Letter to the Editor

Dear Editor

Numerous aspects of Bodiat's[1] opinion-piece require a response in the interests of a broader understanding of hypoxic foetal brain injury. Bodiat is of the incorrect opinion that any sudden injury affecting the foetus without apparent warning is an instance of adverse outcome to which no liability can be attached. An obvious example is injudicious clinical management leading to a sudden crisis. Bodiat also misleads the readership by implying that radiologically termed "acute" foetal injury always results from a perinatal sentinel event (PSE). The foetal brain may be damaged by hypoxia resulting from a profound reduction in circulating oxygen content or milder degrees of hypoxia as a result of adaptive reduced perfusion of certain areas of the brain. These mechanisms are not mutually exclusive. Aside from any sudden complete disruption of placental function in a normally oxygenated foetus, (PSE), consideration must be given to circumstances where progressive, intermittent hypoxaemia results from normal labour in the absence of a PSE. This insidious process may be intensified by a number of events. Varied patterns of injury may occur, determined by the presence or absence of foetal compensatory redistribution of blood flow and the occurrence of sub-threshold hypoxaemia during early labour with later acute exacerbation leading to brainstem injury or a mixed pattern. Bodiat cited the case of Shange as an instance in which the Court dismissed what she claims to be theoretical views about the pathogenesis of profound injury, which she states was unsubstantiated by any evidence and presented by experts who strayed from their field of expertise. Furthermore, Bodiat has incorrectly opined that subthreshold hypoxia is 'new' and 'a new medical theory'. Subthreshold foetal hypoxia is a recognised and accepted mechanism predisposing to in utero foetal brain injury.[2,3] Gunn and associates, referring to research performed in foetal sheep, wrote that "Critically, for understanding labour insults, experimental studies show that a single 'sub-threshold' insult that causes either minor or no neural injury can lead to a phase of increased vulnerability to further insults in a similar window of around six or more hours".[4–10] With regard to an MRI revealing a so-called 'acute' brain lesion, Gunn et al., Pasternak and Gorey have emphasised that an experimental association exists between relatively widely spaced, but prolonged episodes of asphyxia and selective neuronal damage to the striatal nuclei (central nuclei or basal ganglia), which is the so-called 'acute' brain injury.[3,4,10] These studies also showed that significant striatal involvement was seen after prolonged partial asphyxia.[4,10] The conclusion arising from the preponderance of striatal damage, following spaced hypoxaemic insults, suggests that it is, in part, a consequence of the evolving neural dysfunction and sensitivity triggered by non-injurious single insults. Of particular interest to clinicians, is that repeated, relatively prolonged episodes of asphyxia or ischaemia (5 to 10 minutes) are associated with selective basal ganglia damage, with the proportion of basal ganglia damage relative to cortical injury increasing as the interval between insults is increased. This emphasises the importance of interaction between even relatively benign, non-injurious individual periods of hypoxia-ischaemia in labour that can lead to regionally specific, compounding damage. Selective neuronal loss in striatal nuclei develops when relatively prolonged periods of asphyxia or ischaemia are repeated.[7,8] The pathogenesis of striatal involvement in the near-term foetus is related to the precise timing of the relatively prolonged episodes of asphyxia and not to more severe local hypoperfusion. Bodiat argues that 'evidence relied on (especially if written evidence is used such as textbooks), should be reliable, reputable and authoritative'.[1] In this regard, several authoritative textbooks refer to a mechanistic role for subthreshold hypoxia in foetal brain injury.[11,12] Specifically, Bennet emphasised that a critical aspect is that a single subthreshold insult that causes either minor or no neural injury leads to a phase of increased vulnerability to further insults.[12] Inder and Volpe referred to the potentiating effect of infection or inflammation on subthreshold hypoxic-ischaemic insults.[11] Consequently, Bodiat's opinions need to be assessed in the light of the preceding trail of scientific evidence which lends strong credibility to the existence of subthreshold foetal hypoxia. Furthermore, it is apparent that research evidence shows repeated and relatively prolonged exposure to in utero hypoxia or ischaemia (as with umbilical cord compression in foetal sheep) and timing thereof, leads preferentially to injury to the striatal (basal ganglia) structures, which radiologists chose to report as 'acute profound' hypoxic ischaemic injury in the human foetal brain. In the light of all the preceding evidence it is scientifically unsustainable to argue that basal ganglia injury seen on an MRI scan should be interpreted as an injury resulting from an insult which is both acute and profound. So-called 'acute' profound foetal brain injury occurs as a consequence of an unexpected PSE or in the absence of such PSE.[13] Both situations have to be considered when faced with a radiological report in which 'acute profound' central grey matter (basal ganglia/striatal) hypoxic ischaemic injury is reported and therefore that each case should be assessed on its own merits.

J Smith,[1] J Anthony,[2] R van Toorn[1]
[1] Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa.
[2] Department of Obstetrics and Gynaecology, University of Cape Town, South Africa

References

1. Bodiat A. Medical malpractice insurance: Notification obligations under a medical malpractice insurance policy. Prof Nurs Today. 2020;24(3):22. Available from: http://www.pntonline.co.za/index.php/PNT/article/view/1061. Accessed 2 Nov 2020.
2. Perlman JM. Intrapartum asphyxia and cerebral palsy: is there a link? Clin Perinatol. 2006;33(2):335-53. https://doi.org/10.1016/j.

clp.2006.03.004.

3. Pasternak JF, Gorey MT. The syndrome of acute near-total intrauterine asphyxia in the term infant. Pediatr Neurol. 1998;18(5):391-8. https://doi.org/10.1016/S0887-8994(98)00002-2.
4. Gunn AJ, Bennet L. Fetal hypoxia insults and patterns of brain injury: insights from animal models. Clin Perinatol. 2009;36(3):579-93. https://doi.org/10.1016/j.clp.2009.06.007.
5. Mallard EC, Williams CE, Gunn AJ, Gunning MI, Gluckman PD. Frequent episodes of brief ischemia sensitize the fetal sheep brain to neuronal loss and induce striatal injury. Pediatr Res. 1993;33(1):61-5. https://doi.org/10.1203/00006450-199301000-00013.
6. Mallard EC, Williams CE, Johnston BM, Gluckman PD. Increased vulnerability to neuronal damage after umbilical cord occlusion in fetal sheep with advancing gestation. Am J Obstet Gynecol. 1994;170(1):206-14. https://doi.org/10.1016/S0002-9378(94)70409-0.
7. Mallard EC, Williams CE, Johnston BM, Gunning MI, Davis S, Gluckman PD. Repeated episodes of umbilical cord occlusion in fetal sheep lead to preferential damage to the striatum and sensitize the heart to further insults. Pediatr Res. 1995;37(6):707-13. https://doi.org/10.1203/00006450-199506000-00006.
8. De Haan HH, Gunn AJ, Williams CE, Gluckman PD. Brief repeated umbilical cord occlusions cause sustained cytotoxic cerebral edema and focal infarcts in near-term fetal lambs. Pediatr Res. 1997;41(1):96-104. https://doi.org/10.1203/00006450-199701000-00015.
9. Pulgar VM, Zhang J, Massmann GA, Figueroa JP. Mild chronic hypoxia modifies the fetal sheep neural and cardiovascular responses to repeated umbilical cord occlusion. Brain Res. 2007;1176(1):18-26. https://doi.org/10.1016/j.brainres.2007.07.089.
10. Gunn AJ, Thoresen M. Neonatal encephalopathy and hypoxic–ischemic encephalopathy. In: Handbook of Clinical Neurology. Vol 162. Elsevier B.V.; 2019. p. 217-37. https://doi.org/10.1016/B978-0-444-64029-1.00010-2.
11. Inder T, Volpe J. Volpe's Neurology of the newborn. In: Volpe J, Inder TE, Darras B, De Vries LS, Du Plessis AJ, Neil J, editors. Neurology of the newborn. 6th ed. Amsterdam: Elsevier; 2017. p. 354, 368. Available from: https://www.elsevier.com/books/volpes-neurology-of-the-newborn/volpe/978-0-323-42876-7. Accessed 2 Nov 2020.
12. Bennet L, Westgate JA, Gluckman PD, Gunn AJ. Pathophysiology of asphyxia. In: Levene M, Chervenak FA, eds. Fetal and neonatal neurology and neurosurgery. 4th ed. Amsterdam: Elsevier; 2009. p. 480. Available from: https://www.elsevier.com/books/fetal-and-neonatal-neurology-and-neurosurgery/levene/978-0-443-10407-7. Accessed 2 Nov 2020.
13. Shankaran S, Laptook AR, McDonald SA, et al. Acute perinatal sentinel events, neonatal brain injury pattern, and outcome of infants undergoing a trial of hypothermia for neonatal hypoxic-ischemic encephalopathy. J Pediatr. 2017;180:275-8. https://doi.org/10.1016/j.jpeds.2016.09.026.