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A Note from the Editor-in-Chief

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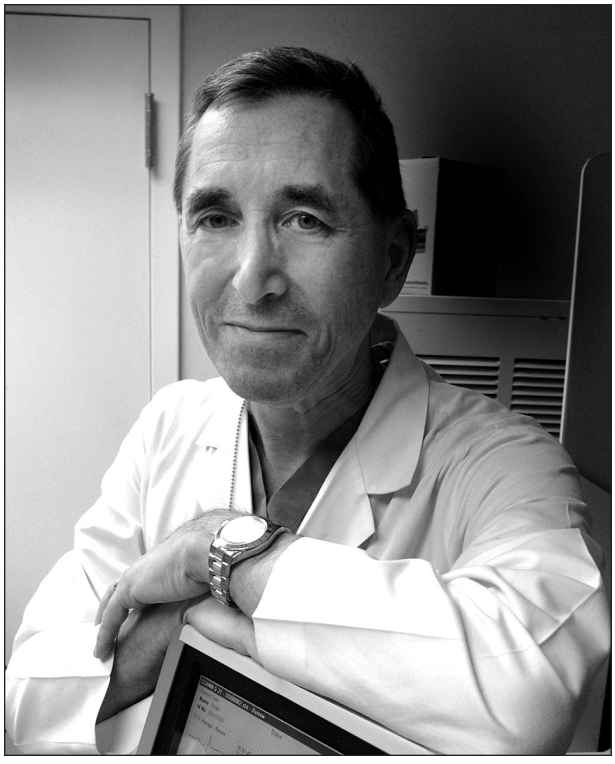
Welcome to the November-December 2019 Editor-in-Chief's page. This editorial column will be on a single clinical issue: the use of progestogens in patients with previous spontaneous preterm birth.



Lawrence D. Devoe, M.D., Editor-in-Chief

In This Issue

Vaginal Versus Intramuscular Progestogen for Prevention of Recurrent Spontaneous Preterm Birth: A Pragmatic Study in a High-Risk Patient Population
T. L. Glenn, R. A. Maxwell, and D. S. McKenna

This retrospective study compared the use of vaginal progestogen (VP) with intramuscular (IM) progestogen to prevent recurrent spontaneous preterm birth (SPTB). While they found no significant difference between the VP and IM groups for delivery at <37 weeks, there was a trend toward a lower percentage of term births in the former. The IM group had a greater number of days gained when compared to the timing of their patients' earliest SPTB.

Editorial Comment

While the study by Glenn and colleagues may lack the power to determine whether VP is as effective as IM progestogen in preventing SPTB, a larger question has been raised recently concerning the effectiveness of IM 17α-hydroxyprogesterone caproate (17α-OHP). It is quite timely to revisit this question that has been lingering for more than 4 decades after J. W. Johnson's initial study[1] showed promising results for the use of this progestogen. Nearly 30 years later, the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network performed a much larger randomized trial[2] that supported

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Johnson's earlier study. The American College of Obstetricians and Gynecologists (ACOG) published a Committee Opinion[3] that effectively endorsed progestogen supplementation for prevention of recurrent SPTB in high-risk women. The Society for Maternal-Fetal Medicine (SMFM) has repeatedly supported this practice recommendation. In 2011 the U.S. Food and Drug Administration (FDA) approved Makena, KV Pharmaceutical Company's trade name for 17α-OHP, for prevention of recurrent SPTB.

Recently, several studies have raised concerns that 17α-OHP supplementation for high-risk women may not be as effective as once believed. The largest of these investigations,[4] the same size as the original Maternal-Fetal Medicine Unit Network study, not only failed to show benefit from the use of this drug, but also demonstrated an increased risk for gestational diabetes in study subjects. In March 2019 the much anticipated PROLONG (Progestin's Role in Optimizing Neonatal Gestation) trial, intended to be the largest randomized trial of progestogen supplementation, revealed its results. AMAG Pharmaceuticals, the company that now manufactures Makena, announced that the rate of SPTB was the same in both treated and placebo groups. The PROLONG study was criticized for the composition of its study population (more than 75% of its subjects were enrolled outside of the United States) and its unusually low rates of SPTB (11% in both study and control groups). The study's findings led to a recent FDA advisory committee review of Makena's effectiveness that resulted in a recommendation to withdraw this drug from the market.

Both ACOG and SMFM have continued to recommend that obstetricians offer Makena to patients considered to be at high risk for SPTB, but the PROLONG study has certainly muddied the clinical waters. As it is highly unlikely that a large randomized trial of Makena will be conducted in the United States any time soon, the debate over whether IM progestogens actually work will probably continue. Meanwhile, AMAG Pharmaceuticals is supporting several subgroup analyses of the PROLONG trial results to look for factors that might have contributed to the study's negative results.

Anecdotally, after the publication of the original Johnson study,[1] my former colleagues and I began to use 17α-OHP in clinical practice. We stopped doing this after a few years when we did not see the kind of successes that we expected. I then became a 17α-OHP skeptic (and still am) although for the last 16 years, the ACOG Committee Opinions and Practice Bulletins continue to support progestogen supplementation in high-risk women. Perhaps our professional organizations will see things differently if and when the PROLONG study's subgroup analyses see the light of day.

References

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