formation from their study can help us reduce the incidence of birth-related CP. We believe that the adverse obstetric events associated with CP, whether relatively frequent such as fetal distress, or rare such as cord prolapse, in part remain a problem because care is suboptimal despite the best of intentions. Even in instances in which guidelines exist, they are often not implemented appropriately at the forefront of care. Embedded practical team training for all maternity staff on how to use evidence-based systems to support practice, and how to apply knowledge in the heat of emergencies, has been associated with fewer adverse events and better neonatal outcomes.[2-4]

Further to training, prospective surveillance with appropriate tools may ensure that rates of adverse events remain low, by early identification of any deterioration, and instigation of targeted safety interventions.[5]

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REPLY DECLINED

REFERENCES

1. Gilbert WM, Jacoby BN, Xing G, Danielsen B, Smith LH. Adverse obstetric events are associated with significant risk of cerebral palsy. Am J Obstet Gynecol 2010;203:328.e1-5.
2. Siassakos D, Hasafa Z, Sibanda T, et al. Retrospective cohort study of diagnosis-delivery interval with umbilical cord prolapse: the effect of team training. BJOG 2009;116:1089-96.
3. Draycott TJ, Crofts JF, Ash JP, et al. Improving neonatal outcome through practical shoulder dystocia training. Obstet Gynecol 2008; 112:14-20.
4. Draycott T, Sibanda T, Owen L, et al. Does training in obstetric emergencies improve neonatal outcome? BJOG 2006;113:177-82.
5. Sibanda T, Sibanda N, Siassakos D, et al. Prospective evaluation of a continuous monitoring and quality-improvement system for reducing adverse neonatal outcomes. Am J Obstet Gynecol 2009;201:480.e1-6.

 doi: 10.1016/j.ajog.2010.11.035

17-hydroxyprogesterone caproate, progesterone, preterm birth prevention, and safety: who decides? Someone should

TO THE EDITORS: The synthetic progestin 17-hydroxyprogesterone caproate (17-OHP-C) and natural progesterone differ remarkably in their structure and relative affinity for progesterone receptors (the binding affinity of 17OHP-C is only 26-30% of the binding affinity of progesterone).[1] Furthermore, the synthetic is not metabolized into a naturally occurring compound.[2] This varied biochemistry may elicit varied responses, which have been observed in laboratory experiments (some of which are negative regarding exposure to the synthetic). Combs et al[3] describe a randomized controlled trial that adds further suspicion regarding the safety of 17-OHP-C because fetal death caused by midtrimester loss was significantly more common with this treatment.

That death is the safety outcome that is significantly different between groups is alarming, especially for an intervention that is considered to be prophylactic therapeutic. Combs et al highlight a Food and Drug Administration evaluation that identified the same safety signal. Metaanalysis has also raised concern for an association between 17-OHP-C and second-trimester miscarriage.[4] Therefore, biologic plausibility for harm exists, given the relative differences in binding affinity for progesterone receptors, and suspicion for harm related to the synthetic is present from human data and experimentation.

Progesterone has not been associated with death, and efficacy for the prevention of preterm birth has been observed in randomized controlled trials. Hence, several essential questions arise for the specialty of obstetrics:

1. Will proven rare adverse events regarding fetal outcomes be treated in a similar manner to rare adverse events that are observed in adults? If so, could much publicized warnings lead to distrust for American College of Obstetricians and Gynecologist–supported treatments and undermine our specialty's goal for the prevention of preterm birth?
2. In the absence of Food and Drug Administration approval of either medication for this indication, what entity will best evaluate the risk/benefit ratio for these medications and suggest the safest course for the practice of obstetrics?
3. How much evidence for harm is necessary before alternative therapies are more definitively supported for prophylactic treatments?
4. Should progesterone be identified as the safest treatment option, based in part on anthropologic evidence regarding biologic selection that this particular compound is ubiquitous throughout the class Mammalia and that no synthetic could potentially be safer to stimulate progesterone receptors to enhance reproductive functions than progesterone?

Finally, do the authors suggest the American College of Obstetricians and Gynecologists Obstetric Practice Committee, Agency for Healthcare Research and Quality, both, or neither should comment on the safest practice for preterm birth prevention with these agents; or should those leaders wait to opine, despite the potential for a starker action/reaction from regulators at the FDA, the legal system, and the public if their findings are ultimately validated? ■

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REFERENCES

1. Attardi B, Zeleznik A, Simhan H, et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alphahydroxyprogesterone caproate, and related progestins. Am J Obstet Gynecol 2007;197:599.e1-7.
2. Yan R, Fokina V, Hankins GDV, et al. The effect of esterases on 17alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol 2008;198:229.e1-15.
3. Combs CA, Garite T, Maurel K, et al. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol 2010;203:248.e1-9.
4. O'Brien JM, Lewis DF. Progestins for the prevention of spontaneous preterm birth: review and implications of recent studies. J Reprod Med 2009;54:73-87.

 doi: 10.1016/j.ajog.2010.12.001

REPLY

We appreciate Dr O'Brien's concerns regarding the possible association of 17-hydroxyprogesterone caproate (17-OHP-C) and midtrimester pregnancy loss. However, the results that have been published to date do not allow a definitive conclusion that 17-OHP-C causes midtrimester loss. The summary Table IV of O'Brien's metaanalysis of 4 placebo controlled trials (his reference 4) showed that the absolute risk of miscarriage was quite low in both 17-OHP-C (2.6%) and placebo groups (1.3%); the difference did not reach statistical significance in any trial. In our trial of 17-OHP-C for triplet pregnancy,[1] we observed a higher rate of loss in the treatment group than in the placebo group. However, in a similar trial, Caritis et al[2] reported opposite findings, 6 perinatal deaths with placebo vs 1 with treatment. The latter death involved a fetus with multiple anomalies. Several new studies of 17-OHP-C are underway; these studies are listed on the clinicaltrials.gov website. One of these studies has a planned enrollment of >1700 subjects. This will certainly provide much more definitive data about the safety of this agent.

About whether natural progesterone may be superior to 17-OHP-C in this regard, we must caution that the STOPPIT trial reported a 1.2% fetal death rate with natural progesterone vs 0.8% with placebo,[3] which is not a statistically significant difference but a difference of roughly the same magnitude and in the same direction as that suggested for 17-OHP-C. New studies are underway that directly compare the 2 agents. These studies undoubtedly will shed light on the question about whether 1 or the other is safer or more efficacious. The notion that natural compounds intrinsically must be better than synthetic ones is a matter of faith, not science. Much of the enterprise of medicine is predicated on the proposition that we can improve on the outcomes that natural history would yield.

Until new results are available, we reiterate the caution with which we closed our article[1]: Because questions exist regarding miscarriage and other risks, progestins should be used only for indications where benefit has been established or in controlled clinical trials. ■

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REFERENCES

1. Combs CA, Garite T, Maurel K, et al. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol 2010;203:248.e1-9.
2. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17-alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol 2009;113:285-92.
3. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomized, double-blind, placebo-controlled study and meta-analysis. Lancet 2009;373:2034-40.

 doi: 10.1016/j.ajog.2010.12.002