Fetal stress. Focus on “Effects of acute acidemia on the fetal cardiovascular defense to acute hypoxemia” by Thakor and Giussani

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WHAT CONSTITUTES FETAL STRESS, and what are the implications of fetal stress in the course of fetal development? Thakor and Giussani (17) address a fundamental component of the fetal stress response: acidemia and it role as a modulator of the hypothalamus-pituitary-adrenal (HPA) axis responsiveness to hypoxia.

Fetal stress responsiveness has long been studied from the perspective of fetal survival in utero. Classic studies by Itskovitz et al. (9) demonstrated, for example, that fetal hypoxia stimulates reflex responses that redistribute fetal-combined ventricular output toward the placenta, the organ of gas exchange in the fetus. Other studies have explored hemorrhage, hypotension, and insults unrelated to cardiovascular function, such as vibroacoustic stimulation. The principle that ties together the stimuli of hemorrhage, hypotension, hypoxia, hypercapnia, and acidemia is that the actual reflex responses to these stimuli are most likely mediated by chemosensation by both peripheral and central nervous system chemoreceptors. The Giussani laboratory has contributed greatly to our understanding of the reflex responsiveness of the fetus to disturbances in fetal blood gases, having elucidated dynamic vaso-motor responses to hypoxia and their physiological and pharmacological modulators (5–8). The present study by Thakor and Giussani is an important addition to our understanding of the relationship between the nature of the stimulus and the responsiveness of the fetal HPA axis, sometimes dubbed the “stress axis” of the fetus.

Understanding the relationship between insult and HPA response is particularly relevant to fetal physiology because, on the one hand there is a clinically-observed relationship between fetal stress and prematurity, and on the other hand there is a cause-and-effect relationship between fetal HPA activity and parturition (2, 20). In sheep, increased fetal ACTH secretion stimulates premature parturition by stimulating increases in fetal plasma cortisol concentration that, in turn, increase placental CYP17, thereby increasing estrogen production by the placenta. There is no consensus on the role played by the fetal HPA axis in human and nonhuman primate parturition. Although infusion of glucocorticoid stimulates premature parturition only in sheep (10, 12), in both sheep and primates, infusion of ACTH into the fetus results in premature parturition (10, 11). Fetal ACTH is known to increase placental estrogen production in primates by increasing fetal adrenal secretion of estrogen biosynthetic precursors (4, 14). Disturbances in hypothalamo-pituitary regulation, such as occurs as a result of anencephaly in the human or as a result of teratogen exposure early in pregnancy in the sheep, interrupt the normal timing of parturition (1, 11).

Fetal somatic growth and development, fetal neuroendocrine development and activity, and fetal arterial blood gas status are interrelated. As the fetus grows, it tends to become progressively hypoxic and acidemic (19). At the same time, autonomic and neuroendocrine activity and reflex responsiveness increase (13, 15). The importance of chronic and acute changes in fetal arterial blood pH (pHₐ) is not fully understood. Interestingly, while changes in fetal pHₐ are sometimes used as a marker of severity of acute hypoxia or hypovolemia, there are few studies that have experimentally isolated the effect of pHₐ on the fetus.

Acute decreases in pHₐ caused by intravenous infusion of acid stimulate fetal cardiovascular and endocrine responses (3). Acidemia resulting from metabolic disturbance in the fetus can have more lasting effects, raising the question of where the pH changes are sensed. It has been recently reported by Ramadoss et al. (16) that neuronal damage in the fetal central nervous system after repeated exposure to alcohol (perhaps one of the sequelae of fetal alcohol syndrome) is actually secondary to acidemia that results from maternal “binge” exposure to alcohol. In that model of fetal acidemia, neuronal damage could be prevented by blockade of TWIK-related acid-sensitive potassium channels (TASK channels), strongly suggesting that H⁺ in blood acts directly in the fetal brain, bypassing the fetal blood-brain barrier.

Fetal hypoxia, as produced in the work by Thakor and Giussani (17), is arguably the most physiologically-relevant model of fetal stress. Any disturbance in maternal oxygen delivery to the uterus, perhaps resulting from maternal hypotension or maternal ventilatory hypoxia, will cause fetal hypoxia. Similarly, any disturbance in the ability of the fetus to regulate blood pressure will disturb fetal blood gases because fetal gas exchange depends on perfusion of the umbilical-placental vascular bed. Hemorrhage, for example, (as might occur after placental abruption or during cordocentesis) reduces umbilical-placental blood flow (18). Thakor and Giussani demonstrate that acute acidemia augments the cardiovascular and endocrine reflex response to hypoxia, essentially increasing the sensitivity of the fetus to hypoxia. The augmentation in reflex responsiveness to hypoxia could result from synergism between acidemia and hypoxia at the peripheral chemoreceptor or, as perhaps suggested by Ramadoss et al. (16), by a direct action of H⁺ within the fetal central nervous system.

It is likely that the lessons learned from Thakor and Giussani (17) apply to the developing human fetus. Stress responsiveness of the fetus in utero is highly dependent on the blood acid-base status, itself greatly influenced by challenges to fetal homeostasis. How many of our unsolved problems related to fetal stress will be solved by a better understanding of the interaction between fetal blood gas status and fetal central nervous system responsiveness to stressors?
REFERENCES