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Briefly Legal: Term pregnancy, Uterine Rupture, Hypoxic-Ischemic Encephalopathy, Autism Spectrum Disorder – Part I

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Prenatal Course:

The patient is a 40 y/o G3 P1 Caucasian, married with a reliable menstrual history confirmed by ultrasound. She is of short stature, 62" tall, and weighs 141 lbs. at the outset of pregnancy. Beginning at 26 2/7 weeks, she complains of uterine contractions (UC's) and pain at the site of the cesarean section scar. She is admitted twice to the hospital for these complaints to rule out preterm labor (PTL). At 32 4/7 weeks, she receives two doses of Celestone and is scheduled for elective repeat cesarean section at 39 5/7 weeks gestation should she not go into labor before then. At 36 5/7 weeks, she has an episode of back and severe suprapubic pain with urinary retention of 850 cc urine. She is catheterized and treated for UTI with the resolution of the pain.

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She returns labor & delivery at 39 1/7 weeks in the morning complaining of painful contractions for the last five days, getting much stronger, and she is exhausted. She is there to rule out labor and ask for the cesarean section to be moved up from the scheduled procedure four days later. Her cervix is 1.5/50%/-4, and contractions are coming every 3-6 minutes. The FHR pattern is Category I with accelerations and normal variability. Her providers agree to move the cesarean section to the next day at 08:00. She is discharged with instructions.

She returns to L&D about 4 hours later, complaining of pain (10/10). Her cervix is now 4-5 cm., 80% effaced with the vertex at -3 station. At this time, the caregiver notes that she will be given a trial of labor – there is no formal discussion. She is placed on a monitor where the FHR is about 120 bpm with accelerations - a "Category I" tracing. Contractions, however, are prolonged and frequent. Epidural anesthesia (for labor) is implemented with a continuous dose of Fentanyl and Bupivacaine.

Her cervix dilates rapidly to 7-8 cm with the head in the OP position when membranes rupture spontaneously (SROM). Immediately following SROM, there appear repetitive and increasingly severe variables and then prolonged and late decelerations – denoted as "Category 2." An intrauterine pressure catheter (IUPC) is placed, and an amnioinfusion is administered, which successfully relieves the decelerations. Hematuria is noted to be draining from the Foley catheter, with the patient feeling pain along her right lower abdomen despite the epidural anesthesia. Shortly thereafter, she reaches full dilatation (10 cm) with the fetal head at 0 station in the occipital posterior (OP). Immediately, there is a prolonged deceleration. Terbutaline, 25 mcg, is administered to diminish uterine contractions emergently. Simultaneously, the patient is taken to the operating room (OR) for an emergency cesarean section. Upon arrival in the OR, the deceleration has recovered.

"There is a stable baseline at 130 beats per minute (bpm) with good variability. The decision to perform a cesarean section is canceled, and shortly thereafter, she begins pushing. After 2 hours of pushing, she complains of severe pain (8/10) in the lower abdomen. An epidural bolus of Fentanyl/Bupivacaine is given (apparently without examining the abdomen). By this time, the fetal baseline heart rate has risen to 165 bpm (from 120) with obvious late and prolonged decelerations and indications of sinusoidal pattern."

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At birth, the male infant weighs 3070 gm (25th percentile), length of 50.3 cm (50-75th percentile), and head circumference of 35.5 cm (90%). He receives "unexpectedly" low Apgar scores of 4 and 6 at 1 and 5 minutes, respectively. He is floppy and pale.". The umbilical venous pH is 7.03 with a base deficit (BD) 17; the arterial values are pH 6.96 with a BD of 18. The initial arterial blood gas at 30 minutes shows a pH of 6.96, with a BD. 24. These values represent a severe metabolic acidosis reflecting significant oxygen deprivation during late labor. The infant requires immediate resuscitation and is placed on continuous positive airway pressure (CPAP), and appropriately, is immediately referred for head cooling (therapeutic hypothermia - TH) for 72 hours. At 8.5 hours of age, he is intubated for apneas, thought to be related to seizures, and he is loaded with phenobarbital. His platelets are low and creatinine elevated. His diagnoses include hypoxic-ischemic encephalopathy (HIE), mild disseminated intravascular coagula-

tion (DIC), and renal insufficiency. Magnetic resonance imaging (MRI) and an electroencephalogram (EEG) on day 3 of life are interpreted as "normal."

He had a normal neurological examination after completion of the cooling protocol. His slow feeding improved, neonatal apnea resolved, hypotension resolved, and he passed his newborn hearing screen. He was sent home at eight days of life on phenobarbital with "normal tone, but sleepy."

At seven months of age, he was still on phenobarbital, with Keppra added along with vitamin D3. By 12 months of age, the baby is diagnosed with macrocephaly, cerebral palsy (CP), developmental delay, tremors, seizures, for which he is maintained on Keppra. At 18 months of age, the MRI is again "normal"; the infant has been weaned off of anticonvulsants, and various genetic tests are negative. At 27 months of age, the child underwent Bayley developmental testing, which showed significant speech and movement skills delays. The current clinical diagnosis from the medical records is Autism Spectrum Disorder (ASD).

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Allegations:

Numerous forensic issues surround the mother's obstetrical care, including the response to the abnormal FHR patterns, the timeliness of the delivery, and issues with informed consent; those will be considered in a subsequent submission. Irrespective, there was universal agreement that the fetus suffered a hypoxic-ischemic event during labor and delivery (a sentinel event) due to rupture of the uterus. From a forensic standpoint, however, the major issue with the case was the relationship of the events of labor and delivery to the subsequent diagnosis of autism spectrum disorder (ASD).

Discussion:

It is not the obstetrician's role to assign provenance to the child's signs and symptoms of neurological handicap; that is the role of the pediatric neurologist or other qualified individuals. It is the role of the obstetrical expert, however, to affirm that the fetus, neurologically responsive and without hypoxic or mechanical threat at the outset of labor; and irrespective of any genetic predisposition, affirmatively suffered a neurological injury during labor and delivery and that the literature strongly supports a relationship between the events of labor and subsequent neurological handicap including behavior abnormalities.

Thus, the plaintiff's pediatric neurologist, armed with the above, alleged that those behavioral abnormalities resulted from the neurological injury sustained during labor and were initially labeled as cerebral palsy. The defense alleged that the events of labor, dramatic as they were, were unrelated to the ultimate diagnosis of ASD. - a disorder of undeterminable provenance.

ASD is a neurodevelopmental condition that presents as a spectrum of lifelong problems of communication and social and behavioral challenges. A generation ago, studies estimated the prevalence of ASD at perhaps 5 / 10,000. Current estimates in the United States range between 1 in 54 and 1 in 36 children., *This dramatic increase in the US and other developed countries cannot be explained by ASD diagnostic criteria or case identification changes*. Further, ASD is not the only developmental disability increasing over this time. By 2010, there had been a 33 percent increase over the preceding decade in developmental disabilities of all types, including ASD, attention-deficit/hyperactivity disorder (ADHD), and other developmental delays. These statistics are paralleled by those related to the costs of diagnosing and treating patients assessed for ASD.

While much progress has been made in the neurodiversity movement, and many people with ASD live productive, even exceptionally successful lives, at least 25 percent of people with ASD have minimal language skills despite early intervention efforts, presenting life-long challenges.

The associated costs of dealing with ASD or its potential have become prohibitive. Costs are predicted to reach $461 billion by 2025 in the US. There is also an incalculable impact on the lives not only of the children but on the parents themselves. A recent study estimates the average cost for therapy for a child diagnosed with autism is $60,000 per year from when they are diagnosed (typically at age 3) until entering school at age 6 or 7—the total cost for these four years of treatment: $240,000. Costs increase in ASD patients with intellectual disabilities. Children diagnosed with autism incur further costs: 40% more visits to a pediatrician than children not diagnosed with autism, as well as more psychiatric visits for children older than four years old, etc. Nor can the enormous financial and spiritual toll on the family of children with ASD be overlooked. Half of the families of ASD children report the need to reduce or stop work; one-third report experiencing financial burdens related to ASD health care costs. 46% of parents need more help or information managing emotional and physical stress; 40% need more help or information balancing work/family responsibilities.

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With regard to causation, ASD is described as a behavioral disorder resulting from a complex interaction between genetics, the environment, and a host of maternal risk factors. However, results in each category have been inconsistent. A genetics-linked etiology of ASD was appealing and was the primary defense position in this case. But, of the more than 100 genes that have been associated with ASD (as well as ADHD and others), none, alone or in combination, appears directly causative, nor has any synergistic environmental factor been identified. While neither the cause of ASD nor the reason for its increasing prevalence is known or (for the purposes of litigation) deemed preventable, theories and initiatives for early detection and treatment abound.

Of the numerous attempts to elucidate the timing and mechanism

of the disorder, seemingly the most amenable to establishing a cause and effect relationship to ASD are the events of labor and delivery. Correlations have already been drawn between such "adverse" perinatal events as prematurity, intrauterine growth restriction, fetal distress, prolonged labor, use of oxytocin, operative delivery, anesthesia technique, evidence of hypoxia-ischemia, low Apgar scores, and the subsequent development of CP and ASD. (Figure 1) There also appears to be a protective benefit of elective cesarean section prior to labor, not only for ASD but also for a host of adverse fetal outcomes, including birth trauma, birth asphyxia, subdural hemorrhage, retinal hemorrhage, and CP.

"A further clue from beyond the perinatal period comes from the characterization of ASD as a dysregulation of the autonomic nervous system (ANS) often assessed by measuring Heart Rate Variability (HRV). Compared to typically developing children, those with ASD exhibit altered autonomic tone, evidenced by a diminished vagal tone and increased sympathetic activity. It must be remembered that the determination of heart rate variability (HRV) is one of the most important features of assessing fetal heart rate patterns in labor."

A further clue from beyond the perinatal period comes from the characterization of ASD as a dysregulation of the autonomic nervous system (ANS) often assessed by measuring Heart Rate Variability (HRV). Compared to typically developing children, those with ASD exhibit altered autonomic tone, evidenced by a diminished vagal tone and increased sympathetic activity. It must be remembered that the determination of heart rate variability (HRV) is one of the most important features of assessing fetal heart rate patterns in labor. (*see* below) The most obvious deficiency in these studies is the lack of demonstration that the fetus is neurologically (behaviorally) normal at the outset of labor.

Beyond these correlations, various authors have drawn parallels between the meteoric rise in ASD and changes in obstetrical practices, including the almost universal implementation of EFM and increases in the mean duration of labor, especially of the 2nd stage. Between the 1960s and 1990s, the mean duration of uncomplicated deliveries doubled from 8.5 hours to 17.5 hours for first-time mothers and from 7 hours to 13.8 hours for women who had previously given birth. Similarly, the rising use of epidural analgesia for labor has been associated with both longer labor, the need for operative delivery, and ASD. It has been alleged that even continuous EFM (exposure to doppler throughout labor) itself contributes towards longer labors and ASD. Compared to one-half a century ago, today's parturient is more likely than her predecessor to be overweight, older at first delivery, and have diabetes. These factors contribute statistically to both longer labors and ASD-affected offspring. These past several decades have also witnessed the increased use of Pitocin for the induction and augmentation of labor, cesarean section, and even assisted reproductive technology. All of these have been associated with ASD. Several meta-analyses examining over 60 perinatal and neonatal risk factors for ASD have implicated perinatal events in the genesis of ASD. Still, they offer no specific insight into the timing or mechanism of the problem or any testable hypothesis.

In none of these studies, including those alleging a relationship to "fetal distress," prolonged labor, or HRV of older children with ASD, has an assessment been undertaken of the behavioral responses of the individual fetus to the anticipated challenges of labor and delivery, *i.e.*, the tactile and hypoxemic effects of contractions and the ischemic effects of repetitive head compression? Thus, the studies have failed to include the features of fetal behavior (neurological responsiveness) illustrated by rest-activity cycles, quiet sleep, REM sleep, activity – all of which are readily seen on the FHR tracing along with fetal responses suggesting provocation, hypoxia/ischemia, trauma/hemorrhage, and infection. As in the case of subdural hemorrhage (SDH), retinal hemorrhages, cerebral palsy, and "stroke," such injuries during labor may not be evidenced in the immediate neonatal period, although they are discernible on the FHR pattern.

The dramatic increase in cesarean sections (often deemed "unnecessary") has failed to show obvious improvement in the prevalence of CP. The risk of stroke and ASD has been increasing. Most babies injured during labor are NOT asphyxiated at birth, whether the outcome is CP or stroke. Some with autistic features and the vast majority of asphyxiated are not injured. Succinctly put, the premise of the critical relationship of FHR patterns to fetal hypoxia/acidosis was flawed from the outset. In contrast, the behavioral, neurological insights provided by FHR patterns have been overlooked or undervalued for reasons of both scientific myopia and political (medicolegal) defensiveness.

There have been many attempts to "re-engineer" the approach to fetal heart rate patterns and the conduct of labor based upon them. These publications have shown strong correlations between certain specific FHR patterns and the subsequent development of CP and stroke. These have developed strategies for preventive obstetrical care whose objective is to keep the fetus out of trouble in the first place, thereby avoiding the need to "rescue" the fetus in severe distress.

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In this experience, often derived from medicolegal cases, alleging a relationship of obstetrical factors and the subsequent development of CP, there have been a limited number of patients with CP with signs of ASD as a complicating feature of CP. In a small subset of these patients, such as the present case, the diagnosis of ASD was considered exclusive, seemingly unattributed to the events of labor and delivery.

In this case, the child suffered a hypoxic-ischemic brain injury, demonstrable on the FHR pattern that then went on to have cognitive delays, behavioral problems, considered by the plaintiff as a manifestation of cerebral palsy. Notwithstanding the number of treating physicians, pediatricians, pediatric neurologists, social workers, and behavioral specialists who operated under the notion that the child has autism.

" When the case was adjudicated, the plaintiff's child neurology expert did not disagree with those who identified the problem as autism but pointed out that that approach took the child as he appeared to them without considering the perinatal history and a proper differential diagnosis. At a superficial level, autism is regarded as a behavioral diagnosis in children. At the same time, cerebral palsy is considered an affliction of posture and movement."

When the case was adjudicated, the plaintiff's child neurology expert did not disagree with those who identified the problem as autism but pointed out that that approach took the child as he appeared to them without considering the perinatal history and a proper differential diagnosis. At a superficial level, autism is regarded as a behavioral diagnosis in children. At the same time, cerebral palsy is considered an affliction of posture and movement. The relationship of ASD and CP was changed in 2006, however, when the definition of CP was revised to acknowledge that the motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, as well as by secondary musculoskeletal problems. The limited data regarding their co-occurrence suggest that ASD is more frequent among children with CP (about 20%) and epilepsy (about 30%) than in the general population.

The pediatric neurology expert affirmed that the child indeed had autistic behavior, but that is not equivalent to a diagnosis of autism. One of the criteria for the diagnosis of autism requires that another etiology does not better explain the behavioral abnormalities. As pointed out, behavioral abnormalities are a well-recognized manifestation of a perinatally acquired hypoxic-ischemic injury, including CP. In the face of the obvious HI injury to his brain during labor and delivery, the expert opined that the injury was the cause of the constellation of findings, including the autistic behaviors.

The proof of hypoxia was incontrovertible. At birth, the pH of the umbilical artery was less than 7.0, with a base deficit of -18 and an elevated lactate level. At birth, the newborn was encephalopathic; he was pale and floppy, with a weak cry and poor respiratory effort. This constellation of acidemia and neurological findings was sufficient to qualify him for therapeutic hypothermia (TH). He then had seizure activity within the first 24 hours of life and was placed on phenobarbital. Subsequently, he was shown to have multiorgan failure, including respiratory distress, cardiac issues, renal failure, liver failure. all consistent with a severe hypoxic-ischemic injury to the brain.

While the decision to treat with TH should not by itself be considered an indication of injury, and while there is considerable creep away from the original diagnostic criteria for TH, this child met all those original criteria. Irrespective of the cooling, sufficient clinical features were indicated to underscore a hypoxic-ischemic injury.

The presence of macrocephaly at birth is another recognized feature of both ASD and hypoxic-ischemic injury. A recent study found that large fetal head size, a factor sometimes associated with ASD, was associated with a prohibitive incidence of cerebral white matter injury in the newborn. The authors consider prolonged labor the "missing link" in the causation cascade of subsequent neurological handicaps.

In the expert's opinion - the MRI does not have to be abnormal for a hypoxic-ischemic injury to the brain to have occurred. Perhaps as many as 25% of obviously injured children will fail to show lesions on the MRI. In this case, there was disagreement about the findings on the second MRI between the radiologist who wrote the report and the expert. The expert found "watershed" abnormalities on that MRI. "Irrespective," he opined, "MRI is just a test; it is necessary to look at the full clinical picture."

Did the child have epilepsy? As pointed out, both EEGs were normal. The expert considered the diagnosis of epilepsy as uncertain. The baby had had two seizures a month until he was 12 months of age. He was placed on phenobarbital, started on Keppra, and ultimately weaned off both.

The persistence of deficits after cooling was discussed with the expert who opined that at least some deficits encountered during injurious labor often remained after TH. The main benefits of TH are decreased mortality and some benefit in terms of profound cognitive delays. But, TH does not necessarily normalize children.

"Environmental influences can relate to exposure to different chemicals, antidepressants during pregnancy, even vaccination for a while (but now disregarded). However, consideration of uncertain environmental influences is moot under the current fact pattern. There was no demonstrable infectious, genetic, chemical, metabolic, or other discernible environmental etiology."

Concerning the failure to find any genetic markers for autism, the defense questioned whether that actually excluded a genetic etiology. The expert opined that autism is more often considered a combination of genetics and environmental influences. Environmental influences can relate to exposure to different chemicals, antidepressants during pregnancy, even vaccination for a while (but now disregarded). However, consideration of uncertain environmental influences is moot under the current fact pattern. There was no demonstrable infectious, genetic, chemical, metabolic, or other discernible environmental etiology. Still, there was an obvious hypoxic-ischemic injury related to a perinatal sentinel event which qualifies as causation in this case. The sequelae of that event, more properly deemed cerebral palsy, are the delays in his motor function that have not worsened over time. He manifests hypertonia with delays in speech and fine motor skills and other

motor functions. He also has behavioral sequelae, including his abnormalities in social interactions, his difficulties in groups, and problems with communication skills; His speech is vastly delayed, and he has abnormal reactions to environmental stimuli.

The case resulted in a structured settlement on behalf of the plaintiff.

Future research with long-term outcomes must attempt to better define the role of obstetrical care during labor, including a more nuanced approach to the neurological responses of the fetus and whether those are normal at the outset of labor. Further research should attempt to discern whether the wide spectrum of ASD behaviors can be explained by the multitude of perinatal variables influencing immediate and long-term outcomes.

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