

Commentary on the published position statement regarding the pathogenesis of fetal basal ganglia-thalamic hypoxic-ischaemic injury

To the Editor: Borhat *et al.*^[1] have published a 'position statement' regarding the provenance of basal ganglia and thalamic (BGT) injury following perinatal hypoxia-ischaemia. The authors buttress their position statement designed for litigation defence, with literature that unfortunately does not support their premise.

Rennie and Rosenbloom^[2]

Bhorat *et al.*^[1] begin by citing Rennie and Rosenbloom's^[2] 2011 article in which they examined the question of how long obstetric intervention could be deferred before fetal neurological injury occurred.

Bhorat *et al.*^[1] cite this article in support of their notion that a gradual onset of hypoxia may damage only the watershed areas of the brain without affecting the central deep nuclei. Rennie and Rosenbloom, however, never examined whether gradual onset of prolonged hypoxia in labour could lead to BGT injury. All their cases reflected either sentinel events or persistent fetal bradycardia. Irrespective, Borhat *et al.*^[1] wish to infer that the two patterns are immiscible, with prolonged hypoxia causing watershed injuries, and all BGT patterns are linked to acute and profound hypoxic events.

Shankaran *et al.*^[3] and Sie *et al.*^[4]

Bhorat *et al.*^[1] go on to describe 'a strong association between BGT pattern injury and sudden-onset hypoxic-ischaemic events', which they refer to as perinatal sentinel events (PSEs). Citing articles from Shankaran *et al.*^[3] and Sie *et al.*^[4] they append to the definition of sentinel event what they call 'concealed events' such as (occult) cord compression.

The definitions offered by Shankaran *et al.* and Sie *et al.* were unique to their specific research and are not generally accepted nor consistent with the definition promulgated by the American College of Obstetricians and Gynecologists (ACOG)/American Academy of Pediatrics (AAP)^[5] (whose definitions in this regard Borhat *et al.*^[1] singularly fail to cite). Irrespective of this, Shankaran *et al.*^[3] found no significant difference between the number of BGT injuries in their designated PSE group compared with the study subjects who lacked such criteria.

Whereas there is no disputing the association between BGT pattern injury and sentinel events (as defined by ACOG/AAP^[5]), there is no basis for making such statements as 'a large proportion of BGT injuries follow PSEs that are not clinically obvious', and 'there is no reason to believe that brain injury pathogenesis differs between clinically obvious PSEs and those of uncertain origin.' Continuing this syllogistic cascade, Borhat *et al.*^[1] provide the exculpatory assertion that 'typically, PSEs are not foreseeable ...', asserting that the injury could not be averted by obstetric intervention because it was sudden, severe and profound. However, both published evidence^[6] and clinical experience, including articles cited by the author, fail to support this position. For example: instances of cord prolapse, uterine rupture and prolonged bradycardia may be foreseeable and manageable, to the point that adverse perinatal outcomes may be avoided.

Pasternak and Gorey,^[7] Okumura *et al.*^[8]

Bhorat *et al.*^[1] cite Pasternak and Gorey.^[7] This article examined eleven instances of infants delivered following the onset of persistent bradycardia. Four cases were associated with uterine rupture; two cases were related to cord problems (cord thrombus, cord rupture), and five had bradycardia of unknown origin without further description of the obstetric events preceding delivery. Magnetic resonance imaging (MRI) scans were performed in eight cases. In one, the MRI was normal (case 8). Of the rest, MRI revealed BGT involvement with relative sparing of the cerebral cortex. None of the cases had specific periorlandic cortex (PRC) involvement. Case 2 had parasagittal cortex ('watershed') involvement; case 9 left frontal cortex, and case 11, 'parasagittal cortex'. The heterogeneity of the findings aside, there is no description or suspicion of any preceding 'concealed' SE.

Bhorat *et al.*^[1] then cite two cases of bradycardia leading to BGT injury for which there were no 'apparent causes', as reported by Okumura *et al.*^[8] This narrative cannot justify the inference that there must have been some 'occult' SE leading to the described outcome. In addition, neither Okumura nor Pasternak and Gorey's work contradicts the more recent work of Baxter,^[9] showing the importance of the duration of persistent terminal bradycardia and BGT (and white matter) injury. Again, there is no mention of any occult injury.

It is unknown (but unlikely) that every fetal bradycardia is the consequence of some sudden but unknowable 'sentinel' event. More common than the sudden unpredictable bradycardia related to placental abruption, a prolapsed cord, ruptured uterus, uterine tetany or compulsive maternal pushing is the predictable, discoverable appearance of prolonged bradycardia following a prolonged series of decelerations or associated with excessive uterine activity, and unrestrained pushing.

Citing Pasternak,^[7] whose publication never addressed that question, Borhat *et al.*^[1] double down on their previous assertions, stating that 'the BGT pattern is rarely seen in the absence of an (overt) PSE'.

Murray *et al.*^[10]

In further support of their approach, Borhat *et al.*^[1] cite Murray *et al.*^[10] relating to the benefits of this argument in the 'successful defendant viewpoint in South African courts in the late 2010s'. The gist of this argument is that BGT injury is always associated with sudden sentinel events (SEs) or SEs of 'unknown origin', rendering obstetric intervention ineffective because of the suddenness and severity of the insult.

The article by Murray *et al.*^[10] examined 35 babies with hypoxic-ischaemic encephalopathy (HIE). SEs were found in 11.5% of affected infants. It describes the affected infants' cardiocotographic (CTG) patterns, noting that the time from evident abnormality to delivery was 22 minutes in the case of SEs (underscoring the difficulty of successful intervention). In contrast, the interval from abnormality to delivery was 145 minutes in the other cases (illustrating the period during which intervention may have made a meaningful difference to the outcome).

This research did not address specific neuroradiological patterns and is consistent with other evidence, including the work of Martinez-Biarge *et al.*^[11] and Smith *et al.*^[12]

Further, the publication of Murray *et al.*^[10] therefore, does not support the notion propagated by Borhat *et al.*^[1] that sudden known and unknown SEs cause BGT injury in the majority of cases, nor the idea that such injury is unavoidable.

The ACOG/AAP consensus statement^[5] and Volpe *et al.*^[13]

Bhorat *et al.*^[1] concede that expert witnesses for plaintiffs offer an alternative view on the pathogenesis of BGT injury consistent with the ACOG/AAP consensus statement as well as the writings of Volpe *et al.*^[13] an internationally recognised authority in the field of paediatric neurology.

Bhorat *et al.*^[1] suggest that ACOG has been imprecise in their use of the terms 'prolonged' and 'partial' hypoxia when describing the pathogenesis of cerebral-deep nuclear neuronal injury because it contradicted 'terminology introduced in our first paragraph'. However, the ACOG/AAP position terminology also appears in a multidisciplinary article on 'Neuroimaging in the term newborn with neonatal encephalopathy' published under the auspices of the Neonatal Brain Society.^[14] In this article, the associated risk factors for 'central/BGT (also known as 'cerebrocortical-deep nuclear') brain injury were 'sentinel events; severe partial asphyxia with prolonged duration or combination of partial and near-total asphyxia'.

Bhorat *et al.*^[1] disagree.

Smith *et al.*^[12]

Bhorat *et al.*^[1] take issue with a publication by Smith *et al.*^[12] who also offered evidence in support of prolonged hypoxia as a cause for BGT injury in the absence of any identifiable PSE.

Bhorat *et al.*^[1] and Buchmann and Borhat^[15] refer to 'criticism' of the article, citing their own objections (rebutted in a published response by Smith *et al.*^[16]). The comments by Borhat *et al.* are the only published criticism of Smith *et al.*^[16] In this respect they seem to stand alone in the international community.

Baxter^[9]

Bhorat *et al.*^[1] cite Baxter,^[9] who analysed the perinatal outcome in pregnancies complicated by known prolonged and persistent fetal bradycardia to determine how long a known insult must be present before injury ensued.

The data establish an increasing likelihood of BGT injury with an expanding duration of insult defined as a persistent fetal bradycardia 'with or without sentinel events'. In this article, 25% of infants were affected when bradycardia lasted >11 minutes, whereas 85% were affected by a duration of ≥20 minutes.

In their discussion, Borhat *et al.*^[1] focus on a comment made by Baxter that perirolandic injury may not require a more chronic partial type of insult (contrary to that suggested by Volpe *et al.*^[13] and others^[5,14]) and may be compatible with a more rapidly developing hypoxic insult. With this commentary, Borhat *et al.*^[1] presumably suggest that ACOG/AAP,^[5] Volpe *et al.*^[13] and Wisnowski *et al.*^[14] have been mistaken in the notion that PRC injury is indicative of a more insidious prolonged, partial hypoxia. While this may (or may not) be true, Borhat *et al.*^[1] are citing a comment, out of context, about an aspect of hypoxic-ischaemic injury that went unaddressed in the data-analysis provided by Baxter. Not only is this discussion peripheral to the focus of the publication, but it also obfuscates a more pertinent observation, namely that Baxter

only addressed one kind of event leading to BGT injury rather than an examination of all BGT injuries in the context of all known preceding risk factors.

Nakao *et al.*^[17]

The subsequent publication addressed in the 'position statement' is the work of Nakao *et al.*^[17] This article discussed the issue of cerebral palsy (as distinct from neonatal encephalopathy (NE)). The aim was to investigate the association between the timing of a hypoxic-ischaemic insult and brain injury in infants with cerebral palsy (CP). The research was based upon fetal heart rate (FHR) patterns, grouped as prenatal and intrapartum patterns, compared with neuropathology defined as either a BGT pattern (indicated in their assumptions as due to acute profound hypoxia) or watershed injury, which arose from prolonged hypoxia.

It should be self-evident that no assumptions can be made when data are unavailable for analysis or interrogation. In that regard, the publication is confusing. Of 1 593 subjects considered by Nakao *et al.*^[17] the majority were excluded from analysis. Those excluded from the analysis were infants who died within 6 months of birth, infants deemed to have less than severe CP and those whose records were missing. The remaining cases were a mixture of preterm and term births, of whom three-quarters had a BGT pattern and one-quarter a purely watershed injury.

The authors interpreted persistently abnormal CTG tracings beginning before the onset of labour as indicative of a hypoxic insult causing BGT injury. However, many of these study subjects suffered abruptio placentae before the onset of labour. This occurrence is a recognised SE leading to adverse outcomes independently of whether or not it occurred during labour.

In interpreting their data, the authors subsequently indicated that intrapartum CTG patterns that change from reactive tracings to ones with prolonged decelerations should indicate 'acute' stress. In contrast, patterns changing from a reactive tracing to a Hon pattern (recurrent decelerations in FHR, high baseline FHR and decreased variability followed by low baseline FHR) were considered indicative of 'subacute' stress. There was no evidentiary basis presented for these assertions.

Nakao *et al.*^[17] concluded that BGT lesions were more prevalent in situations of acute stress than in subacute stress, but that BGT lesions with cortical involvement followed a gradual, partial insult. The data to support these various contentions are not evident from the published material. However, the conclusions reached make it clear that some BGT injury may follow prolonged partial hypoxia. The authors state: 'Furthermore, severe BGT lesions were more prevalent in acute and total insult, and cortical involvement accompanying BGT damage was characterised by a gradual and partial insult'. Personal communication (between Smith and Nakao, 31 August 2023) has revealed that 'abnormal cortical highlighting was observed mostly in the perirolandic cortex within the BGT group of severe CP cases, often accompanied by the abnormal signs around the interhemispheric fissure and/or insular cortex'.

The issue of the pathogenesis and patterns of cortical damage associated with BGT injury due to hypoxic ischaemia is a developing field, as was recently highlighted by the article of Misser *et al.*^[18] They described a spectrum of BGT and PRC involvement, including extension of the cortical injury beyond the PRC. The damage may be very subtle or limited to the sensorimotor strip (PRC) with little or no widening of the central sulcus (mild subtype). Moderate PRC injury showed paracentral lobule and sensorimotor cortex injury, resulting in some widening of the interhemispheric fissure. In the third subtype, severe PRC injury subtype, there is

extension of the injury to the margins of the paracentral lobule and the lateral edges of the central sulcus, with involvement of the subcortical white matter. The fourth subtype is the newly described 'massive paramedian injury' (MPI) type characterised by broad widening of the interhemispheric fissure secondary to near-complete destruction of the paracentral lobule, with resultant diamond-shaped excavation of the central core of the cerebrum, including part of the centrum ovale. This injury extends towards the superior frontal gyrus (anteriorly) and variably towards the superior parietal lobule (posteriorly). The authors concluded that the combination of periorlandic, basal ganglia, thalamic and other high metabolic substrate injuries shown in their MPI group closely approximates the study findings reported in experimental animals.

The obstetric correlates of 11 of the patients were analysed by Misser *et al.*,^[18] but obstetricians were not included. The data derived from 'comprehensive clinical details from the base hospitals' were used to infer that the MPI group corresponded *in vivo* with prolongation of the second stage of labour (a feature identified in all patients with MPI), and consequent severe, sustained hypoxic-ischaemic insult to the susceptible fetus. Common to all their 11 cases were significant intrapartum factors, including prolongation of labour, particularly the second stage, often with impaction of the fetus in the birth canal for prolonged periods leading to fetal compromise, augmentation of labour by oxytocin (27%), and failed operative vaginal delivery (27%).

Despite the limited clinical analysis provided, their cases illustrate that parasagittal central type hypoxic-ischaemic brain injury can sometimes be identified in more severe sustained hypoxia ischaemia, and is consistent with the observations of Nakao *et al.*^[17]

Overall, the Nakao publication is open to criticism due to the retrospective analysis accompanied by numerous exclusions, as well as failure to consider acknowledged obstetric precedents of hypoxic injury (which include failure of monitoring and iatrogenic factors, including the use of oxytocin). Failure to consider all cases and failure to account for all known risk factors precludes adequate logistic regression as a means of determining independently associated risk factors for neurological injury.

Selecting from a large medicolegal database, Elsingery *et al.*^[19] studied the distribution frequency of individual deep nuclei injury in children with CP demonstrating isolated BGT, v. those with a BGT-watershed (WS) pattern of hypoxic-ischaemic injury. Of 762 MRI reports, 435 (57%) had isolated BGT involvement. Borhat *et al.*^[1] would like us to believe that these 435 children all either had SEs or had severe but undetectable events that happened so quickly and quietly ('silently') that the hospital staff involved were not able to act in a reasonable time to affect the outcome. Is this a realistic probability?

The concluding paragraph of Borhat *et al.*^[1] refers to the need for 'holistic' and 'unbiased' review of information aimed at 'fair resolution without waste of time and resources'. These comments are patronising and emotive in the sense that the terms 'bias', 'fair' and 'waste' suggest that adherents of any view other than those espoused by Borhat *et al.* cause unfair biased practice ending in wasteful expenditure.

The onus is on Borhat *et al.*^[1] to prove the theory they present – it is not good enough to get together as a group and just decide what is convenient.

The article by Nakao *et al.*^[17] has been used by Borhat *et al.*^[1] in an uncritical manner to suggest that fetal priming related to intrauterine infection, fetal growth restriction and cord abnormalities renders the fetus susceptible to injury from 'relatively mild hypoxic-ischaemic insult'. At best, such a view is disingenuous. While there may be some truth in the assertions made, the priming factors were never

examined in any detail by Nakao *et al.*, and the notion of 'mild' hypoxia is inchoate, existing only in considerations peculiar to the reasoning of Borhat *et al.*^[1]

In summary: Borhat *et al.*^[1] lump together and reject all the expert opinions provided by ACOG/AAP,^[5] Wisnowski *et al.*^[14] on behalf of the Neonatal Brain Society, as well as Volpe *et al.*^[13] and Kinney and Volpe^[20] whose views do not coincide with their own.

The 'Position Statement'

Borhat *et al.*^[1] use their 'summary of the current state of knowledge' to promulgate their position statement, which they assert should be used by obstetricians engaged as defence experts in CP litigation cases. In suggesting this, they display remarkable certainty about the validity of their own views. This attitude starkly contrasts with any philosophical enquiry (including medical science), which disavows finality of thought.

The position statement links BGT pattern of injury to SEs. These events are sudden and 'typically unforeseen and unpreventable'. The article maintains an unsustainable bias mitigated only by the subsequent statement that 'concealed' sentinel events (a linguistic contradiction) may be detectable using continuous CTG monitoring. This suggestion would, however, seem to validate the data presented by Smith *et al.*,^[12] even in the authors' estimation.

Borhat *et al.*^[1] also state that a PSE may occur before labour and result in BGT injury. This assumption is valid when talking of abruptio placentae or a ruptured uterus. However, there is currently no evidence that other 'priming' factors are associated with the antepartum pathogenesis of BGT injury. Volpe *et al.*,^[21] reviewing recent evidence linking placental vascular mal-perfusion of the fetus (FVM) to the risk of neonatal HIE, conclude that 'the finding that FVM is associated with neonatal encephalopathy and particularly HIE raises the question of whether detection of FVM *in utero* could lead to institution of preventative measures prior to labour'. While predisposition to injury may be present, the occurrence of injury is currently considered to require both the predisposition as well as a 'second-hit' exposure to hypoxic stress as a result of labour itself.

The notion that 'priming' causes susceptibility to hypoxic injury is uncontested. Placental insufficiency causing fetal growth restriction ending in birth-related asphyxia is a long-accepted epidemiological association. However, the notion that 'relatively mild hypoxia' may cause injury (while possibly true) is currently a notion without factual basis. In the context of labour, there is no evidence of undefined 'mild' hypoxia leading to sudden or undetectable (and therefore unpreventable) injury.

Borhat *et al.*^[1] concede that BGT injury may follow gradual-onset FHR rate pattern deterioration over ≥ 1 hour. However, they indicate that this is 'uncommon'. Borhat *et al.*^[1] have no evidence to substantiate this, as no systematic, population-based study of the provenance of BGT injury exists. None of the data reviewed here and in the Borhat article provide this. Hence the notion that BGT injury due to gradual deterioration in the FHR is uncommon is not only unsupported, but flies in the face of inferential data that are available.

Borhat *et al.*^[1] use the Baxter^[9] data to infer that the prevention of BGT injury would require intervention within 10 minutes. Again, this is highly disingenuous, implying that all BGT injuries are the same and caused by the same mechanism (namely persistent fetal bradycardia). They state that such rapid intervention cannot be attained in South Africa. While this may be true, it needs to be pointed out that baseline fetal bradycardia is just one known risk factor giving rise to BGT injury. More significantly, the emergency

management of suspected fetal distress encompasses not only operative delivery but also fetal resuscitation *in utero*. It is incorrect to infer that nothing can be achieved through intervention, even if the goal of rapid caesarean delivery may not be attainable.

Bhorat *et al.*^[1] reiterate that BGT injury patterns, with or without cortical involvement, are both equally associated with PSEs. This view is inconsistent with the cited literature and promotes an idiosyncratic definition of PSE, leading to the incongruous (oxymoronic) notion of unknown SEs. The accepted definition of SEs has been set out in the ACOG/AAP^[5] consensus statement on NE, and it is clear that not all instances of BGT injury are associated with SEs, much less unpreventable.

Conclusion

Bhorat *et al.*^[1] have provided a self-styled 'position statement' on BGT injury. In doing so, they have uncritically referenced literature and inappropriately used it as the inferential basis for their views, which are unashamedly offered to preferentially assist in the defence of allegations of medical negligence, to which cause they have allied themselves. Its acceptance would also confound the fair adjudication of medicolegal matters. This position is unconscionable and is not helpful to society at large, nor does it assist in better understanding the preventable risks associated with BGT injuries or reducing its incidence in the future.

The onus is on Bhorat *et al.*^[1] to marshal more compelling support for their idiosyncratic theory, and more equipoise. Expert witnesses in CP matters should examine all clinical case evidence, as well as critically evaluate available medical literature to provide unbiased, evidence-based opinions.

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Response to 'Commentary on the published position statement regarding the pathogenesis of fetal basal ganglia-thalamic hypoxic-ischaemic injury' (Anthony *et al.*)

To the Editor: We thank Anthony *et al.* for their response to our review and position statement.^[1] To start, we need to correct the respondents' remark that our position statement was intended for the use of 'defence experts in cerebral palsy (CP) litigation cases'. In fact, we wrote that it was 'for obstetricians engaged as experts in CP litigation'. We offered a fair and evidence-based summary, based on pertinent peer-reviewed research on humans. The aim was to help experts assist South African (SA) courts, irrespective of whether they are instructed by plaintiff or defendant representatives.

We cited five original research works in humans that showed positive associations between acute profound hypoxic-ischaemic (HI) brain insult and basal ganglia-thalamus (BGT) pattern injury on imaging.^[2-6] A sixth source, the landmark work of Nakao *et al.*^[7] from 2022, is considered by the respondents to be of limited value. On the association between sudden-onset fetal bradycardia and BGT lesions found in Nakao *et al.*, the respondents write that the 'data to support these various contentions are not evident from the published material'. This is incorrect. The data are in the text and in accompanying figures and tables. The weight of evidence in the six cited works supports the association between acute profound HI brain insult and BGT pattern injury. The evidence reasonably fulfils seven of Bradford Hill's nine causal criteria – strength of association, consistency, specificity, temporality, plausibility, coherence and experiment.^[8] Consistency is especially strong, with the same direction of association across all studies. The respondents have added no new research works to reduce our confidence in this association. The only divergent original research is that of Smith *et al.*^[9] (co-authored by six of the respondents), which has methodological deficiencies, as has previously been pointed out.^[10]

The respondents take issue with our terminology for perinatal sentinel events (PSEs), considering it 'oxymoronic' to describe certain PSEs as 'concealed'. For greater clarity, we could instead have used 'not contemporaneously clinically identifiable'. An example is sudden intrapartum kinking of a non-prolapsed umbilical cord, as included by Sie *et al.*^[4] as a possible PSE. Such an event would show only on cardiotocography as sustained bradycardia of sudden onset. Intrapartum cardiotocography is of course not routine in SA practice, being mandatory in high-risk labour only. Such events do not display dramatic maternal collapse, intrapartum haemorrhage or cord prolapse. Our review showed that 'concealed' PSEs are frequent antecedents of intrapartum HI injuries, especially considering the results of Nakao *et al.*^[11] from 2020. Restricting the definition of PSE to a list (not necessarily a definition) given in the American College of Obstetricians

and Gynecologists/American Academy of Pediatrics (ACOG/AAP) document^[12] on neonatal encephalopathy makes no pathophysiological sense. What matters is whether the fetus experiences a sustained HI insult of sudden onset, irrespective of whether the cause is clinically obvious. The respondents misrepresent the findings of Shankaran *et al.*^[5] on the association of BGT injuries with PSEs, writing that the authors found no significant difference in BGT injuries between cases with and without PSEs. However, Shankaran *et al.* calculated a *p*-value of 0.03 for this difference, indicating statistical significance, and noted the higher frequency of BGT injury in infants with PSEs in their abstract, results and discussion.

The respondents introduce a recent research contribution on perinatal BGT pattern injuries by Misser *et al.*,^[13] who establish perirolandic cortex involvement as an integral part of the BGT pattern injury, preferring to use the epithet 'Rolandic-basal ganglia-thalamus (RBGT)'. Our position statement on perirolandic involvement aligns with the descriptions of Misser *et al.* Selected case summaries are provided by Misser *et al.*, which are incorrectly reported by the respondents. For example, only 9% (not 27%) of births followed failed operative vaginal delivery in cases with massive paramedian injury. Misser *et al.* include a 'mixed RBGT + watershed pattern' in their classification of magnetic resonance imaging patterns of HI injury. We are aware of this subgroup and do not, as the respondents believe, see BGT and watershed patterns as 'immiscible'.

The respondents suggest that BGT pattern injury results from a predictable, discoverable, gradual-onset HI insult, unless there is an overt PSE as listed in the ACOG/AAP document. Their evidence for this comes not from original research data, but from interpretation of three opinion sources: the ACOG/AAP document,^[12] *Volpe's Neurology of the Newborn* textbook,^[14] and an opinion article by Wisnowski *et al.*^[15] We have dealt with the respondents' use of these three sources in our review. These are respected sources, but they cover broad topics without sharp focus on timing and mode of causation of BGT pattern injury. They also cannot match original human research data for strength of evidence. In our review, we covered two narrative review articles that were sufficiently focused,^[16,17] and our position statement is largely in line with their authors' findings.

While accepting priming as possibly contributory in HI injury, the respondents dispute our concern that antepartum factors 'may result in fetal priming, leading to vulnerability to BGT injury by relatively mild hypoxic insults'. Our concern, that this 'may' occur, is based on published evidence.^[18-24] For example, late-onset

fetal growth restriction is a priming disorder easily missed in the antepartum period, leaving the fetus without reserve in the hypoxic-centric intrapartum process.^[23,24] The modern approach in fetal medicine tries to identify priming factors in the antepartum period to determine the timing and mode of delivery. Other examples are recurrent maternal infections,^[20-22] umbilical cord abnormalities and fetomaternal hypoperfusion,^[11] metabolic disorders^[25] and genetic predispositions.^[25-28] To deny fetal priming in the aetiology of neonatal encephalopathy and cerebral palsy is to deny the modern approach to prevent adverse perinatal outcomes. Exclusive focus on intrapartum factors is fundamentally flawed. Techniques to identify primed fetuses include sonographic estimation of the cerebroplacental ratio,^[24] and assessment of biomarkers such as soluble fms-like tyrosine kinase-1 and placental growth factor.^[29] Reasonable certainty on scientific causality can only be achieved after holistic exhaustive assessment of each case, including antepartum, intrapartum and neonatal exposures.

No new data or opinion have been provided by the respondents for us to rethink any of the points in our position statement. We respectfully urge Anthony *et al.* to carefully evaluate the applicable scientific literature on causation of BGT pattern HI brain injury.

The position paper^[1] has been endorsed by the Expert Opinion Panel of the South African Society of Obstetricians and Gynaecologists (SASOG).

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