Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma

TO THE EDITORS: Kramer et al[1] reported a doubling of the incidence of severe postpartum hemorrhage (PPH) over recent years (1999-2008), although were unable to explain the overall temporal trend despite analyzing traditional risk factors. An audit of 2 UK units, delivering more than 4000 babies per year, showed increases in PPH greater than 1000 mL, and PPH greater than 2000 mL, of greater than 500% (2003-2012).

Traditional risk factors (increased maternal age, parity, fetal macrosomia, etc) appeared to be less significant because many cases occurred in young, nulliparous women undergoing induction of labor that resulted in the delivery of an appropriate-for-gestational-age baby by cesarean section.

There is evidence for prepregnancy injuries to the myometrium resulting from physical efforts during defecation, which is endemic (>30%) in Western populations[2] and excessive traction to the cervix during minor gynecologic procedures.[3] Both injure uterine and tubal nerves in their course through the uterosacral ligaments, and both continue to increase in frequency in Western societies. There is also direct evidence for minor gynecological procedures causing adverse reproductive outcomes (eg, preterm labor) that may also result from prepregnancy denervatory injuries.[4]

Whether injured uteri respond to oxytocic agents, prostaglandins, and, surgical maneuvers may be an important question in contemporary intrapartum care. ■

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The author reports no conflict of interest.

REPLY DECLINED

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Amniocentesis for fetal lung maturity testing

TO THE EDITORS: We read with great interest the editorial by Towers, et al[1] regarding amniocentesis for fetal lung maturity (FLM) testing in the late preterm period for delivery planning. We had 3 concerns with the authors' argument.

First, although the authors discussed respiratory distress syndrome (RDS) and common short-term morbidities in the newborn period, they failed to mention the significant long-term risks associated with late preterm birth, including increased infant mortality and impaired neurodevelopment,[2] consequences commonly underestimated by obstetricians. Of note, the 34 week brain is only 65% of term brain weight and volume,[2] making the late preterm period a time of critical importance in neurodevelopment. Increasing evidence supporting these risks should be weighed in decisions regarding delivery timing.

Second, the authors do not report the weaknesses of FLM testing, apart from the fact that lung maturity is not equivalent to overall maturity. Amniotic fluid FLM testing has high negative predictive value for postnatal absence of RDS; however, approximately 50% of infants with immature FLM testing do not have RDS. Further, RDS risk can be as high as 8% in 34 week newborns despite mature FLM testing,[3] indicating substantial opportunity exists for improving FLM testing.

Finally, the authors state that antenatal corticosteroids (ANCS) followed by delivery for immature FLM indices is a possible treatment option. We feel clinical equipoise remains regarding benefit of ANCS administration after 34 weeks gestation. Our previous work evaluated outcomes of infants who received ANCS after immature fetal lung indices and were subsequently delivered within 1 week. Compared with expectant management with later delivery or waiting until mature FLM testing, respiratory morbidity was highest following ANCS administration and delivery than with the other management approaches. Furthermore, infants with immature FLM followed by ANCS and delivery had higher rates of hypoglycemia and sepsis evaluation, indicating this approach may incur some newborn risk.[4] Even if ANCS were effective to reduce RDS risk at later preterm gestational ages, considering a baseline risk of RDS of 15% in newborns greater than 34 weeks' gestation, the number needed to treat is quite high, approximately 145 to prevent 1 case of RDS.[5] The Maternal-Fetal Medicine Units Network ALPS trial is underway to assess the benefit of ANCS administration at

>34 weeks. Considering the unknown risk-benefit ratio of ANCS following immature FLM testing for delivery planning purposes, we urge caution with this practice until clinical trial results are available. ■

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REPLY

Drs Kamath-Rayne and DeFranco have addressed 3 primary concerns with our recent editorial regarding the case for using amniocentesis in the management of complicated pregnancies that are late-preterm and/or early-term. In response to the first concern of potential long-term concerns for preterm neonates, we are not proposing the "elective" delivery of 34 weeks' gestations or any late-preterm and/or early-term pregnancy before 39 weeks' gestation. This should only occur if a clinical disorder suggests that delivery may be better than nondelivery for the mother or the fetus, especially if we can anticipate a benign neonatal course. We concur that preterm neonates probably have more long-term consequences than term newborns, but early delivery before term will occur regardless if one were to follow the ACOG and SMFM protocols for late-preterm and/or early-term delivery based on certain clinical disorders without FLM testing[1-2] or if one were to use FLM testing in the management scheme. What cannot be pared out in any of the neonatal data, including the information supplied in the recent article by Kugelman et al,[3] is whether neurodevelopment issues are less in those preterm neonates that have mature lungs compared with those that are immature in complicated pregnancies.

The second concern describes a neonate that had mild respiratory distress syndrome (RDS) after delivery at 35 weeks 4 days and a mature lecithin to sphingomyelin ratio test result. Nearly every study that has examined a specific type of FLM test will have a small number of cases where RDS has occurred after a mature test result, and virtually always, these cases are mild and not associated with other major neonatal complications of prematurity. Fetal lung maturity tests do not have a 100% negative predictive value. However, these case reports further argue that all centers that perform FLM testing need to have good quality control measures in place to continually analyze overall performance.

Lastly, concerning the issue of using corticosteroid treatment in late-preterm and/or early-term gestations after an immature fetal lung maturity test, the editorial clearly states that further study needs to occur before this can or cannot be recommended. The study of Kamath et al,[4] compared the outcome of 3 different groups of patients that included those delivered after a mature FLM test, those that were expectantly managed after an immature FLM test, and those that received corticosteroids and were delivered within a week after an immature FLM test. The mature amniocentesis and expectant management groups had less adverse respiratory outcomes when compared with the corticosteroid group. However, the study by Yinon et al,[5] analyzed pregnancies that had immature FLM testing and compared outcomes based on those treated with corticosteroids vs no treatment and showed the opposite where the steroid group had less composite neonatal morbidity. Multiple regression analysis in their study showed that corticosteroid treatment was independently associated with a lower composite morbidity outcome. We would argue that the groups of patients in both of these evaluations may not be comparable as these studies were not randomized and there are often clinical differences that dictate the choice of delivery vs expectant management vs corticosteroids. Neither study fully addresses the question regarding whether corticosteroid treatment is of benefit in the setting of an immature FLM test. The only definitive way to evaluate this clinical question would be to perform a multicenter study of a large number of late-preterm and/or early-term pregnancies that have immature FLM testing and randomize this group to corticosteroids vs placebo with delivery in a week of treatment and analyze overall maternal and neonatal outcome. In addition, many neonates delivered after 34 weeks' gestation will not have significant respiratory complications and the Maternal-Fetal Medicine Units Network ALPS trial will also not fully address the specific question of whether corticosteroids would be beneficial in the setting of an immature FLM test in this gestational age population.

To conclude, not all pregnancies are black and white when it comes to the management of certain complicated obstetric disorders. Many of these pregnancies fall in a gray area and we do not have enough clinical information to abandon FLM amniocentesis as a management option. We would argue that a less selective approach in treating all pregnancies at a given gestational age is a step back in time and the age of fetal medicine was heralded by our ability to determine which neonates are likely to do better in the nursery. Knowing everything we can about mother and fetus will only improve our ability to make the best decision regarding delivery. ■