Relias Media
From Relias

Vol. 37, Issue 11, March 2021
ReliasMedia.com

OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

The Pregnancy Perspective: What Has COVID-19 Affected?

By Jeanine Mikek, MSN, RN, CEN, RNC-NIC

Maternal Child Health Educator, IU Arnett Hospital, Lafayette, IN

SYNOPSIS: In this cross-sectional descriptive study, women using the Ovia pregnancy app expressed receiving adequately safe maternal care during the COVID-19 pandemic, but voiced concerns related to obtaining infant supplies and prenatal education.

SOURCE: Burgess A, Breman RB, Bradley D, et al. Pregnant women's reports of the impact of COVID-19 on pregnancy, prenatal care, and infant feeding plans. *MCN Am J Matern Child Nurs* 2021;46:21-29.

When severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first hit the United States in early 2020, many healthcare facilities adapted their current practices to adhere to recommended infection prevention measures. Some offices and clinics opted to complete virtual visits with patients, and many hospitals restricted the number of visitors allowed. Coronavirus disease 2019 (COVID-19) has led to financial, economic, and health insecurities for many among the general population, including pregnant women and those with small infants at home. Burgess et al aimed to decipher how COVID-19 has changed prenatal maternity practices, infant feeding plans, and other aspects of care for pregnant or postpartum women. Through the use of an app-based survey that was open for one week in May 2020, women were able to score their perceptions of care and write anecdotal comments related to their concerns and experiences.

The majority of participants identified themselves as white (82.9%), married (80.9%), primiparous (62%), actively seeing an OB/GYN for care (81.3%), and more than 24 weeks of gestation (53.9%). Nearly three-fourths of participants stated their chosen birth facility was only allowing one support person during labor and delivery, which 17% found too restrictive. Fifty percent of the women reported interest in childbirth education classes, but 75% of those participants stated classes were canceled while only 54% reported being given an option to attend virtually. An overwhelming

Financial Disclosure: Dr. Rebecca H. Allen, editor, reports that she receives grant/research support from Bayer, and is a consultant for Bayer, Mylan, and Merck. Dr. Sarah J. Betstadt, peer reviewer, reports that she is on the speakers bureau for Merck. All of the relevant financial relationships listed for these individuals have been mitigated. None of the remaining planners or authors for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

OB/GYN Clinical [ALERT]
Evidence-based commentaries on women's reproductive health

OB/GYN Clinical Alert (ISSN 0743-8354) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *OB/GYN Clinical Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Questions & Comments:
Please contact Editor **Jason Schneider**, at jschneider@relias.com

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

2 ANCC contact hours will be awarded to participants who meet the criteria for successful completion.

This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

majority of the women who originally planned to attend classes (93.2%) reported they would have preferred face-to-face classes.

COVID-19 also hindered the perception and emotional aspect of the provider visit. Although more than 60% of the women reported being satisfied with their virtual prenatal visits, many commented that the care seemed inadequate, impersonal, or unsafe. Difficulties in obtaining appointments or missing out on important checks, such as fetal heartbeat or maternal blood pressure, were voiced. Interestingly, six of the women said their infant feeding plan changed because of COVID-19, with five of those participants switching from formula to breast milk. Four of those women reported they thought that breast milk would better protect their baby from infection. From a financial aspect, a large number of canceled baby showers and a seemingly low supply of essential items (such as diapers and wipes) also concerned the women.

■ COMMENTARY

A major limitation to this qualitative study is the small number of women who responded. Although more than 90,000 application users received the link to the survey, only 442 (4%) opened the link and 258 completed the survey (58% of those who opened the survey and 0.2% of eligible participants). Despite the pertinent comments made by the participants, generalization of the results is questionable because of the small sample size. In addition, there are numerous applications and sites that pregnant women use. The survey used for the Ovia app is a good start to review perceptions and experiences, but the results may have varied across other platforms and with a larger participant response. This also would expand the characteristics of study participants, which may factor in socioeconomic difficulties in obtaining care.

Despite the limitation of the study, it is clear that COVID-19 has not only affected healthcare from the provider viewpoint, but from the patient perspective as well. Virtual visits often are applied to reduce the amount of people and foot traffic in an enclosed building, but the impersonal feel may hinder a pregnant woman from feeling comfortable, asking questions, or being reassured that she and the fetus are healthy. In-office visits may be postponed or canceled if the woman is having any COVID-19-associated symptoms, and telehealth may not be an option for those with limited technology access.[1] Prenatal and antenatal education classes can be a remarkable benefit to women and their partners as they prepare for their newborn, and that education should not cease. Although the virtual platform is not ideal in this setting, the education still should be available and shared regardless of the obstacles that COVID-19 has created. Interactions and visits should be used to assess the physical, as well as the emotional, well-being of the mother during this time of uncertainty. ■

REFERENCE

1. Fryer K, Delgado A, Foti T, et al. Implementation of obstetric telehealth during COVID-19 and beyond. *Matern Child Health J* 2020;24:1104-1110.

ABSTRACT & COMMENTARY

Pregnancy After Treatment for Pelvic Floor Disorders

By Chiara Ghetti, MD

Associate Professor, Obstetrics and Gynecology, Division of Female Pelvic Medicine and Reconstructive Surgery, Washington University School of Medicine, St. Louis, MO

SYNOPSIS: This consensus document was developed as a reference for physicians caring for and advising women in pregnancy following prior surgical treatment for pelvic floor disorders.

SOURCE: Wieslander CK, Weinstein MM, Handa VL, Collins SA. Pregnancy in women with prior treatments for pelvic floor disorders. *Female Pelvic Med Reconstr Surg* 2020;26:299-305.

Although the average age of women in my urogynecology practice is 55 years, there is an increasing number of reproductive-age women undergoing pelvic floor reconstructive surgery. Jonsson et al reports 25% of pelvic floor reconstructive surgeries are performed in women younger than age 45 years, some of which also include slings.[1] Concurrently, the birth rate among older women is additionally on the rise. Guidance on pregnancy after surgery for pelvic floor disorders is sparse. The main objective of this study was to summarize evidence regarding the effect of pregnancy on women who previously have undergone treatment for pelvic floor disorders. This was a comprehensive literature review performed in 2018. A literature search for English language publications was performed using Medline and Scopus terms, including pregnancy, delivery, and pelvic floor disorders. Data were not sufficient for a systematic review or for issuance of formal practice guidelines. The overall evidence was Level III, expert opinion. The key findings and recommendations are summarized in three broad categories of pregnancy and childbirth: after surgery for incontinence, after surgery for pelvic organ prolapse, and after repair of obstetric anal sphincter laceration. The major findings are reviewed here.

Pregnancy after surgery for incontinence: The authors reviewed the evidence regarding stress incontinence outcomes following pregnancy and delivery after midurethral sling retropubic colposuspension, pubovaginal sling, and artificial sling. A cohort study comparing women having undergone midurethral sling to women undergoing pregnancy and delivery without prior sling found there was not an increased risk of stress incontinence following pregnancy and delivery in women with prior sling. The remainder of cited studies consists of case reports and case series. These also suggest that women maintain continence following pregnancy after surgical treatment of stress incontinence. Regarding risk and safety concerns for pregnant women who previously have had surgery, a 2012 systematic review concluded there is not a significant risk.[2] However, case reports describe the possibility of voiding dysfunction and urethral obstruction that may present in the second trimester and may require sling revision. In pregnant women with a prior sling, there are insufficient data to determine whether rates of recurrent incontinence differ between women delivering vaginally or via cesarean section. The authors of this summary concur that it is reasonable to make the decision regarding route of delivery on an individual basis.

Evidence was reviewed regarding pregnancy in women who previously have had implantation of sacral neuromodulation. Both the device manufacturer and the International Urogynecological Association recommend turning off a neurostimulator device during a pregnancy.[3] Survey and case series data suggest that one-third of women may leave their device turned on. Women who did not turn off the device reported stable symptoms during pregnancy, while those who discontinued its use experienced bothersome urinary symptoms. Data are insufficient to make precise conclusions about the risks of sacral neuromodulation in pregnancy and regarding the effect of the mode of delivery on device malfunction. Again, it is recommended that sacral neuromodulation devices be turned off during pregnancy.

Pregnancy after surgery for pelvic organ prolapse: Women who undergo hysteropexy, and, therefore, retain their uterus, may subsequently experience a pregnancy. Data are very limited regarding the risk of recurrence, safety concerns, and mode of delivery. Extensive preoperative counseling is recommended before uterine-sparing procedures. This counseling should include the recommendation of effective and long-acting contraception. Preoperative counseling should discuss the possibility of a prolapse recurrence following pregnancy and the possible need for cesarean delivery. An informed discussion of prolapse management always includes conservative management; in this instance, pessary management until the completion of childbearing should be discussed for women who have not completed childbearing.

Pregnancy after surgery for repair of obstetrical anal sphincter laceration: Data on which to base recommendations regarding obstetric anal sphincter injury (OASI) vary widely. The risk of recurrence of OASI is estimated to be between 4% and 10%, and the risk appears to be similar to the risk of primary OASI. Reducing the risk of recurrent OASI was discussed in a 2014 Cochrane review and included interventions ranging from pelvic floor muscle strengthening to elective cesarean delivery.[4] The risk of long-term anal incontinence with recurrent OASI may be significant. Recommendations regarding the mode of delivery after a prior OASI vary widely also. Vaginal delivery may be a safe option in women with prior OASI and no anal incontinence symptoms. Providers are urged to counsel pregnant women with a history of prior OASI extensively regarding mode of delivery options, with consideration of anal incontinence symptoms, risks of repeat OASI, and the surgical risk of cesarean delivery.

■ COMMENTARY

This review illustrates that overall there is a paucity of data to guide counseling for women regarding the risks and possible effects of surgery for pelvic floor disorders on future pregnancy and delivery, as well

as the effects of pregnancy on surgery outcomes. Women should be informed about the limited data available. Counseling at the time of initial surgery and during subsequent pregnancies should include the full range of management options and include contraceptive management options. Women and providers are encouraged to participate in a shared decision-making model. ■

REFERENCES

1. Jonsson Funk M, Levin PJ, Wu JM. Trends in the surgical management of stress urinary incontinence. *Obstet Gynecol* 2012;119:845-851.
2. Pollard ME, Morrisroe S, Anger JT. Outcomes of pregnancy following surgery for stress urinary incontinence: A systematic review. *J Urol* 2012;187:1966-1970.
3. International Urogynecological Association. Sacral neuromodulation: A guide for women. https://www.yourpelvicfloor.org/media/Sacral_Neuromodulation_RV1.pdf
4. Farrar D, Tuffnell DJ, Ramage C. Interventions for women in subsequent pregnancies following obstetric anal sphincter injury to reduce the risk of recurrent injury and associated harms. *Cochrane Database Syst Rev* 2014 Nov 6;CD010374. doi: 10.1002/14651858.CD010374.pub2.

ABSTRACT & COMMENTARY

Is HPV Testing Superior to Pap Testing Alone in Women at Risk of Cervical Cancer?

By Rebecca B. Perkins, MD, MSc

Associate Professor, Department of Obstetrics and Gynecology, Boston University School of Medicine/Boston Medical Center, Boston, MA

SYNOPSIS: In this registry-based screening study of women in Catalonia, Spain, a negative human papillomavirus (HPV) and cytology co-test at baseline was associated with a cumulative incidence of cervical precancer of 0.4% at five years and 1.3% at nine years, compared to 27% among women with abnormal HPV testing at baseline.

SOURCE: Ibáñez R, Roura E, Monfil L, et al. Long-term protection of HPV test in women at risk of cervical cancer. *PLoS One* 2020;15:e0237988.

Cervical cancer screening is considered one of the most effective cancer prevention tests. The screening guidelines released in 2018 by the U.S. Preventive Services Task Force (USPSTF) allow screening with either cervical cytology (Pap tests) alone, cervical cytology with oncogenic human papillomavirus (HPV) co-testing, or HPV testing alone.[1] However, guidelines released in July 2020 by the American Cancer Society favor HPV testing over co-testing or Pap testing alone.[2] In addition, revised 2020 guidelines for follow-up after abnormal screening test results also favor HPV testing, with or without a Pap test, because of higher sensitivity for detection of precancer.[3] Both USPSTF and the American College of Obstetricians and Gynecologists (ACOG) allow choice at the practice, provider, and patient levels among screening modalities; therefore, understanding the relative risks and benefits is paramount.[1,4]

In this study, a cohort of underscreened women enrolled in the public health system in Catalonia, Spain, were followed for nine years after a baseline HPV and Pap co-test. A total of 1,831 underscreened women were identified in 2007 and followed through 2016. Women were screened with co-testing at baseline, then followed with cytology every three years through age 65 years if results were negative or followed with repeat testing or colposcopy if tests were abnormal, as recommended by national guidelines. Overall, 92.4% of women had negative HPV and Pap results, 1.3% had abnormal results on both tests, 6.7% were HPV-positive, and 2.2% had an abnormal Pap test. During the nine-year follow-up period, 23 women were diagnosed with cervical intraepithelial neoplasia grade 2 or higher (CIN2+), including nine cases of CIN3 and CIN4 cancers. A single positive HPV test detected 83% of all lesions, while the Pap test alone detected 35%. All cancers were positive on both HPV and Pap testing. No CIN3 or cancers were detected within five years of a negative HPV test, regardless of the cytology result. Among HPV-negative women, the cumulative incidence was 0.3% at nine years. Adherence to continued screening was low, consistent with the population of women who were underscreened at baseline. Within the nine-year follow-up period, only 60.2% of women with negative screening results on both tests obtained follow-up. Adherence was higher after an abnormal result: 74.5% within three years and 83.7% within nine years underwent follow-up testing.

■ COMMENTARY

This study adds important evidence to help providers and patients choose between screening options. In this population of underscreened women aged 40 years and older, HPV testing clearly is superior to Pap testing alone. HPV testing missed only one case of CIN3+, while Pap testing missed six

cases. As noted in other settings, Pap testing added little to HPV testing alone.[5] Women with negative HPV test results had a low risk for precancer that remained low up to nine years after the initial screen, regardless of Pap test results. In addition, no women with a negative HPV test and abnormal Pap test developed precancer. The finding that a negative HPV test provides long-term reassurance against the development of precancer and cancer, and that the addition of a Pap test adds relatively little risk stratification, also is supported by other large randomized controlled studies from the United States and Europe.[6-8] Overall, these findings support the most recent recommendations for cervical cancer screening, made by the American Cancer Society, the European Society of Gynaecologic Oncology, and the European Federation of Colposcopy, which favor HPV testing as the first-line screening test over co-testing or cytology alone.[2,9]

Another important finding from this study is relatively low rates of subsequent adherence to screening after negative results. Educating patients on the importance of returning for screening over extended intervals, as well as the establishment of reminder or recall systems that can track patients over five-year intervals, is critical.[10]

Obstetrician-gynecologists often are the primary source of information on cervical cancer screening for our patients, our colleagues, and our communities. This study and others indicate that including HPV testing in screening detects more precancer than Pap testing alone, and can lead to a decrease in cervical cancer mortality within eight years of instituting HPV screening.[5-8,11] Co-testing with Pap and HPV testing together is used widely in the United States, and also has been associated with extremely low cancer rates.[12] HPV testing alone has the advantages of lower costs and fewer false-positive results than co-testing, and superior precancer detection compared to Pap testing alone. HPV testing also may be used for self-collected samples, which currently are pending Food and Drug Administration approval in the United States. Self-sampling, when available, may be helpful to extend screening to populations who currently do not have screening access or for whom pelvic exams are difficult, painful, or traumatic.[9,13,14] ■

REFERENCES

1. 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.
2. Fontham ET, Wolf AM, 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.
3. 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.
4. The American College of Obstetricians and Gynecologists. Cervical cancer screening (update). August 2018. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2018/08/cervical-cancer-screening-update
5. Schiffman M, Kinney WK, Cheung LC, et al. Relative performance of HPV and cytology components of cotesting in cervical screening. *J Natl Cancer Inst* 2018;110:501-508.
6. Elfstrom KM, Smelov V, Johansson AL, et al. Long term duration of protective effect for HPV negative women: Follow-up of primary HPV screening randomised controlled trial. *BMJ* 2014;348:g130.
7. Wright TC, Stoler MH, Behrens CM, et al. Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol* 2015;136:189-197.
8. Dijkstra MG, van Zummeren M, Rozendaal L, et al. Safety of extending screening intervals beyond five years in cervical screening programmes with testing for high risk human papillomavirus: 14 year follow-up of population based randomised cohort in the Netherlands. *BMJ* 2016;355:i4924.
9. Kyrgiou M, Arbyn M, Bergeron C, et al. Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). *Br J Cancer* 2020;123:510-517.
10. Tsoa E, Kone Pefoyo AJ, Tsiplova K, Kupets R. Evaluation of recall and reminder letters on retention rates in an organized cervical screening program. *J Obstet Gynaecol Can* 2017;39:845-853.
11. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009;360:1385-1394.
12. Castle PE, Kinney WK, Xue X, et al. Effect of several negative rounds of human papillomavirus and cytology co-testing on safety against cervical cancer: An observational cohort study. *Ann Intern Med* 2018;168: 20-29.
13. Goldstein Z, Martinson T, Ramachandran S, et al. Improved rates of cervical cancer screening among transmasculine patients through self-collected swabs for high-risk human papillomavirus DNA testing. *Transgend Health* 2020;5:10-17.
14. Arbyn M, Smith SB, Temin S, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: Updated meta-analyses. *BMJ* 2018;363:k4823.

ABSTRACT & COMMENTARY

Oral Progestogens for Prevention of Miscarriage

By Ahizechukwu C. Eke, MD, PhD, MPH

Assistant Professor in Maternal Fetal Medicine, Division of Maternal Fetal Medicine, Department of Gynecology & Obstetrics, Johns Hopkins University School of Medicine, Baltimore

SYNOPSIS: In this double-blind, randomized clinical trial, 406 pregnant women were randomized to dydrogesterone or placebo. There were no statistically significant differences in the primary outcome (miscarriage before 20 weeks of gestation; relative risk, 0.897; 95% confidence interval, 0.548-1.467; $P = 0.772$), which occurred in 12.8% and 14.3% in the dydrogesterone and placebo arms, respectively. The use of dydrogesterone in women with threatened miscarriage for the prevention of early pregnancy loss in the first trimester failed to decrease the miscarriage rate or increase the live birth rate.

SOURCE: Chan DMK, Cheung KW, Ko JKY, et al. Use of oral progestogen in women with threatened miscarriage in the first trimester: A randomized double-blind controlled trial. *Human Reprod* 2020: Dec 17;deaa327. doi: 10.1093/humrep/deaa327. [Online ahead of print].

Miscarriage (early pregnancy loss), the loss of an intrauterine confirmed pregnancy before 20 weeks of gestation, occurs in approximately 10% to 25% of all pregnancies.[1] A miscarriage usually is a distressing experience, and can be associated with enormous psychologic effect.[2] Although there are no proven effective medical therapies to prevent miscarriage, studies have suggested that some women who experience miscarriage have insufficient serum progesterone in early pregnancy.[3] Therefore, progestogen supplementation in these women has been suggested for the prevention of early pregnancy loss.[3]

[The rationale for the use of progestogens in the prevention of miscarriage is based on their uterine-relaxant, anti-estrogenic, immunomodulatory, and anti-inflammatory effects. However, there are sparse data to support the use of oral progestogens that are stable in plasma for the prevention of miscarriage.]

Progestogens (medications identical to endogenous progesterone) in the form of vaginal suppositories have been studied extensively for the prevention of miscarriage. The rationale for the use of progestogens in the prevention of miscarriage is based on their uterine-relaxant, anti-estrogenic, immunomodulatory, and anti-inflammatory effects. However, there are sparse data to support the use of oral progestogens that are stable in plasma for the prevention of miscarriage. To answer this research question, Chan and colleagues conducted a double-blind, randomized controlled trial in three public hospitals in Hong Kong: Queen Mary, Kwong Wah, and Pamela Youde Nethersole Eastern hospitals.[4] Inclusion criteria included women between 18 and 40 years of age presenting with threatened miscarriage (vaginal bleeding with or without abdominal pain, with a viable intrauterine pregnancy determined by gestational sac diameter and crown-rump length) between five weeks and 12 weeks of gestation; absence of fever (temperature ≥ 38.5°C); singleton gestations; and women with a history of one or two prior miscarriages.[4] Exclusion criteria included heavy vaginal bleeding; history of recurrent miscarriage (three or more consecutive spontaneous miscarriages); history of known parental chromo-somal abnormalities; severe abdominal pain requiring surgical intervention; absence of fetal tones in a fetus with crown-rump length of ≥ 7 mm on transvaginal ultrasound; use of human chorionic gonadotrophin (hCG)/progestogens for threatened miscarriage prior to recruitment; and women with current or suspected breast or genital cancers, hepatic disease, or tumors.[4]

Using computer randomization, the participants were randomized to dydrogesterone (Duphaston, Abbott, Chicago) and placebo groups. The dose of the medications (dydrogesterone and placebo) was a 40-mg loading dose, followed by 10 mg three times daily (according to prescription instructions). The primary outcome was miscarriage before 20 weeks of gestation, while secondary outcomes included gestational weight at delivery, live birth rate, Apgar score, and obstetric complications, including antepartum hemorrhage, placenta previa, pregnancy-induced hypertension, preeclampsia, preterm

labor, low birthweight at term, and congenital abnormality.[4] The participants had weekly follow-up with pelvic ultrasounds until 12 weeks of gestation, missed abortion, severe vaginal bleeding requiring surgical management, or one week after vaginal bleeding ceased, whichever came last. A sample size of at least 171 women per group was sufficient to demonstrate statistically significant differences between the treatment and placebo groups based on a baseline miscarriage prevalence rate of 14.8% in the progestogen group and 27.1% in the control group, assuming 80% power and a type 1 error rate of 5%.

From March 2016 to May 2018, a total of 406 pregnant women met inclusion criteria. A total of 203 women were randomized to the dydrogesterone arm, and 203 were randomized to the placebo group. The baseline characteristics were similar in both groups. The primary outcome (miscarriage at < 20 weeks of gestation) was 12.8% and 14.3% in the dydrogesterone and placebo groups, respectively (relative risk, 0.897; 95% confidence interval, 0.548-1.467; $P = 0.772$). Subgroup analyses of women aged ≥ 35 years, those with positive fetal heart tones on ultrasound, those with drug compliance of > 80%, and exclusion of abnormal fetal karyotypes did not show a significant difference in the miscarriage rate between the two groups. There were no significant differences in all secondary outcomes by intention-to-treat or by per-protocol analysis. There were no differences in adverse effects between the groups.

■ COMMENTARY

Progesterone is essential for both implantation and continued maintenance of pregnancy. For a long time, vaginal progesterone was used off-label for the prevention of miscarriages, but data from the progesterone in recurrent miscarriage (PROMISE)[5] and the progesterone in early pregnancy bleeding (PRISM)[6] trials did not show vaginal progesterone as a promising drug for preventing early pregnancy loss.

The PROMISE trial was a double-blind, placebo-controlled, multicenter, randomized clinical trial involving more than 800 women with a history of miscarriage to evaluate the efficacy of vaginal progesterone (when compared to placebo) in increasing live-birth rates and neonatal survival in women with unexplained miscarriage, while the PRISM trial is a multicenter, randomized, double-blind, placebo-controlled trial involving more than 4,000 women with threatened miscarriage.

Both trials demonstrated that vaginal progesterone suppositories were not effective in preventing early pregnancy loss when compared to placebo. Therefore, the research question of the efficacy of oral progestogens in the prevention of early pregnancy loss is pertinent and relevant.

Because of the extensive hepatic first-pass effect of oral progestogens, the bioavailability of most orally administered progestogens is low (4% to 8%). Although this is true for most progestogens, dydrogesterone is an exception. Dydrogesterone, a synthetic pregnane retro-progesterone derivative, is rapidly absorbed from the intestines, achieving a bioavailability of 28% within one to three hours of ingestion, with a steady-state concentration achieved after 72 hours of therapy.[7] Metabolism of dydrogesterone to its active metabolite, 20-dihydrodydrogesterone, increases its half-life from five to seven hours (dydrogesterone) to 14 to 17 hours (20-dihydrodydrogesterone).[7] These pharmacokinetic properties confer on 20-dihydrodydrogesterone longer pharmacodynamic effects compared to other oral progestogens. In this study by Chan et al, no significant differences were demonstrated in the primary and secondary outcomes between participants treated with dydrogesterone compared to placebo. It is possible that plasma concentrations of dydrogesterone and 20-dihydrodydrogesterone were below the minimum trough concentration (Ctrough) needed to prevent miscarriage in these participants. However, it is difficult to tell, because plasma dydrogesterone or 20-dihydrodydrogesterone concentrations were not assayed in the trial participants. Based on these data, oral progestogens are not recommended for prevention of early pregnancy loss. ■

REFERENCES

1. Ventura SJ, Curtin SC, Abma JC, Henshaw SK. Estimated pregnancy rates and rates of pregnancy outcomes for the United States, 1990-2008. *Natl Vital Stat Rep* 2012;60:1-21.
2. Nynas J, Narang P, Kolikonda MK, Lippmann S. Depression and anxiety following early pregnancy loss: Recommendations for primary care providers. *Prim Care Companion CNS Discord* 2015;17:10.4088/PCC.14r01721.
3. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev* 2019;2019:CD003511.
4. Chan DMK, Cheung KW, Ko JKY, et al. Use of oral progestogen in women with threatened miscarriage in the first trimester: A randomized double-blind controlled trial. *Human Reprod* 2020; Dec 17. doi: 10.1093/humrep/deaa327. [Online ahead of print].
5. Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med* 2015;373:2141-2148.
6. Coomarasamy A, Devall AJ, Cheed V, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med* 2019;380:1815-1824.
7. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens used in postmenopausal hormone therapy: Differences in their pharmacological properties, intracellular actions, and clinical effects. *Endocr Rev* 2013;34:171-208.

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to ReliasMedia.com and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on your mailing label, invoice, or renewal notice.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. Tests are taken with each issue.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME/CE QUESTIONS

1. **According to the women who responded to the Ovia app survey, most expressed:**
   a. satisfaction with virtual childbirth education.
   b. dissatisfaction with hospital visitation restrictions.
   c. satisfaction with prenatal care, despite virtual visits.
   d. dissatisfaction with an inability to obtain formula.
2. **Based on the study by Wieslander et al regarding pregnancy in women with prior treatment for pelvic floor disorders, which of the following is correct?**
   a. There are extensive data to guide recommendations.
   b. Women should be counseled extensively about the limited data available to help guide their decisions and should be encouraged to participate in a shared decision-making model.
   c. Clear recommendations exist about the route of delivery after surgery for pelvic floor disorders.
   d. Recurrence of urinary incontinence after pregnancy following sling is certain.
3. **Which of the following statements about the study by Ibáñez et al is *false*?**
   a. Human papillomavirus (HPV) testing detects more cervical precancer than Pap testing alone.
   b. A negative HPV test provides reassurance against developing pre-cancer for up to nine years.
   c. More than 90% of women undergoing screening have negative HPV test results.
   d. Adherence to follow-up screening was high after a negative HPV screening test.
4. **Which of the following was *not* a secondary outcome in the randomized trial by Chan et al?**
   a. Gestational weight at delivery
   b. Intrauterine fetal death
   c. Pregnancy-induced hypertension
   d. Low birthweight

[IN FUTURE ISSUES]

Loop Electrosurgical Excision Procedure of the Cervix: Which Is the Best Method of Anesthesia?