COMMENTARY

Consequences of cesarean delivery for neural development

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For over 50 million years, every single mammal on Earth had to enter the world through a harrowing passage: the birth canal. The hazards of this journey, short in distance but potentially prolonged in duration, may have peaked in our own species, where the evolution of larger and larger brains at birth seems to have been limited by increasing risks to the survival of mother and child. With the development of animal husbandry and the near-mythic arrival of Gaius Julius Caesar, a few individuals began entering via another route, avoiding the "big squeeze" to spring forth fully formed from their mothers' incisions. Today, several factors, including efforts to limit the liability for medical malpractice, have resulted in ever more babies bypassing vaginal delivery in favor of cesarean delivery, accounting for 30% of American births. Because the survival rate after cesarean section (C-section) is excellent for both mother and offspring, the procedure has been largely regarded as benign.

Now comes a report in PNAS from Castillo-Ruiz et al. (1) that, in mice, cesarean delivery has a rather unexpected effect on brain development that is both profound and widespread. Using caspase-3 production to identify cells about to "give up the ghost", they surveyed naturally occurring cell death (apoptosis) in 13 different brain regions and carefully controlled for a variety of factors to compare development in cesarean-delivered versus vaginally delivered newborns. The brains of mice delivered the old-fashioned way, through vaginal delivery, exhibited an abrupt and widespread pause in the normal process of cell death in almost every brain region examined, increasing the number of surviving cells. In cesarean-delivered pups, in contrast, the rates of cell death in the brain either continued unabated or even increased at delivery, resulting in a greater loss of cells than was seen in vaginally delivered mice. Mouse pups also differed in their vocalization after maternal separation, depending on whether they had undergone vaginal or cesarean delivery. These results raise a host of questions about whether cesarean delivery has a similar effect in humans, subjecting newborns to a greater loss of brain cells and potential alterations in neonatal behavior that could have lifelong consequences. Castillo-Ruiz et al. (1) cite several studies indicating an increased risk for autism and attention deficit hyperactivity disorder in cesarean-delivered babies, but point out that the studies are controversial, in large part, because of the difficulty in adequately controlling for all of the confounding factors that distinguish women who delivery vaginally versus by C-section. Hence, they examined the question in mice so that they could control for other factors to show unequivocally that the mode of delivery affects brain development.

Considering the circumstances around vaginal versus cesarean delivery, it may seem counterintuitive that vaginal delivery would host more benefits than cesarean delivery, because cesarean delivery is generally considered to be less stressful for the mother and newborn (2), albeit postdelivery recovery is longer for mothers after C-sections. While neonatal stress is generally associated with increases in cell death (e.g., ref. 3) and impairments in affective development (e.g., ref. 4), these effects are reportedly higher in the less stressful cesarean delivery condition. The findings of Castillo-Ruiz et al. (1) suggest that mammals developed mechanisms to protect the brain against stress during vaginal delivery.

Searching for a Mechanism

What signals the disparate brain regions that vaginal delivery has occurred? One possible mechanism investigated by Castillo-Ruiz et al. (1) is the peptide hormone, vasopressin. A surge in vasopressin is reported with vaginal delivery in both rodent and human neonates, and circulating levels of vasopressin generally correlate with concentrations in the central nervous system (CNS). In contrast, increases in vasopressin levels after cesarean delivery are quite small. In line with this hypothesis, vasopressin has been shown to decrease neuronal apoptosis in cell culture

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Author contributions: A.S.-G., C.L.J., and S.M.B. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 11826.

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Published online October 29, 2018.

(5). Based on these previous reports, Castillo-Ruiz et al. (1) evaluated vasopressin-expressing neurons in the paraventricular nucleus (PVN; a region known to play a role in stress response). While they found no differences in the total number of PVN neurons between groups, vaginal delivery resulted in more vasopressin-expressing neurons in the PVN as compared to cesarean delivery. These findings are consistent with the idea that increased vasopressin during vaginal delivery increases vasopressin-expressing neurons in the PVN, which could explain the neuroprotective effects of vaginal delivery and the differences in pup stress response after maternal separation depending on delivery mode.

Other mechanisms that may be at play include exposure to maternal microbes during vaginal delivery, the mechanical pressure on the brain in the birth canal, other hormones such as oxytocin, and hypoxia. A strong case can be made for a role of the microbiome. Castillo-Ruiz et al. (1) previously reported that altering the microbiomial environment increases cell death in the PVN a few hours after birth [i.e., in germ-free mice (6)], and others have found differences in cell death-related genes in response to altering the bacterial environment of neonates (7, 8). Furthermore, the microbiome is associated with the immune system, including cytokines that can cross into the CNS via the blood–brain barrier. Thus, a difference in response due to maternal microbes during vaginal birth could activate the immune system to somehow (e.g., cytokines?) decrease cell death. Alternatively, oxytocin or other hormones, including stress-related endocrine factors, which are increased in the mother during delivery, could affect newborns (e.g., ref. 9). For one thing, it is possible that with a vaginal delivery, these hormones are higher in mothers (i.e., given that many of these hormones induce labor and assist with vaginal delivery and that increased stress is associated with this delivery mode). Also, there may be greater opportunity for hormones from the mother to enter a newborn's blood stream during vaginal delivery. Conversely, cesarean delivery may offer less opportunity for maternal factors to enter the neonate's circulation. Castillo-Ruiz et al. (1) also consider whether changes in CO_2 levels at birth might alter brain apoptosis and offer persuasive evidence to rule out that mechanism.

Cesarean Contribution to the Obesity Epidemic

Another unexpected finding is the difference in body weight between mice delivered vaginally and by C-section. While birth weight was no different between newborns delivered via C-section or vaginally, the cesarean-delivered mice grew to be heavier than vaginally delivered mice. These results suggest that increases in cesarean births may contribute to our ever-increasing rates of obesity. Indeed, a metaanalysis in humans has indicated that C-section is moderately associated with overweight and obesity (10). Future research could consider the possible mechanisms underlying the increase in obesity (e.g., do differences in neural development, stress vulnerability, or differential hormone exposure at delivery affect future weight gain?).

Castillo-Ruiz et al. provide a carefully controlled mouse experiment with exhaustive measures to control for gestational length, circadian rhythm, and maternal effects, a feat that would be difficult to accomplish with human studies.

Cesarean delivery is higher among the most developed nations [e.g., 7.3% in Africa compared with over 30% in North America (11)], and, globally, there was an average 4.4% increase in C-sections annually between 1990 and 2014 (11). However, this increase in C-sections has brought no apparent decrease in infant or maternal morbidity or mortality (12). Although correlational, these findings suggest that cesarean delivery may be overused. Caughey et al. (12) indicate that the most frequent reasons for cesarean delivery include labor dystocia, abnormal or indeterminate fetal heart rate tracking, fetal malpresentation, and multiple gestation; a thorough investigation into each of these reasons is likely warranted, given the findings from Castillo-Ruiz et al. (1) For example, Caughey et al. (12) indicate, among other suggestions, that the parameters for labor dystocia need to be revised because labor progresses at a slower rate now than what has been historically taught. It is likely that with such research, the apparent need for C-sections could be reduced.

In conclusion, Castillo-Ruiz et al. (1) provide a carefully controlled mouse experiment with exhaustive measures to control for gestational length, circadian rhythm, and maternal effects, a feat that would be difficult to accomplish with human studies. While previous studies have also evaluated the effects of delivery mode in select brain regions, such as the hippocampus (13, 14), Castillo-Ruiz et al. (1) evaluated many regions from a diversity of neural networks and see a remarkably consistent pattern across the brain. Their findings, together with other reports confirming an effect of birth mode on the brain, suggest that this area of research deserves more research and resources. While cesarean delivery can be life-saving in some circumstances, this latest research indicates that we should give pause when electing for cesarean delivery. Additional research should investigate the possible mechanisms that may underlie the neural and behavioral effects of vaginal delivery, as it may be possible to trigger these sparing mechanisms in newborns delivered via C-section to provide them with any benefits of vaginal delivery. In the meantime, we should be mindful of these results indicating that, sometimes, the old way of doing things may, in fact, be the best way.

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