Review Article

METHOD OF DELIVERY, THE MICROBIOME AND NEURODEVELOPMENT

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ABSTRACT

Caesarean sections, and especially elective Caesarean sections, are on the increase worldwide.

The grey-matter volume of the foetal brain undergoes a linear increase of 1,4% per week from 29 weeks until 40 weeks of gestation. This is followed by an accelerated period of brain growth, during which 50% of the increase in cortical volume occurs, between 34 and 40 weeks of gestation. Between 37 and 40 weeks of gestation, cortical grey matter increases by 50% and myelinated white matter increases three-fold.

According to the World Health Organisation (WHO), a baby is born prematurely if it is delivered before 37 completed weeks' gestational age (GA), or before 259 days after the last normal menstrual period. As a result, the American College of Gynecologists and Obstetricians (ACOG) has adopted a new maturity classification that refers to babies born from 37 to 39 weeks as 'early term'. Early-term neonates are at increased risk of morbidity.

Prematurity is associated with impaired cortical development, and ex-premature infants never achieve the same degree of cortical folding as that seen in babies born at term. Prematurity is also a major risk factor for cerebral palsy, which occurs in 35% of cases. The increased risk is directly proportional to decreasing GA. The global prevalence of cerebral palsy is 2/1 000 births. Between 32 and 36 weeks of gestation, the risk increases to 6.75/1 000 births. Importantly for the timing of elective Caesarean section, there is still an increased risk of 1.35/1 000 births even after 36 weeks of gestation. Babies who are born in the early term period (between 37 and 39 weeks GA) will later constitute 5,5% of children with special educational needs (SEN). Even those babies born at 39 weeks GA carry an elevated risk and constitute 1,7% of total SEN cases.

Normal vaginal delivery is associated with neonatal acquisition of a maternally derived microbiome that has a rich diversity. Through bacterial peptides, the microbiome stimulates immune, endocrine and neuronal cells to release cytokines and neurotransmitters, which access the central nervous system via the blood or the vagal nerve. In this way, enteric bacteria can influence mood and behaviour, sleep–wake cycles and feeding patterns. During Caesarean section, however, the foetus is colonised instead by bacteria from the mother's skin. The microbiome that results from this has far less richness and diversity. This in turn is associated with significant risk for chronic inflammatory disorders in later life. New to our understanding of chronic inflammatory disorders that result from dysbiosis is a range of neuro-developmental problems in childhood and adults.

INTRODUCTION

Although the worldwide incidence of Caesarean section is 25,7%,[1] the incidence of Caesarean section in China – which, along with South Africa, is considered a developing country – rose dramatically from 22% in 1994 to 56% in 2006.[2] Elective Caesarean sections are following a similar trend, with the WHO confirming that such sections now represent 10% of births worldwide.[3]

Elective Caesarean sections, and the reduced gestation with which they come, may, however, come at a neuro-developmental cost. The last four weeks of gestation are essential for brain programming.[4] Foetal and neonatal brain development take place along a continuum, and

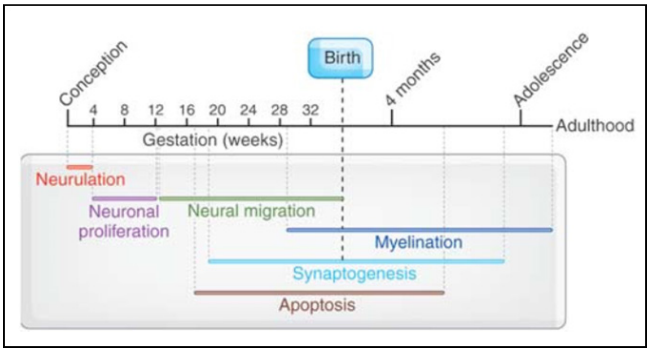

Figure 1: The end of the third trimester is a critical period for the formation of synapses and apoptosis of redundant neurons.

complex organisational changes occur during both intra- and extrauterine development (Figure 1).[5]

DEVELOPMENT OF THE BRAIN

The grey matter volume of the foetal brain undergoes a linear increase of 1.4% per week from 29 weeks until 40 weeks of gestation.[6] This is followed by an accelerated period of brain growth, during which 50% of the increase in cortical volume occurs between 34 and 40 weeks of gestation.[6] Between 37 and 40 weeks of gestation, cortical grey matter increases by 50% and myelinated white matter increases three-fold.[7] Synaptogenesis (the connectivity between neurons) occurs at the rate of 40 000 synapses per minute during foetal development,[7] so that by the end of gestation, the foetal brain should consist of approximately 100 billion neurons (Figure 2).[8] It is essential that such a number be reached, as a significant proportion of these immature neurons will have to be pruned through the process of apoptosis during the first year of infancy.[8] Foetal neurons contain elevated levels of intracellular chloride.[9] Activation by gamma-amino butyric acid (GABA) on GABA-A receptors causes chloride efflux, with resultant depolarisation.[9] Therefore GABA, which is the inhibitory neurotransmitter in extrauterine life, has an excitatory effect in utero. By the end of the third trimester, the six layers of the cerebral cortex have undergone rapid expansion resulting from dendrite proliferation, axonal arborisation, synaptogenesis and myelination.[5] The enteric nervous system consists of 100 million neurons and eventually weighs the same as the adult brain (Figure 3).

HEALTH AND DEVELOPMENTAL OUTCOMES FOR EARLY AND ELECTIVE CAESAREAN DELIVERY

According to the WHO, a baby is born prematurely if delivered before 37 completed weeks gestational age (GA) or 259 days after the last normal menstrual period.[10] It was formerly thought that babies born a week or two early (between 37 and 39 weeks) would be just as mature as babies born after 39 weeks. However, babies develop throughout the entire pregnancy, and as a result the American College of Gynecologists and Obstetricians (ACOG) has adopted a new maturity classification that refers to babies born from 37 to 39 weeks as 'early term'.[11]

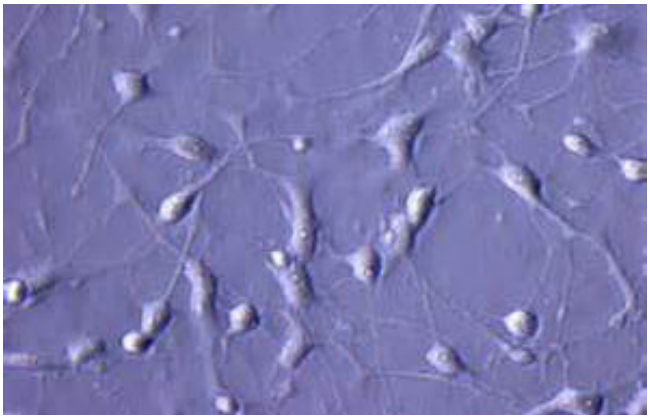

Figure 2: Synaptogenesis (the connectivity between neurons) occurs at the rate of 40 000 synapses per minute during foetal development so that by the end of gestation, the foetal brain should consist of approximately 100 million neurons.[7,8]

There has been a dramatic rise in preterm births globally.[10] The associated mortality is significant as 28% of all early neonatal deaths (i.e. deaths within the first seven days of life) are due to preterm birth.[10] Major contributing factors are iatrogenic prematurity resulting from in-vitro fertilisation and multiple births, and elective Caesarean sections.[10] It has been shown that advanced maternal age is associated with preterm birth,[12] and that elective Caesarean section is also associated with advanced maternal age,[13] which only compounds the risk factors.

Not only are continuing brain differentiation and maturation essential for the neonate, but they could be significant for future neurodevelopment.[14] Prematurity is associated with impaired cortical development[14] and ex-premature infants never achieve the same degree of cortical folding as is seen in babies born at term.[14] Prematurity is also a major risk factor for cerebral palsy, which occurs in 35% of cases[15] – the global prevalence of cerebral palsy is 2/1 000 births.The increased risk is directly proportional to decreasing GA.[15] Between 32 and 36 weeks of gestation, the risk increases to 6.75/1 000 births.[15] Importantly for the timing of an elective Caesarean section, there is still an increased risk of cerebral palsy in 1.35/1 000 births, even after 36 weeks of gestation.[15]

Another cause for concern is that both the last menstrual period (LMP) and an early ultrasound are imperfect measures in determining the GA of a foetus.[16] Using urinary hormone profiles to gauge the precise timing of ovulation, fertilisation, implantation and corpus luteum rescue, it has been found that these early physiological events have a natural variation that affects the length of pregnancy.[16] This variation, between women, in length of pregnancy spans a period of 37 days,[16] which suggests that the pace of development can vary between foetuses. If the normal duration of gestation is 280 days after the LMP, then only 4% of women will deliver precisely at this time, and only 70% of women will deliver within ten days of this due date.[16] As women tend to give birth to their

Figure 3: The enteric nervous system consists of 100 million neurons and eventually weighs the same as the adult brain.

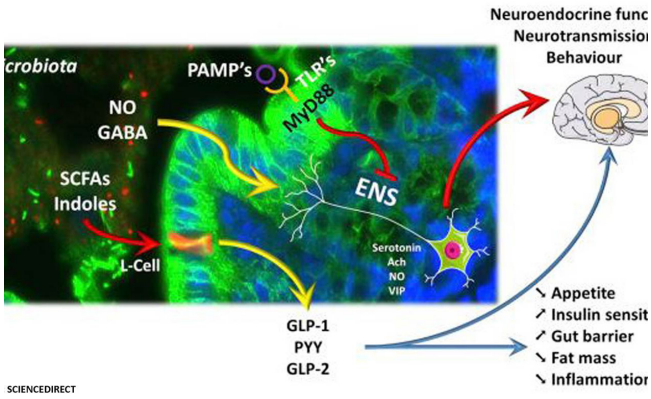

Figure 4: Enteric bacteria make the same neurotransmitters which affect mood and behavior in the brain.

babies at similar GAs,[16] there is a natural variation in foetal maturation and the timing of delivery. The unique individual programme of development is, however, disrupted by the unnatural timing of an elective Caesarean section.

As elective Caesarean deliveries are often scheduled at around 37–39 weeks of gestation,[16] it is important to be aware that babies born before 37 completed weeks of gestation are more likely to die than babies born from 37 to 42 completed weeks of gestation,[4] and that many electively delivered babies will experience both short- and long-term health sequelae.[4]

It has also been found that a linear and dose-dependent risk of special educational need (SEN) – defined as a learning difficulty that requires special educational provision – exists across the entire range of gestation, from 24 weeks until 40 weeks of gestation.[4] Babies who are born in the early term period (between 37 and 39 weeks of GA) will later constitute 5.5% of children with SEN, whereas those born prematurely (before 37 completed weeks GA) will constitute 3.6% of cases.[4] This is because there are now more early term than preterm deliveries, with 75% of deliveries at 39 weeks GA now being elective.[4] But even babies born at 39 weeks of GA carry an elevated risk and constitute 1.7% of total SEN cases.[4]

Significantly higher incidences of deafness, visual impairment, dyslexia and dyspraxia, as well as of lower scores for intelligence and school performance, are associated with delivery before 37 completed weeks GA.[4] Apart from learning disabilities and effects on cognition, language disorders and behavioural problems are also more prevalent in this group.[4] It is alarming that 10% of SEN cases in the population are directly related to delivery before 39 completed weeks of gestation. A large Danish study found that children who had been delivered from 37 to 38 weeks GA had a significantly greater risk of developing subsequent reading and spelling difficulties.[17] Finally, improved cognitive and motor development at three months, six months and one year of age is associated with longer gestation.[6]

Apart from the timing of delivery, the method also directly influences cognitive development in the foetus. Mitochondrial uncoupling protein-2 (MUCP-2) is a growth factor in the hippocampus that regulates energy homeostasis in neurons through the proliferation of mitochondria.[18] It regulates neurogenesis, the increase in the number and size of neurons, as well as dendrite formation and synaptogenesis in the part of the brain that is critical in the conversion of short- to long-term memory. It has been shown that infants born by elective Caesarean section have significantly lower levels of MUCP-2 than those born by normal vaginal delivery, and have a diminished ability to process spatial memory as adults.[18] The motor domains of the foetal cortex undergo cortical folding and myelination towards the end of the third trimester.[14] Either premature delivery or disruption of the neuroendocrine interactions during normal vaginal delivery, can therefore result in motor, social and cognitive delays in an infant. Although the aetiology is multifaceted, infants born by elective Caesarean section have been found to reveal significant delays in cognitive development, gross motor function and social skills at the age of nine months when compared to infants born by normal vaginal delivery.[19]

Between 38 and 39 weeks of gestation there is an unexplained stillbirth rate of one in 730 pregnancies[20] and elective Caesarean section is associated with a significant

increase in 'all-cause death' by the age of 21 years.[3] Both neonatal and childhood immunity are adversely affected by Caesarean section. The mechanical stress of labour releases an array of cytokines into the foetal circulation that provides adaptive immunity in the neonatal period.[21] As is discussed below, during Caesarean section non-beneficial bacteria from the woman's skin, instead of beneficial bacteria from the vagina and alimentary tract, colonise the neonate's gastrointestinal tract. This dysbiosis in the gut of the newborn has been linked to immune dysregulation and the development of asthma, diabetes, and gastrointestinal and rheumatologic disease in childhood.[22]

The greatest concern after elective Caesarean delivery in the early term period is, however, that of respiratory insufficiency due to prematurity and immaturity. The United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines of 2011 state that there is a significantly higher rate of admission to the neonatal intensive care unit after elective Caesarean section.[23] Similarly, a 2013 ACOG committee opinion is that an infant born by elective Caesarean section is at a significantly higher risk of developing respiratory complications.[24] Such is the risk to the neonate that the Societies of Obstetrics in both the United States and the United Kingdom have recommended that elective Caesarean section be scheduled only after 39 completed weeks of gestation.[25] As rates of this procedure are particularly high in developing countries,[20] the WHO in 2015 responded to the problem with the statement: 'There is no evidence of elective Caesarean section giving benefit to either mothers or infants who did not require the procedure.'[26]

Given this conclusion, and the benefits of normal vaginal delivery that are discussed below, it can be argued that advocacy of the rights of the foetus, including the right to vaginal delivery when Caesarean delivery is not medically required, is of great importance.

THE GUT MICROBIOME AND CAESAREAN DELIVERY

During parturition, as the foetus passes through the birth canal the vaginal and faecal microflora of the mother are ingested. These bacteria colonise the infant gut in the first few postnatal days and the colonies are established over the first year of infancy. Eventually, trillions of bacteria line the gut, until there are a hundred bacterial genes for every human gene in the body.[27] This maternally derived microbiome has a rich diversity and can be viewed as a separate organ system. Through bacterial peptides, the microbiome stimulates immune, endocrine and neuronal cells to release cytokines and neurotransmitters, which access the central nervous system (CNS) via the blood or vagal nerve. In this way, enteric bacteria can influence mood and behaviour, sleep–wake cycles, and feeding patterns. During Caesarean section, however, the foetus is colonised instead by bacteria from the mother's skin. The microbiome that results from this has far less richness and diversity.[28]

Bacterial colonisation of the neonatal gut occurs during a developmental window in which the wiring of stress circuits in the CNS is established. Gut bacteria produce neurotransmitters identical to those involved in neurotransmission in the CNS (Figure 4). Serotonin, GABA, norepinephrine, dopamine, acetylcholine and melatonin pass through the vagal nerve, which connects the enteric nervous system to the brain stem and regulates higher functions such as mood and cognition in the brain.[29] Enteric bacteria activate enterochromaffin cells, which in turn produce 95% of the total amount of serotonin in the body. Serotonin is a key neurotransmitter involved in memory and learning as well as in the regulation of mood and anxiety.[30] The gut microbiome programmes the hypothalamic-pituitary-adrenal axis (HPA axis) early in life. Dysbiosis can upregulate stress reactivity and corticosterone release within the axis – either indirectly, by modulating stress circuits, or directly, through the action of immune-mediated mechanisms on the hypothalamus. Episodes of depression are associated with increased cortisol release and dysregulation of the HPA axis.[30] Symbiotic bacteria enhance GABA production and increase the formation of GABA receptors in the brain.[31] GABA is a calming amino acid which subdues anxiety and panic in areas of the limbic system, or the emotional brain. Enteric bacteria increase the levels of brain-derived neurotropic growth factor (BDNF) in the hippocampus, which is the site of memory and learning. BDNF is a growth factor for neurons that also suppresses anxiety and elevates mood.[32]

In addition to mood and stress reactions, the gut microbiome manipulates the host's circadian rhythms, and therefore sleep–wake cycles and feeding patterns. The colonies of bacteria that line the gut are not stationary but dynamic, and move a certain number of micrometres along the alimentary tract in cycles throughout the day and night. As they move, each colony deposits a specific concentration of metabolites that act as epigenetic modifiers on the DNA of local host cells. As a result, oscillations in metabolite production cause changes in gene expression at tissue level. Bacteria have their own biological clocks that enable them to alter the clocks of the peripheral tissues. Bacteria can also manipulate the behaviour of the host by sending signals to parts of the brain responsible for emotions, hunger and satiety, and exploratory behaviour. This ensures that the biological rhythms of the bacteria and host are synchronised so that both may benefit from a common energy source.[33] Bacteria can also shift circadian rhythms and alter sleep–wake cycles through interactions with the HPA axis and the release of cortisol, which has a direct effect on sleep architecture.[34] Bacteria furthermore stimulate the release of sleep-inducing cytokines (interleukin-16, interleukin-18 and tumour necrosis factor alpha) from macrophages and T-lymphocytes.

In addition, the gut microbiome can alter feeding behaviour. Enteric bacteria produce peptides similar to hormones that regulate hunger and satiety in the brain.[35] Pathogenic bacteria form benzodiazepine-like compounds from the decomposition of sugars and fats. This generates cravings in the brain for food of low nutritional value.[27] In the absence of nutrients, pathogens release toxins and induce dysphoria.[27] This results in feeding refusal and a reluctance in the child to experiment with new tastes.

The microbiome has its own circadian rhythms, which are affected by the timing of eating and the composition of food. It can be seen as a network of circadian genes that interacts with circadian genes in the entire body. This interaction allows bacteria to organise our behaviour temporally.[36] If circadian rhythms can be manipulated, then so can sleep–wake cycles and feeding patterns. Metabolism requires our cells to be synchronised minute by minute with the environment.[37] The link is the gut microbiome, which is constantly exposed to the environment within the intestinal lumen. Elective Caesarean section not only disrupts these rhythms through the prematurity and immaturity of the brain, but also deprives the body of the gut microbiome, and therefore its link with the outside world.

SLEEP AND CAESAREAN DELIVERY

The growing infant needs sleep as much as nurture and nutrition.[38] The young brain is opening up to a vast array of visual, auditory and tactile sensations that bombard it constantly. If these early experiences are to facilitate the development of reliable coping mechanisms, they need to be sifted through and filed daily, and stored as memories in the labyrinths of the cerebral cortex and cerebellum. During sleep spindle formation, rotating waves sweep across each hemisphere and organise experiences into patterns. These revolutions occur at regular intervals throughout the night and allow the infant to relive the events of the day and capture them as memory.[39] Sleep, therefore, is crucial to consolidating brain circuitry and creating a mechanism for learning and memory, which form the basis of neurodevelopment.[40] The earliest childhood memories are often the most crucial in determining character. The physiology of sleep is so fundamental to neuroplasticity that the sleep–wake cycle is a critical predictor of future cognitive and motor development.[41]

In order to survive, the foetus must practice how to move and sleep. The neurology of behaviour is programmed in utero and becomes experience-driven after birth. From 34 to 40 weeks of gestation, neurobehavioural systems are integrated to form organised patterns.[42] During this developmental window, sleep architecture is modified so that two distinct phases can exist, namely, active sleep and passive sleep. During active sleep, body movements in the form of twitches, startles and rapid eye movements are subconsciously rehearsed and primed in order for synchronisation between sensory organs and the neuromuscular junction to occur.[43] Sleep behaviour, therefore, not only predicts neurodevelopmental outcome but is also a functional marker of the state of the CNS.[44]

The crucial period between 34 and 40 weeks of gestation, during which behavioural patterns are being refined, coincides with the proliferation and functional maturation of the cerebellum, the centre for motor memory, and the cerebral cortex, where the senses are integrated and stored. As sleep is derived from brainstem oscillations that spread to the cerebral cortex, any disruption to the cerebral cortex will affect the initiation and maintenance of sleep.[44]

Elective Caesarean section not only results in sleep that is poor in quality because of primitive sleep architecture and erratic sleep patterns, but also deprives the premature infant of sleep that is sufficient in quantity, which is critical for brain growth and development. In fact, sleep deprivation is a major contributor to developmental delay in premature infants.[45] It is the little person who needs sleep the most, who is unable to get it. And to make matters worse, sleep patterns evolve during infancy and can persist into adulthood.[46] Elective Caesarean section may therefore help to explain the current prevalence of difficult sleepers among preschool children; one study has indeed found that infants born by this procedure experienced a significantly greater incidence of sleep problems as preschool children.[47]

Prematurity has still further effects on infant sleep, though. In the foetus, sleep state regulates activity. However, during the first year of life, active sleep diminishes and quiet sleep increases, so that activity becomes less dependent on sleep and more dependent on the sleep–wake state.[46] The reason for this is twofold: initially, in the first few months, the capacity for memory must be increased. After sleep onset, the newborn drifts almost immediately into rapid eye movement sleep and spends long periods in this slow-wave sleep in which sleep spindles are generated and memory is consolidated. Memory formation precedes activity, so that future responses may be experience-driven. Secondly, during the following year, sleep–wake cycles dominate sleep quality, as activity must be modelled into organised responses for effective social interaction. The infant should be sufficiently alert and awake for long enough to sustain mutual gaze, smile and be able to respond to the mother's touch. Owing to their disregulated sleep cycles, premature infants exhibit disorganised responses to physical cues from their mothers.[48] As a compensatory mechanism, the biology of premature infants shifts to meet social needs, and their activity or behaviour is altered through sleep: premature infants indulge in more frequent naps in order to reorganise engagement with the social environment.[49] This further jeopardises infant attachment and responsive parenting, so that mothers of premature infants eventually show less sensitivity to their babies' physiological cues.[49]

FEEDING AND CAESAREAN DELIVERY

Sensory organs are intimately interwoven with brain development: so much so that the sensory organs of the head are established by two months of gestation. The foetus starts practising pharyngeal swallowing at 15 weeks' gestation, and by 24 weeks' gestation is attempting suckling motions. The combination of swallowing and suckling then requires a third component – breathing – in order to become an effective unit. Once the foetus can perform all three of these motions coherently, amniotic fluid is ingested and distributed to the lungs and the digestive tract. Filling of the lungs enables the stimulation of respiration, and the passage of amniotic fluid through the oral cavity stimulates the formation of primordial taste receptors on the sides of the tongue and at the back of the throat. Amniotic fluid consists of sugars, salts, fatty acids, amino acids and proteins, and aroma compounds that can be found in the mother's diet.[50] The foetus samples and learns to like what the mother is eating. By swallowing the mother's amniotic fluid, the foetus inherits the cultural food preferences of its society.[50] The foetus develops preferences for tastes as early as 28 weeks of gestation, and if the mother consumes a compound which is either sour or bitter, the foetus can even demonstrate disapproval through facial grimacing. This reflex, which is linked to the chemo-sensing of taste receptors at 28 weeks' gestation, also enables the foetus to purse the lips and restrict further ingestion.[51]

Late in the third trimester is a critical period for fine-tuning feeding behaviour. The foetus can now voluntarily regulate the amount of amniotic fluid consumed by increasing the frequency of coordinated suckling, swallowing and breathing. If the amniotic fluid is sweet, the foetus will drink more. If the taste is sour, the opposite will occur. This intricate process is in place by 32 weeks' gestation, and is continuously refined during the last few weeks of pregnancy.

Sweetness creates the sensation of safety, as carbohydrates represent an effective energy supply, whereas acidic or sour tastes represent spoiled foods and bitterness signifies food toxicity. Recognition of all these taste combinations and warning signals develops prenatally, and enables the foetus to recognise immediately the mother's breast milk after birth. This is why a neonate's sense of taste, which is tethered to the sense of smell, is the most important and most developed of all the senses. The stimulation of taste receptors also results in increased saliva flow and tongue movements. As breast milk is essentially sweet, this alone can induce non-nutritive suckling in the neonate.

Near term, the foetus swallows between 500 mL and 1 000 mL of amniotic fluid per day. This is a huge volume and is much more than was previously thought. For this reason, the integration of suckling, swallowing and breathing must be exquisitely timed.[52] In order to prevent aspiration, this highly complex sequence of manoeuvres becomes coordinated only between 34 and 36 weeks' gestation; in other words, just before the baby is born. In 'late premature' infants – those born before 39 completed weeks – this pattern is disorganised, resulting in bursts of suckling interspersed with pauses. The risk of aspiration is greatly increased, which may result in feeding refusal. Another crucial reflex that represents the onset of food-seeking behaviour is the rooting reflex. From 32 weeks until full term, the foetus's head turns when the face is touched in preparation for seeking the nipple. Critically, both food-seeking behaviour and the reflexes for the ingestion of food are primed together during the last few weeks of pregnancy, and for this reason feeding behaviour is also a marker of neurological maturation.

Elective Caesarean section disrupts this critical window for the development of feeding behaviour. Motor control does not develop in isolation, and sensation of the larynx continues to mature until the very last day of pregnancy. Only term infants show rooting or food-seeking behaviour, and premature infants integrate rooting with suckling and swallowing only as they get closer to term.[52] The complexity of suckling makes it the most difficult task that the neonate needs to perform, and because feeding behaviour evolves during the first year,[53] and food experiences persist into adulthood,[54] the baby must be given every chance to feed successfully from the outset. The disruption of this critical window in which suckling develops may have significant consequences. Immature cough reflexes and poor swallowing make the 'late preterm' infant particularly vulnerable to recurrent, silent aspiration. Perhaps of greater concern is that feeding and language pathways share the same circuitry and feeding problems in infancy may lead to speech problems in preschool children. Compounding these neurological issues is that, after the Caesarean section, the woman lacks the hormones necessary to offer her baby breast milk,[55] and so the establishment of normal feeding already begins to fail at birth.[56]

Feeding problems in preschool children may also be related to other events in early infancy, and in utero. Taste depends on smell for fast-tracked learning,[57] and neonates learn about odours within the first minutes after birth.[58] After Caesarean section, the baby may be separated from the mother and placed in an incubator. This breach of skin-to-skin contact prevents the baby from recognising the mother's milk odour.[59] As taste receptors mature fully only at 40 weeks' gestation, and as taste is coupled with smell, feeding refusal is inevitable in such cases. It is therefore evident that elective Caesarean section may contribute significantly to the current prevalence of fussy eaters in the paediatric population.

AUTISM AND CAESAREAN DELIVERY

Autism spectrum disorder is characterised by impaired communication and social interaction in the presence of restricted interests and repetitive behaviour.[60] It affects

0.62% of children worldwide,[60] and boys are affected four times more often than girls.[61] Although it is highly heritable, which accounts for about 50% of cases,[62] the concordance in monozygotic twins is only 60%,[61] and the recurrence rate if one sibling is affected is 8%.[63] This suggests that environmental factors may contribute to the aetiology to a greater extent than previously thought, probably accounting for 50% of the risk.[64]

The incidence of Caesarean sections has been increasing at an alarming rate over the last few decades in both developed and developing countries.[2] The rates of induction of labour and perinatal adverse events have also been increasing steadily.[65] As a result, researchers have sought a link between prenatal, perinatal and neonatal risk factors and the development of autism. The genetic causes of autism have remained stable at 10% over the last decade.[66] This suggests that other factors, including Caesarean section, may act as environmental triggers on genetically susceptible individuals.[60] Even a small increase in the rate of autism due to the alarming increase in the rate of Caesarean sections worldwide would have a significant impact on society.[67]

The contemporary increase in the rate of autism cannot be explained solely on the basis that case definition has changed over the past decade, although this is known to affect the incidence of autism.[68] Changes in the diagnostic criteria for autism spectrum disorder account for only 60% of the rise in incidence;[60] the search therefore continues for other environmental triggers. One compounding factor is that the trajectory of the disorder has an impact on diagnosis, with many more boys being diagnosed at a much younger age.[69] However, very few studies have investigated sibling controls in order to determine the relative roles of genetic factors and environmental ones, which may also act as confounders.[70] Sibling design studies adjust for these shared factors in order for the causality of obstetric interventions to be measurable.[71] One problem with this type of study method is, however, that a woman who has previously had a Caesarean section will most often elect to have a subsequent Caesarean delivery.[72]

Other environmental factors have been linked to the aetiology of autism. It has been noted that the risk of autism in Australian aboriginal children is very low.[73] Urban living, however, increases the risk of the disorder two-fold,[74] although it should be borne in mind that a greater availability of specialist physicians will increase the diagnostic yield in cities.[74] It has also been suggested that advancing maternal and paternal age may be contributing to the increase in autism. In the case of the mother, expanding trinucleotide sequences of DNA may be the link to advanced parental age.[75] As these repeats become longer and are passed down to the offspring, they become progressively more unstable, resulting in aberrant programming of genetic material. In the case of the father, Penrose's theory may be considered.[76] During adolescence, spermatozoa divide roughly every 16 days. This implies that by the age of 35, 540 cycles of cell division have occurred. After this age, DNA repair mechanisms gradually deteriorate, resulting in a greater number of frameshift mutations in subsequent cycles. The picture remains unclear, because although it has been suggested that advancing parental age is associated with autism, no consistent association has been found.[77]

There is also no association between maternal characteristics such as obesity, hypertension or diabetes during pregnancy and an increased risk of autism.[60] (Maternal factors such as low maternal weight, smoking and alcohol consumption during pregnancy, and infections, are, however, strongly associated with lower socio-economic status and the development of intellectual disability in the foetus.[78]) Other prenatal factors, such as foetal lie (breech presentation), low birth weight and foetal malformations are not associated with autism.[79] Similarly, perinatal complications have provided scant statistical significance. Markers of perinatal asphyxia, for example, a short nuchal cord, low 5-minute Apgar score and meconium-stained liquor, are not predictive of the development of autism.[79] Therefore, obstetric optimality and birth interventions are poor measures of risk.[63,80] Of growing interest, however, is the state of the placenta around the time of delivery. Placental complications are rife after previous Caesarean section. The incidence of placenta accreta, or abnormal adherence of the chorion to the myometrium of the uterus, is less than 1/5 000 in the general population. The incidence increases by 11% with two previous Caesarean sections, and by 40% with three previous Caesarean sections.[81] Abnormal placentation may impair foetal brain development, and placental abnormalities are significantly increased in the placentas of foetuses who have a familial risk of autism.[82]

What has become clear is that the genetic expression of the foetus around parturition is more dynamic than was previously thought.[83] It follows that gene–environment interactions are important for both foetal and neonatal development.[83] Caesarean section has been shown to increase DNA-methylation in white blood cells of the foetus.[66] This epigenetic modification results in the long-term alteration of 'transcriptional permissiveness',[83] and suggests that an environmental trigger could result in aberrant wiring of the brain and the development of autism. Epigenetic dysregulation is more prevalent in autism.[66] However, there is currently no known association between neonatal risk factors and autism.[77] Although prematurity has a strong dose-dependent and linear association with intellectual disability, the same association cannot be found for autism.[78] It would appear that autism originates in the vulnerable period of early embryogenesis, from fertilisation and implantation of the embryo up until the end of the first trimester.[61,80,84] During this time, relatively few genes regulate the organogenesis of many diffuse body

parts. It stands to reason that minor genetic changes may have far-reaching effects.

THE IMMATURE BRAIN AND ADHD

There are very few studies that have investigated a link between attention-deficit/hyperactivity disorder (ADHD) and Caesarean delivery.[67] One problem lies in methodology, because only a minority of studies have differentiated elective from emergency Caesarean section.[85] In summary, although environmental factors are important in the aetiologies of both autism and ADHD,[86] no association has been found between Caesarean section and the development of these disorders.[60,77,80,85,87] There is also no relationship between autism and prematurity,[79,80,88,89] or autism and obstetric complications.[60]

EMOTIONAL AND BEHAVIOURAL OUTCOMES FOR PARTURITION

As discussed above, however, prematurity and early elective Caesarean section do have significant relationships with a large variety of negative health and neurodevelopmental outcomes, including those in relation to the gut microbiome, sleep and feeding. Outcomes for normal vaginal delivery present a powerful contrast to this picture.

This is largely because parturition is not merely a mechanical event. It is a physical trigger that is necessary for permanent physiological and psychological changes to take place in both the mother's and the neonate's brain. Certain areas within the mother's brain become 'plastic' around the time of delivery, and can be influenced by hormones in the maternal circulation that are released after interaction with the foetus.[9] Magnocellular neurons in the hypothalamus of the woman are primed to release oxytocin in a pulsatile manner once the foetal head has stimulated the vagina and the cervix through direct contact.[9] The oxytocin enters the cerebrospinal fluid of the woman, where it directly sensitises her olfactory bulbs to the scent of her baby. Oxytocin also crosses the placenta, where it sets up the same response by sensitising the foetus to the mother's odour. The oxytocin surge also initiates the ejection reflex. Labour, therefore, is essential in coordinating this 'mother–child synchrony' in the first few hours of life, whereas oxytocin consolidates the birth experience through feelings of wellbeing, affiliative behaviour and bonding. The foetus manipulates the mother's brain chemistry, and in doing so fosters caring behaviour that is essential to child survival.

Not only oxytocin but also vasopressin is released after compression of the vagina and cervix by the foetal head.[9] Vasopressin release in the amygdala of the woman combats maternal anxiety in the limbic system and hones her responsiveness to physiological cues from her baby. In the neonate, vasopressin has an analgesic effect and counteracts persistent crying.

Labour also has a 'plastic' effect on the CNS of the foetus, and, through endocrine mechanisms, primes the foetal genome for survival during the neonatal period. Strong mechanical compression of the foetal head during passage through the birth canal activates the HPA axis of the foetus and induces a surge of cortisol and catecholamines into the foetal circulation. This milieu of catabolic hormones rapidly mobilises and burns fuel reserves and increases blood flow to the brain and other vital organs. This occurs so that the foetus can survive the period of hypoxia resulting from compression of the placental vessels during labour and passage through the birth canal. Cortisol leads to a rapid absorption of fluid from pulmonary alveoli, and neurotransmitters, neuro-hormones and neuropeptides activate the CNS and elevate the baby's sensorium to one of quiet alertness.[90]

The greater sympathetic tone creates a vigorous baby with an enhanced ability to suckle. The 'stress of labour' is therefore crucial to establishing a 'sensitive period' during which breastfeeding and mother–child attachment can occur.[90] After the trials of labour, the action of suckling, and skin-to-skin contact between the woman and her baby, causes stimulation of the vagal nerve in the baby, and the metabolic storm is subdued by a blanket of parasympathetic calmness. The baby sleeps better and the woman becomes more satisfied with the birth experience. The quality of this interaction is imprinted during this time of neuroplasticity in the neural pathways of both the woman and her baby. By way of contrast, in one study women who underwent elective Caesarean section expressed less satisfaction regarding the birth experience and had lower levels of self-esteem afterwards, whereas infants who had been born by elective Caesarean section experienced a significantly greater incidence of sleep problems as preschool children.[47]

REASONS WOMEN OPT FOR ELECTIVE CAESAREAN SECTION

In view of the positive outcomes of normal vaginal birth and the many negative outcomes of elective Caesarean delivery, the increase in this form of delivery could be described as cause for concern. Although the media have highlighted women's individual preferences as the main reason for the increase, there is, in fact, little supporting evidence for the idea that it is a significant contributor to the rising rate of Caesarean sections that some women consider themselves 'too posh to push'.[91] Another assumption is that Caesarean section is viewed by older (over 35 years) and more educated women as an expression of maternal autonomy,[92] which in turn may reflect an unrecognised or unmet social need. However, research reveals that few women request a Caesarean section in the absence of current or previous obstetric complications.[91] According to the principles of medical ethics, autonomy may be considered for these few only if the choice they make is fully informed. The problem is that

the question of elective Caesarean section has become one of social critique instead of a health issue.[93] This is compounded by the fact that a woman who chose to have an elective Caesarean section in her first pregnancy will probably forgo a trial of labour, and continue instead to opt for the same procedure in subsequent pregnancies.[94]

A further contributing factor in the increase in Caesarean sections is the fact that there is a misrecognition of indications for Caesarean delivery among both women and their physicians.[93] Among women, more than 80% of those who have had a Caesarean section will elect to have a Caesarean delivery in their next pregnancy for fear of uterine rupture during labour, even though such rupture is a rare occurrence.[95] The maternal mortality rate of Caesarean delivery is three to five times higher than that of normal vaginal delivery.[91] Maternal demand cannot justify this risk,[91] and the maternal desire for predictability must not come at the expense of optimal health for both the woman and her baby.

Among physicians, scheduled Caesarean section is often used as a 'prophylactic' in order to avoid physical harm.[93] However, in cases where this follows from an expectation of foetal macrosomia, it should be borne in mind that screening for foetal macrosomia in pregnancy is often inaccurate and, crucially, an elective Caesarean section neither prevents complications nor improves outcome.[96]

Other factors that contribute to the high rate of Caesarean deliveries include a lack of expertise in the handling of non-progressive labour and breech deliveries,[93] together with the fear of litigation.[21] Physicians are then drawn into 'the practice of deviance'. When we do something that is wrong repeatedly and successfully, it becomes the new accepted standard, and we continue to do it without question. Parents, lawyers and obstetricians have come to believe that elective Caesarean section is the best way of delivering babies, and are no longer questioning it. Instead, they should avoid the first Caesarean section at all costs. Every Caesarean section becomes a previous Caesarean section, and vaginal birth after Caesarean section is not safe.[97] In order to avoid adopting the maxim – 'Once a Caesarean, always a Caesarean' – we must avoid the first Caesarean.

CONCLUSION

Elective Caesarean section holds serious risks for both women and infants, whereas normal vaginal delivery holds many known benefits. The choice to deliver by Caesarean section in the absence of emergency should therefore depend on questions of foetal and maternal health rather than on those of convenience or social factors.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

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