV-2 infection during pregnancy.

SOURCE: Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: A systematic review and meta-analysis. *Am J Obstet Gynecol* 2021; Jul 21:S0002-9378(21)00795-X. doi: 10.1016/j.ajog.2021.07.009. [Online ahead of print].

Preeclampsia, which occurs in 2% to 8% of pregnancies globally, is an important cause of maternal mortality as well as a risk factor for later heart disease and stroke. Genetic, epigenetic, environmental, and behavioral factors have been implicated in the development of preeclampsia. Researchers also have long hypothesized that viral infections (e.g., human immunodeficiency virus, human papillomavirus, cytomegalovirus, hepatitis B virus, and herpes simplex virus) during pregnancy could cause preeclampsia. In light of this, Conde-Agudelo and Romero carried out a systematic review and meta-analysis to evaluate whether infection with SARS-CoV-2 during pregnancy increases the risk of developing preeclampsia. They conducted a comprehensive search of databases for all reports of studies on this topic, regardless of publication status or language used, that were available from Dec. 1, 2019, to May 31, 2021. They found 28 eligible studies: 14 prospective cohort studies, 12 retrospective cohort studies, and two cross-sectional studies. The 28 studies included 790,954 pregnant women, 2% of whom (n = 15,524) were diagnosed with SARS-CoV-2. The studies were conducted in numerous countries. The sample sizes ranged from 24 to 406,446 pregnant women.

To be eligible for inclusion, the primary study had to include data on women with and without a diagnosis of SARS-CoV-2 infection during pregnancy, data on preeclampsia status, and either an odds ratio (OR) or a relative risk (RR) for the association between SARS-CoV-2 and preeclampsia and its associated 95% confidence interval (CI) or the data that would allow these estimates to be calculated. The authors used a tight clinical definition of preeclampsia. In contrast, because of the widespread

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lack of diagnostic tests at the beginning of the pandemic, they accepted a range of methods for defining SARS-CoV-2, including those that relied on clinical signs/symptoms or chest images suggestive of the disease as well as laboratory diagnoses from reverse transcriptase-polymerase chain reaction (RT-PCR), antigen, or serum antibody tests.

By pooling data from 26 studies, they found that 7.0% of pregnant women with SARS-CoV-2 during pregnancy had preeclampsia compared to 4.8% of those without SARS-CoV-2. Using a random effects model, the summary odds of preeclampsia for those with SARS-CoV-2 was 1.62 times (95% CI, 1.45-1.82) that of those without SARS-CoV-2. They repeated this analysis after restricting to the 11 studies that accounted for confounders of the association between SARS-CoV-2 and preeclampsia. These confounders typically included maternal age, body mass index, preexisting comorbidities, and race/ethnicity. The summary OR from the adjusted analysis (1.58; 95% CI, 1.39-1.80) was similar to the unadjusted summary estimate.

The authors also evaluated three secondary outcomes instead of preeclampsia and found each to be statistically significantly associated with SARS-CoV-2 during pregnancy. That is, SARS-CoV-2 during pregnancy was associated with higher odds of preeclampsia with severe features (summary OR, 1.76; 95% CI, 1.18-2.63); eclampsia (summary OR, 1.97; 95% CI, 1.01-3.84); and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome (summary OR, 2.10; 95% CI, 1.48-2.97). Finally, they conducted several subgroup analyses and sensitivity analyses to explore further the relationship between SARS-CoV-2 and preeclampsia and to assess how robust the study findings were to the choice of analytic methods. These analyses suggested a possible dose effect with higher odds among those with symptomatic illness (summary OR, 2.11; 95% CI, 1.59-2.81) than the odds among those with asymptomatic illness (summary OR, 1.59; 95% CI, 1.21-2.10). Only six of the 28 studies were judged to be at low risk of bias for at least five of the six domains of bias evaluated. When the authors restricted the analysis to these six studies, they found a similar summary OR for the association between SARS-CoV-2 infection during pregnancy and preeclampsia (1.74; 95% CI, 1.35-2.23).

■ COMMENTARY

This systematic review and meta-analysis by Conde-Agudelo and Romero builds on a growing body of evidence that warns of increased health risks from SARS-CoV-2 during pregnancy. Previous research has indicated that SARS-CoV-2 infection during pregnancy poses greater risks relative to SARS-CoV-2 infection outside of pregnancy and that, among pregnant women, those with SARS-CoV-2 infection face higher risks of maternal mortality and adverse birth outcomes, including preterm birth and stillbirth, compared to those without this infection. The present article adds to this literature by synthesizing the available evidence on the association between SARS-CoV-2 during pregnancy and an increased risk of preeclampsia. Although the pooled effect estimate (adjusted summary OR, 1.58; 95% CI, 1.39-1.80) is statistically significant, the strength of this association could be considered weak.[1] However, even a weak association can be important on a population level.

Despite the careful work and strong methods used by the authors, their meta-analysis combines evidence that came solely from observational studies. Consequently, the data cannot establish a causal relationship between SARS-CoV-2 and preeclampsia. Because pregnant women were not (and ethically could not be) randomly assigned to SARS-CoV-2 infection, controlling for confounders was critical. Otherwise, for example, the same risk factors that put a woman at higher risk of SARS-CoV-2 infection also could have put her at higher risk of preeclampsia. In this case, an apparent effect of SARS-CoV-2 on preeclampsia could be spurious. The authors addressed this concern by calculating a separate summary measure from the studies that accounted for confounders. The results from this adjusted analysis remained statistically significant, which helps support the interpretation that a true association between SARS-CoV-2 and preeclampsia exists. However, residual confounders could remain if the investigators of the primary studies did not account adequately for all confounding. Note that despite the large, pooled sample size of 790,954 pregnant women, most of the pooled sample (95%) came from only two cross-sectional studies, which were conducted in the United States or the United Kingdom. Although the investigators of these two studies adjusted for potential confounders, they used administrative records (hospital billing records) as their data source. Because administrative data are not collected for research purposes, often they have misclassification and missing data and may fail to collect the full range of relevant measures. Arguably, the limitations of using administrative data might be insurmountable.[2]

The analysis had numerous strengths. Notably, the association between SARS-CoV-2 during pregnancy and preeclampsia remained statistically significant in most subgroup and sensitivity analyses, indicating that the findings were robust. Because the pooled analyses had no, or little, evidence of heterogeneity between studies according to I^2, the studies were appropriate to combine in meta-analysis. The consistency of the individual study findings supports the interpretation that SARS-CoV-2 infection during pregnancy is linked to preeclampsia. Furthermore, possible biological mechanisms by which SARS-CoV-2 during pregnancy could cause preeclampsia have been proposed.[3] Given the strength of this evidence, healthcare providers should recommend that preconception and pregnant people complete the recommended vaccination against COVID-19 and implement protective measures to protect themselves against exposure (e.g., wearing masks in public indoors). The Centers for Disease Control and Prevention recommends vaccination against COVID-19 for people at least 12 years of age, including pregnant women.[4] Healthcare providers should counsel pregnant women about their risks, including the increased risk of preeclampsia, from SARS-CoV-2 infection (including from asymptomatic infection), during pregnancy. Providers should remain aware of the increased risk of preeclampsia among pregnant women with SARS-CoV-2 infection to ensure the early detection and treatment of preeclampsia if needed. ■

REFERENCES

1. Rosenthal JA. Qualitative descriptors of strength of association and effect size. *J Soc Serv Res* 1996;21:37-59.
2. Grimes DA. Epidemiologic research using administrative databases: Garbage in, garbage out. *Obstet Gynecol* 2010;116:1018-1019.
3. Conde-Agudelo A, Romero R. Mechanisms that may underlie a causal association between SARS-CoV-2 infection and preeclampsia. *Am J Obstet Gynecol* 2021; Sep 13. [In press].
4. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA COVID-19 vaccines preconception and during pregnancy and risk of self-reported spontaneous abortions, CDC v-safe COVID-19 Vaccine Pregnancy Registry 2020-21. *Res Sq* 2021; Aug 9:rs.3.rs-798175. doi: 10.21203/rs.3.rs-798175/v1. [Preprint].

ABSTRACT & COMMENTARY

Do Women 64 to 66 Years of Age Qualify to Discontinue Cervical Screening?

By Rebecca B. Perkins, MD, MSc

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SYNOPSIS: These studies evaluated adherence to national guidelines for exiting from cervical cancer screening at 65 years of age and managing abnormal results on screening with human papillomavirus (HPV) and Pap co-testing and found that the majority of women 64 to 66 years of age do not qualify to discontinue screening, and the majority of women with discordant Pap and HPV test results are managed incorrectly.

SOURCES: Mills JM, Morgan JR, Dhaliwal A, Perkins RB. Eligibility for cervical cancer screening exit: Comparison of a national and safety net cohort. *Gynecol Oncol* 2021;162:308-314.

Perkins RB, Adcock R, Benard V, et al. Clinical follow-up practices after cervical cancer screening by co-testing: A population-based study of adherence to U.S. guideline recommendations. *Prev Med* 2021;153:106770.

Cervical cancer screening has decreased rates of invasive cervical cancer by 80%.[1] In the 1980s through the 2000s, the annual Pap test was the mainstay of cervical cancer prevention. More recently, the discovery that human papillomavirus (HPV) caused nearly all cervical cancers led to the development of HPV testing.[2] In addition, concerns for over-testing and over-treatment led to guidelines recommending longer intervals between screening tests and discontinuation of screening at the age of 65 years in those who fulfilled exit criteria.[3-5] However, correct application of these new guidelines requires risk stratification of patients, including knowledge of current management guidelines and past history of screening and abnormal results.[6]

The study by Mills et al examines the proportion of women 64 to 66 years of age who qualify for screening exit in two cohorts: women receiving care in a safety net setting, the majority of whom have public insurance, and women with employer-based private insurance.[7] The authors applied existing screening exit criteria, which include hysterectomy without evidence of cancer or precancer, no history of human immunodeficiency virus (HIV) or cervical cancer ever, no history of cervical precancer in the past 25 years, no abnormal screening test results in the past 10 years, or adequate screening in the past 10 years, defined as three Pap tests alone or two HPV tests, with or without accompanying Pap tests.

Evaluating women from 2016 to 2019, the investigators found that, of the 590,901 women in the national claims database with employer-based private insurance, only 131,059 (22.2%) were eligible to exit. Approximately one in five (20.6%) had adequate negative screening, and a small minority (1.6%) had undergone hysterectomy.

Among 1,544 women from the safety net health center, only 528 (34.2%) were eligible to exit. Approximately one in four (24.9%) had adequate negative screening, and 9.3% had undergone hysterectomy (9.3%). Therefore, the majority of women lacked sufficient screening to fulfill exit criteria: 382,509 (64.7%) in the national database and 875 (56.7%) in the safety net cohort. Even among women with 10 years of continuous private insurance coverage, only 41.5% qualified to discontinue screening.

The Perkins et al study examined management following abnormal results on Pap/HPV co-testing among 164,522 women screened with co-testing in the state of New Mexico between 2015 and 2019.[8] Guideline-concordant management was high among those who were both HPV-positive and had abnormal Pap test results (62% to 80%). However, when results were discordant, less than half of women were managed according to guidelines (48% to 49%). Guideline nonadherent follow-up in these scenarios included receiving colposcopy when not indicated after a low-grade abnormal Pap test result with an HPV-negative test or failing to receive colposcopy or follow-up in one year for HPV-positive results accompanied by negative Pap tests.

[Evidence-based guidelines have the potential to decrease the number of tests and procedures while maintaining or improving cervical cancer prevention, but only if applied properly.]

■ COMMENTARY

These studies indicate that the potential benefits of newer cervical cancer screening guidelines are not being realized by the majority of women. Guidelines promoting screening cessation at 65 years of age are premised on strict criteria, and these data indicate that only one in three women in this age group fulfill them. The discordance between guidelines and population-level actions may contribute to the finding that approximately 25% of cervical cancers in the United States are diagnosed in women 65 years of age and older, and many of those women had inadequate screening prior to diagnosis.[9,10]

Most women in the United States currently are screened for cervical cancer with Pap/HPV co-testing.[11] Data indicate that one in 10 screening results are abnormal, with the most common abnormal result (40% of all abnormal results) being a positive HPV test with a normal Pap result.[12] However, the data mentioned earlier indicate that most women with discordant results are managed incorrectly. This implies that the added benefits of HPV testing in terms of identifying high-risk patients who may be missed by Pap alone are not being realized.[13] Failure to identify and closely follow high-risk patients increases their risk for cervical cancer. In fact, an estimated 14,400 cervical cancers will be diagnosed in 2021.[14]

Evidence-based guidelines have the potential to decrease the number of tests and procedures while maintaining or improving cervical cancer prevention, but only if applied properly.[6] These papers indicate a need for improved education and support for guideline-adherent care among patients, individual providers, healthcare systems, laboratories, and insurers, including Medicare and Medicaid, to ensure guideline-adherent care to avoid the development of preventable cervical cancers. ■

REFERENCES

1. Gustafsson L, Pontén J, Zack M, Adami HO. International incidence rates of invasive cervical cancer after introduction of cytological screening. *Cancer Causes Control* 1997;8:755-763.
2. Arbyn M, Sasieni P, Meijer CJLM, et al. Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses. *Vaccine* 2006;24(Suppl 3):S3/78-89.
3. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin* 2020;70:321-346.
4. US Preventive Services Task Force; Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2018;320:674-686.
5. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol* 2012;137:516-542.
6. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. *J Low Genit Tract Dis* 2020;24:102-131.
7. Mills JM, Morgan JR, Dhaliwal A, Perkins RB. Eligibility for cervical cancer screening exit: Comparison of a national and safety net cohort. *Gynecol Oncol* 2021;162:308-314.
8. Perkins RB, Adcock R, Benard V, et al. Clinical follow-up practices after cervical cancer screening by co-testing: A population-based study of adherence to U.S. guideline recommendations. *Prev Med* 2021;153:106770.
9. Feldman S, Cook E, Davis M, et al. Cervical cancer incidence among elderly women in Massachusetts compared with younger women. *J Low Genit Tract Dis* 2018;22:314-317.
10. Castañón A, Landy R, Cuzick J, Sasieni P. Cervical screening at age 50-64 years and the risk of cervical cancer at age 65 years and older: Population-based case control study. *PLoS Medicine* 2014;11:e1001585.
11. Cuzick J, Myers O, Hunt WC, et al. Human papillomavirus testing 2007-2012: Co-testing and triage utilization and impact on subsequent clinical management. *Int J Cancer* 2015;136:2854-2863.
12. Egemen D, Cheung LC, Chen X, et al. Risk estimates supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. *J Low Genit Tract Dis* 2020;24:132-143.
13. Castle PE, Glass AG, Rush BB, et al. Clinical human papillomavirus detection forecasts cervical cancer risk in women over 18 years of follow-up. *J Clin Oncol* 2012;30:3044-3050.
14. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Cervical Cancer. http://seer.cancer.gov/statfacts/html/cervix.html#incidence-mortality

ABSTRACT & COMMENTARY

Menopausal Hot Flashes: Can a Plant-Based Diet Provide Effective Treatment?

By Rebecca H. Allen, MD, MPH, Editor

SYNOPSIS: In this clinical trial, women randomized to a low-fat, vegan diet including one-half cup of cooked whole soybeans daily experienced a reduction in total hot flashes of 79% compared to 49% in the control group over 12 weeks of observation.

SOURCE: Barnard ND, Kahleova H, Holtz DN, et al. The Women's Study for the Alleviation of Vasomotor Symptoms (WAVS): A randomized, controlled trial of a plant-based diet and whole soybeans for postmenopausal women. *Menopause* 2021; Jul 12. doi: 10.1097/GME.0000000000001812. [Online ahead of print].

This study was conducted to evaluate the effectiveness of whole soybeans and a plant-based vegan diet in reducing the frequency and severity of menopausal hot flashes. Previous studies have found some indication that soy (phytoestrogen) supplements can modestly reduce hot flashes, although data are limited.[1] This is a randomized controlled trial performed over 12 weeks among women with postmenopausal hot flashes. Inclusion criteria were women 40 to 65 years of age, moderate to severe hot flashes at least twice a day, last menses within the preceding 10 years, and no menses in the preceding 12 months. Exclusion criteria were use of hormonal medications in the previous two months, smoking, substance abuse, history of an eating disorder, use of weight loss medications in the past six months, attempting to lose weight, body mass index (BMI) < 18.5 kg/m^2, soy allergy, and current diet already consisting of the study diet. The intervention group followed a low-fat vegan diet and was provided with soybeans to consume one-half cup per day. Intervention participants attended weekly one-hour group sessions and were given information on meal planning and food preparation (a pressure cooker was provided for the soybeans) and were asked weekly about adherence to the diet. Control group participants followed their usual diet, also were given a pressure cooker, and attended four one-hour group sessions. For both groups, alcohol was limited to one drink per day. Data collection was performed at baseline and at 12 weeks and included three-day dietary intake record, body weight and height, health status, medication use, physical activity, menopausal symptoms (hot flashes), and the Menopause-Specific Quality of Life (MENQOL) questionnaire.

The authors considered this a pilot study and aimed to enroll a total of 40 participants. Women were recruited through social media and screened by telephone. Ultimately, 38 women were randomized. There was no significant difference between the two groups in terms of age, race, and BMI. Mean body weight decreased by 3.5 kg in the vegan diet group compared to a 0.8-kg gain in the control group (P = 0.002). Total hot flashes decreased by 79% in the intervention group (6.2 vs. 1.3 events per seven days) compared to 49% in the control group (4.9 vs. 2.5 events per seven days) (P = 0.01). Moderate to severe hot flashes decreased 84% in the intervention group compared to 42% in the control group (P = 0.013). From 0 to 12 weeks, 59% (10/17) of intervention-group participants reported becoming free of moderate to severe hot flashes compared to no change in the control group (P = 0.0003). The MENQOL questionnaire showed significant reductions in all the vasomotor, psychosocial, physical, and sexual domains compared to the control group.

■ COMMENTARY

Vasomotor symptoms, or hot flashes, are common in the perimenopausal transition and menopause. The most effective treatment for hot flashes is systemic estrogen therapy. For women who do not want to use hormones, there are a few nonhormonal medications that have proven effective: selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, clonidine, and gabapentin.[2] However, the goal of this study was to evaluate the usefulness of whole soybeans because many women are seeking nonhormonal and nonpharmacological options to treat menopausal symptoms.

This study was sponsored by the Physicians Committee for Responsible Medicine, a nonprofit organization that promotes plant-based diets for preventive medicine and conducts clinical research in this area. Phytoestrogens are plant-derived substances with estrogenic biologic activity. Examples include the isoflavones genistein and daidzein, which are found in high amounts in soybeans, soy products, and red clover. Previous studies have shown that soy products may be modestly useful in treating menopausal hot flashes.[1] However, current evidence has not been strong enough to recommend soy products on a routine basis.[2]

This study showed that a vegan diet with whole soybeans (one-half cup per day) reduced hot flashes significantly and almost eliminated moderate to severe hot flashes. The control group also experienced a decrease in hot flashes. The authors speculated this was because the control group also was aware of the vegan diet in the intervention group and possibly also followed it. However, the study was limited by the small sample size and short duration. But the findings were dramatic and deserve further study. Certainly, there may be other health benefits to a plant-based vegan diet, and eating soybeans does not have a downside. Therefore, this may be an option for patients who do not want to use medications and do not find enough benefit from regular

lifestyle changes, such as layering clothing, lowering ambient temperatures, and consuming cool drinks. ■

REFERENCES

1. Franco OH, Chowdhury R, Troup J, et al. Use of plant-based therapies and menopausal symptoms: A systematic review and meta-analysis. *JAMA* 2016;315:2554-2563.
2. The American College of Obstetricians and Gynecologists. Management of menopausal symptoms. Practice Bulletin Number 141. Published January 2014. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2014/01/management-of-menopausal-symptoms

ABSTRACT & COMMENTARY

Use of Ursodeoxycholic Acid in Pregnant Women with Obstetric Cholestasis

By Ahizechukwu C. Eke, MD, PhD, MPH

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SYNOPSIS: Ursodeoxycholic acid might be beneficial in reducing the risk of spontaneous preterm birth and meconium-stained amniotic fluid, but not stillbirths, in women with pregnancies complicated by obstetric cholestasis.

SOURCE: Ovadia C, Sajous J, Seed PT, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: A systematic review and individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:547-558.

Obstetric cholestasis is the most common pregnancy-specific hepatic disorder.[1] In the United States, the prevalence varies between 0.32% and 5.6% of all pregnancies. It is seen most commonly in Hispanic women of South American descent (Chilean and Bolivian).[2-4] It is characterized by generalized itching involving the palms and soles of the feet (typically in the absence of a rash), caused by elevated serum bile acids.[1] The etiology of obstetric cholestasis is not completely understood. However, genetic, hormonal, and environmental factors may contribute to the pathogenesis.[1] Although obstetric cholestasis commonly develops in the third trimester of pregnancy, there have been several reports of cases of obstetric cholestasis in the first and second trimesters of pregnancy.

In pregnancies complicated by obstetric cholestasis, ursodeoxycholic acid therapy often is used for pruritus. It functions by decreasing hepatic cholesterol secretion, an important rate-limiting step in the formation of bile acids.[5] Although there are data to suggest that ursodeoxycholic acid improves itching from obstetric cholestasis, controversy exists as to whether ursodeoxycholic acid improves maternal and fetal outcomes.[6-9] Therefore, Ovadia and colleagues designed this study to determine if ursodeoxycholic acid therapy is beneficial in improving perinatal outcomes.[10] This study is an individual patient data meta-analysis of all observational studies and randomized clinical trials that reported the use of ursodeoxycholic acid during pregnancy in women with intrahepatic cholestasis of pregnancy. Studies met inclusion criteria if they reported at least one of the following outcomes: stillbirth, preterm birth, neonatal intensive care admission, meconium-stained amniotic fluid, or neonatal death.[1] Studies were excluded if they did not report on any maternal or fetal outcomes in women diagnosed with intrahepatic cholestasis of pregnancy.[10] The primary outcome was the prevalence of stillbirth in women using ursodeoxycholic acid therapy for obstetric cholestasis.[10] Secondary maternal outcomes included onset of labor (spontaneous or induced), mode of delivery (spontaneous vaginal, assisted vaginal, elective cesarean, or emergency cesarean), preeclampsia, gestational diabetes, and postpartum hemorrhage, while secondary fetal outcomes included a composite of spontaneous birth, iatrogenic birth, and total preterm birth; early preterm birth (< 34 gestational weeks); neonatal intensive care unit admission; meconium-stained amniotic fluid; umbilical cord arterial pH < 7.0; Apgar score of < 7 at five minutes of life; perinatal death; small for gestational age; large for gestational age; and spontaneous preterm birth.[10]

To compare women who used ursodeoxycholic acid therapy with women who did not, the investigators performed an individual participant data meta-analysis using multilevel mixed-effects logistic regression, or logistic regression with a Huber-White correction. Individual patient data analyses were done for all studies and in different subgroups (observational studies vs. randomized clinical trials). Adjustments were made for bile acid concentrations at baseline, number of fetuses, and maternal parity because of the associations between these confounders and adverse perinatal outcomes. Eighty-five studies met inclusion criteria. However, individual participant data were available for only 32 published studies (6,670 pregnancies), including four randomized controlled trials and two unpublished cohort studies (339 pregnancies), totaling 7,009 participants. Of the 7,009 participants for whom data were provided, 35 were excluded from the analysis (unknown therapy), and 6,974 had sufficient data for inclusion (822 from the four randomized controlled trials), of whom 4,726 (67.8%) took ursodeoxycholic acid therapy and 2,248 (32.2%) did not.

The prevalence of the primary outcome (stillbirth) was not statistically significant between women who received ursodeoxycholic acid therapy compared to those who did

not (0.7; [35/5,097 fetuses] vs. 0.6% [12/2,038 fetuses]; adjusted odds ratio [aOR], 1.04; 95% confidence interval [CI], 0.35-3.07; $P = 0.95$). Ursodeoxycholic acid therapy reduced the prevalence of spontaneous preterm birth in women with obstetric cholestasis compared to those not on therapy (aOR, 0.55; 95% CI, 0.35-0.88; $P = 0.012$). Ursodeoxycholic acid also significantly reduced the prevalence of the composite outcome of spontaneous birth, iatrogenic birth, and total preterm birth in the subgroup analysis involving randomized controlled trials, although this was driven largely by the reduction in total preterm birth (aOR, 0.60; 95% CI, 0.39-0.91; $P = 0.016$). The odds of meconium-stained amniotic fluid was reduced with ursodeoxycholic acid therapy compared to no therapy (aOR, 0.69; 95% CI, 0.50-0.95; $P = 0.02$). There were no statistically significant differences in all other secondary outcomes in pregnant women with obstetric cholestasis treated with ursodeoxycholic acid compared to those not treated.

■ COMMENTARY

Ursodeoxycholic acid therapy was associated with a lower odds of spontaneous preterm birth in all study types (randomized clinical trials and observational studies). The anti-inflammatory actions of ursodeoxycholic acid and reduction of serum bile acid concentrations within the uterine myometrium might explain ursodeoxycholic acid's ability to reduce the prevalence of preterm birth.[11] Although ursodeoxycholic acid is used off-label during pregnancy in cases of obstetric cholestasis, it is thought to be safe, with minimal gastrointestinal adverse effects.[10] Although stillbirth was not shown to be statistically significant in this individual-level data meta-analysis, it is important to understand that stillbirth is a relatively rare pregnancy outcome, and this individual participant meta-analysis was not sufficiently powered to demonstrate differences in stillbirths between women whose pregnancies were complicated by obstetric cholestasis on ursodeoxycholic acid therapy compared to those not on therapy.[8]

In this individual participant meta-analysis, Ovadia and colleagues also demonstrated a reduction in the composite outcome of spontaneous birth, iatrogenic birth, and total preterm birth in the randomized controlled trial-only subgroup analyses.[10] This demonstrates the value of well-designed randomized controlled trials of intervention studies.[10] When considering individual participant data from all study designs, adjustment of comparisons by the main confounders (baseline bile acid concentrations, parity, and number of fetuses) showed a significant effect of ursodeoxycholic acid on the composite outcomes (which was non-significant when all other study types were included), reflecting how poorly matched the treatment groups were in terms of the main influencers of perinatal outcomes obstetric cholestasis.[10] This meta-analysis also demonstrates the advantage of individual patient data meta-analyses compared to aggregate meta-analyses.[12] Prior aggregate meta-analyses overestimated the effect sizes of ursodeoxycholic acid on pregnancy outcomes in women with obstetric cholestasis.[8,13] Individual patient meta-analysis is regarded as the gold standard for aggregation of studies because it allows for more powerful and consistent

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analyses, as well as better characterization of subgroups and outcomes, compared to those that are based on aggregate meta-analyses.[12] In summary, although ursodeoxycholic acid reduced the risk of preterm birth and meconium staining of the amniotic fluid, clinicians should not reassure women with obstetric cholestasis that therapy with ursodeoxycholic acid reduces the risk of stillbirth. The Society for Maternal Fetal Medicine continues to support the use of ursodeoxycholic acid in the management of pruritus in women presenting with obstetric cholestasis.[14] ■

REFERENCES

1. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2009;15:2049-2066.
2. Laifer SA, Stiller RJ, Siddiqui DS, et al. Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy. *J Matern Fetal Med* 2001;10:131-135.
3. Lee RH, Goodwin TM, Greenspoon J, Incerpi M. The prevalence of intrahepatic cholestasis of pregnancy in a primarily Latina Los Angeles population. *J Perinatol* 2006;26:527-532.
4. Bull LN, Hu D, Shah S, et al. Intrahepatic cholestasis of pregnancy (ICP) in U.S. Latinas and Chileans: Clinical features, ancestry analysis, and admixture mapping. *PLoS One* 2015;10:e0131211.
5. Parquet M, Metman EH, Raizman A, et al. Bioavailability, gastrointestinal transit, solubilization and faecal excretion of ursodeoxycholic acid in man. *Eur J Clin Invest* 1985;15:171-178.
6. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: A meta-analysis. *Gastroenterology* 2012;143:1492-1501.
7. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology* 2004;40:467-474.
8. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): A randomised controlled trial. *Lancet* 2019;394:849-860.
9. Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: A series of 70 cases. *BJOG* 2002;109:282-288.
10. Ovadia C, Sajous J, Seed PT, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: A systematic review and individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:547-558.
11. Wan JF, Chu SF, Zhou X, et al. Ursodeoxycholic acid protects interstitial Cajal-like cells in the gallbladder from undergoing apoptosis by inhibiting TNF-α expression. *Acta Pharmacol Sin* 2018;39:1493-1500.
12. Tudur Smith C, Marcucci M, Nolan SJ, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. *Cochrane Database Syst Rev* 2016;9:MR000007.
13. Palma J, Reyes H, Ribalta J, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: A randomized, double-blind study controlled with placebo. *J Heptatol* 1997;27:1022-1028.
14. Society for Maternal-Fetal Medicine (SMFM); Lee RH, Greenberg M, Metz TD, Pettker CM. Society for Maternal-Fetal Medicine Consult Series #53: Intrahepatic cholestasis of pregnancy: Replaces Consult #13, April 2011. *Am J Obstet Gynecol* 2021;224:B2-B9.

CME/CE QUESTIONS

1. In their systematic review and meta-analysis, Conde-Agudelo and Romero found an association between SARS-CoV-2 infection during pregnancy and which outcome or outcomes?
a. Preeclampsia only
b. Preeclampsia and eclampsia only
c. Preeclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome only
d. Preeclampsia, preeclampsia with severe features, eclampsia, and HELLP syndrome

2. Which of the following statements about the study by Mills et al is true?
a. Only approximately one-third of women 64 to 66 years of age qualify for discontinuation of cervical cancer screening.
b. Approximately half of women have undergone hysterectomy by 64 years of age and no longer need screening.
c. Women in safety-net settings are less likely to have adequate screening than women with private insurance.
d. Ninety percent of women with 10 years of continuous employer-based insurance are screened adequately.

3. In the study by Barnard et al, intervention-group participants were asked to follow which of the following diets?
a. Pescatarian (vegetarian plus seafood) diet
b. Paleo diet
c. Vegan diet plus soybeans
d. Vegetarian diet plus black beans

4. Which of the following study outcomes had a statistically significant reduction by ursodeoxycholic acid therapy?
a. Meconium-stained amniotic fluid
b. Preterm premature rupture of fetal membranes
c. Umbilical cord arterial pH of less than 7.0
d. Apgar score of less than 7 at five minutes of life, perinatal death