Stress at Birth and Its Inextricable Link to the Neonatal Transition

The fetal transition to air breathing after birth represents one of the most complex and masterfully executed physiologic events in reproductive biology. There is considerable evidence to show that a host of physiologic changes in the last few weeks of pregnancy, coupled with the hormonal changes accompanying spontaneous labor, orchestrate a smooth transition to neonatal independence from placental gas exchange. A surge in steroids, vasopressin, and catecholamines leads the charge, facilitating developmental changes programmed for full expression at term gestation and after spontaneous labor. Rapid clearance of fetal lung fluid plays a key role in facilitating air exchange and is mediated in large part by transepithelial sodium reabsorption through amiloride-sensitive sodium channels in the alveolar epithelial cells, with only a limited contribution from mechanical factors and Starling forces (Fig. 1). Such changes are inadequate or absent when birth occurs at preterm gestations or in the absence of labor, with a resultant increase in respiratory morbidity.

There is considerable debate about the effects of labor and mode of delivery on subsequent perinatal outcomes. On the one hand, a rise in cesarean births in the past few decades is linked to a significant improvement in perinatal outcomes, with stillbirths, birth asphyxia, and birth trauma dropping to levels never seen before (Fig. 2). Yet a new set of problems has besieged neonatal intensive care units worldwide: a higher incidence of neonatal respiratory distress, mostly related to failed neonatal transition and delayed lung fluid clearance. How, then, do we reconcile the need to balance fetal well-being with unanticipated neonatal complications? What if we had a reliable way to determine which fetuses were at risk for delayed or difficult transition to air breathing in the hours after birth? This would allow obstetricians to objectively consider pros and cons of early delivery, interventions, or both early delivery and interventions that would facilitate the neonatal transition when early and emergent delivery is deemed necessary.

A study by Wellman et al published in this issue of the journal (see page 699) attempts to address this conundrum. Using a bold study design, investigators studied the effects of oxytocin-induced early labor on neonatal copeptin levels. Copeptin, the C-terminal portion of pro–arginine vasopressin, has been shown to be a sensitive marker of fetal stress. In a randomized, placebo-controlled trial, in women with singleton pregnancies who were scheduled to undergo elective cesarean delivery, copeptin levels were compared after a brief oxytocin challenge test to mimic natural labor. It should be noted that mothers who consented to this trial did so to help advance our understanding of normal labor without any clear benefit to their newborns. Authors provide convincing data to show that oxytocin-induced labor contractions before an elective cesarean delivery trigger a robust response of copeptin.
Several aspects of these findings warrant discussion. First, it adds to a growing body of literature supporting a role for stress-related hormones such as arginine vasopressin and steroids in accelerating neonatal respiratory transition. Vasopressin has been shown to increase fetal lung fluid clearance. These findings support the concept that, in elective cesarean deliveries where no labor-related stress is anticipated, fetal preparations for respiratory transition may be enhanced by antenatal administration of agents such as betamethasone. Results of the recently published Antenatal Late Preterm Steroid study support the concept that steroids have an effect on neonatal respiratory transition at gestations past 34 weeks, working primarily through enhanced lung fluid clearance. A previous study by Stutchfield et al also supports this concept.

Second, this study confirms previously reported studies supporting the value of copeptin as a marker of labor-induced stress. Knowledge of copeptin levels potentially could be used to guide antenatal interventions such as betamethasone to help facilitate neonatal respiratory transition. Finally, the study emphasizes the importance of physiologic labor and the need to avoid unnecessary operative births. Clearly, these decisions have to be carefully balanced with the risk of fetal jeopardy if pregnancy were to continue.

There are limitations to the findings reported by Wellman et al and the conclusions noted above. Copeptin is a promising marker, but, as applied currently, it lacks the specificity for identifying various types of fetal stress. It is elevated not just after normal...
labor but in several conditions where there is chronic stress for the fetus such as chorioamnionitis and intrauterine growth restriction. There is also considerable variability in the copeptin response, making its application as a quantitative marker of fetal stress difficult.

These issues notwithstanding, the Wellman study underscores the importance of robust hormonal signaling between the mother, fetus, and placenta in managing the complex interplay of signals during parturition. It also offers a unique opportunity to navigate the application of physiologic principles gleaned from natural birth to interventions when operative birth becomes essential with an eye toward improving fetal and neonatal outcomes.

REFERENCES