

Alexandros Sotiriadis, MD, PhD
 Department of Obstetrics and Gynecology
 School of Medicine
 University of Ioannina
 Ioannina, Greece
 Department of Obstetrics and Gynecology
 Faculty of Medicine
 Aristotle University of Thessaloniki
 Thessaloniki, Greece
 The authors report no conflict of interest.

REFERENCES

1. Enakpene CA, DiGiovanni L, Jones TN, Marshalla M, Mastrogianis D, Della Torre M. Cervical cerclage for singleton pregnant patients on vaginal progesterone with progressive cervical shortening. *Am J Obstet Gynecol* 2018;219:397.e1-397.
2. Romero R, Nicolaides KH, Conde-Agudelo A, et al. Vaginal progesterone decreases preterm birth ≤ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. *Ultrasound Obstet Gynecol* 2016;48:308-17.
3. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med* 2007;357:462-9.

© 2018 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2018.10.020>

REPLY



Thank you so much for your keen interest in our article and your letter to the editor. I must commend you for your excellent work, your observation, and the outcome of your study. Vaginal progesterone appears to work only for women with a short and stable cervix, because the shorter the cervical length (CL), the higher the risk of spontaneous preterm birth.¹ However, in women with a short dynamic cervix and progressively shortening CL, especially <10 mm, vaginal progesterone alone was less effective compared with combined vaginal progesterone and cerclage as shown in our study.

Extremely short CL increases the risk of cervical dilation, which exposes the fetal membranes to pathogenic vaginal microbiomes. There is also the potential risk of stripping of the fetal membranes from the decidua attachment in the lower uterine segment. These 2 events increase the risk of intra-amniotic infection/inflammation that causes the release of cytokines and prostaglandin that invariably result in uterine contraction and spontaneous preterm birth.² There is currently

no recommendation on the optimal surveillance of cervical length once short cervix is diagnosed, but individual institutions should adopt a protocol based on their patients population and available resources. Our institutional policy includes serial CL measurement every 2 weeks for CL 20–25 mm and weekly for CL <20 mm up to 24 weeks when cerclage is placed if CL is <10 mm. After 24 weeks gestation, women with CL <20 mm may be monitored every 2 weeks up to 28 weeks gestation to enable early detection of patients with extreme short cervix who may benefit from betamethasone for fetal lung maturity. Serial CL measurements may require frequent visits by the patient, an increase in the healthcare staff work load, and economy cost; however, the benefits of additional intervention to reduce extreme prematurity quite outweigh the overall burden of CL surveillance. Finally, spontaneous preterm birth is as a result of interaction of multiple pathologic process such as cervical insufficiency, uterine irritability/contraction, and activation of fetal membranes—decidua interface.³ Therefore, interventions to reduce preterm birth will require a multimodal approach such as a combination of cervical cerclage and vaginal progesterone for those women who are at extreme risk of preterm birth. ■

Christopher A Enakpene, MD, MS, FACOG
 Division of Maternal-Fetal Medicine
 Department of Obstetrics and Gynecology
 Texas Tech University Health Sciences Center
 Midland/Odessa, TX

Laura DiGiovanni, MD, FACOG
 Micaela Della Torre, MD, MS, FACOG
 Division of Maternal-Fetal Medicine
 Department of Obstetrics and Gynecology
 University of Illinois at Chicago
 Chicago, IL

The authors report no conflict of interest.

REFERENCES

1. Owen J, Yost N, Berghella V, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network. *JAMA* 2001;286:1340-8.
2. Lee SM, Park KH, Jung EY, Jang Ja, Yoo HN. Frequency and clinical significance of short cervix in patients with preterm premature rupture of membranes. *PLoS One* 2017;12:e0174657.
3. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science* 2014;345:760-5.

© 2018 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2018.10.019>

Re: Maternal age and risk for adverse outcomes



TO THE EDITORS: We believe that the study design of the paper “Maternal age and risk for adverse outcomes”¹ was mischaracterized as a retrospective cohort. As we have noted

previously,^{2,3} in a cohort study, participants are identified as exposed or unexposed to the factor of interest, regardless of outcome, and are then followed over time to determine who

experiences the outcome of interest.⁴ In particular, in a retrospective cohort, exposure occurs in the past and is ascertained from preexisting records, and follow-up time also occurs in the past. Both of these times are with respect to the study initiation, not to when the data were analyzed.³ In contrast, a cross-sectional study ascertains exposure and outcome at the same point in time, which, in this study, was delivery hospitalization. Relatedly, the outcome is measured as prevalent (eg, the prevalence results presented in Figure 2) rather than incident. A cross-sectional study does not measure the passage of people through time as a cohort study does. If hospital discharge data were linked within individuals across time (ie, linking records across multiple hospitalizations), then person-time may elapse, and a retrospective cohort designation might be more appropriate. In such a setting, if investigators examined the association between a variable that occurred during a first hospitalization (eg, administration of a drug or procedure) and an outcome during a subsequent hospitalization (eg, a morbidity that required hospitalization), then they would take advantage of the cohort nature of the study and could calculate, for example, 1-year cumulative incidence. However, this design is not relevant for the effects of exposures such as age, which is a variable for which contemporaneous outcome data are preferred. The aforementioned paper was based on discharge data from the delivery hospitalization, does not consider the passage of time, and thus meets the definition of a cross-sectional study. ■

Jonathan M. Snowden, PhD
School of Public Health
Department of Obstetrics and Gynecology
Oregon Health and Science University
Portland, OR

Mark A. Klebanoff, MD, MPH
Center for Perinatal Research
The Research Institute at Nationwide Children's Hospital
Departments of Pediatrics and Obstetrics and Gynecology
The Ohio State University
Columbus, OH

The authors report no conflict of interest.

REFERENCES

1. Sheen JJ, Wright JD, Goffman D, et al. Maternal age and risk for adverse outcomes. *Am J Obstet Gynecol* 2018;219:390.e1–15.
2. Klebanoff MA, Snowden JM. Re: Trends in operative vaginal delivery, 2005-2013: a population-based study. *BJOG* 2018;125:97.
3. Klebanoff MA, Snowden JM. Historical (retrospective) cohort studies and other epidemiologic study designs in perinatal research. *Am J Obstet Gynecol* 2018;219:447–50.
4. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

© 2018 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2018.12.027>

REPLY



We agree with the thoughtful comment from Drs Snowden and Klebanoff.¹ The discharge hospitalization data that were used are cross sectional and unlinked to previous or subsequent health data.² Given that we are not able to determine whether exposures occurred before individual outcomes, it is appropriate to characterize it as cross sectional. ■

Alexander M. Friedman, MD, MPH
Division of Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Columbia University
New York, NY

The author reports no conflict of interest.

REFERENCES

1. Snowden JM, Klebanoff MA. Re: maternal age and risk for adverse outcomes. *Am J Obstet Gynecol* 2019 (insert reference of the Letter-to-the-Editor L18-122A).
2. Sheen JJ, Wright JD, Goffman D, et al. Maternal age and risk for adverse outcomes. *Am J Obstet Gynecol* 2018;219:390.e1–15.

© 2018 Elsevier Inc. All rights reserved. <https://doi.org/10.1016/j.ajog.2018.12.028>