The Neurological Impact of Preterm and Very Preterm Birth and Influence of IVF Pregnancies on Developmental Outcomes: A Literature Review and Case Study

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Full Text: Headnote ABSTRACT: This article explores the influence on brain development, as well as the neurological and behavioral outcomes, of the preterm and very preterm infant. It also briefly covers the influence of In-Vitro Fertilization (IVF), multiple births, gestational age, and birth weight on development as well as giving a more in depth review of literature that evaluates the impact of preterm birth and very preterm birth on brain development and neurological and behavioral outcomes. Finally, a case study is presented based upon the experience of a woman who delivered one twin at 24 weeks who survived and presently shows no significant abnormalities. KEY WORDS: Preterm infants, very preterm birth, VLBW, IVF, brain development, neurological impairments, behavioral problems. INTRODUCTION In the 1980s, approximately 80% of preterm infants weighing 1000-1500 grams (g) were surviving and 50-60% of those actually weighed only 750-1000 g. During this time, only 5-7% were assessed as having birth abnormalities due to premature birth (Goldberg &DiVitto, 1983). It was once thought that the majority of these survivors were free of serious handicaps, however, once at school age, those born at a very low birth weight (VLBW) were found to have impaired cognitive function and decreased academic performance (Hack et al., 2002). Presently, infants weighing less than 1500g comprise 1.5% of all live births in the U.S. Despite survival rates at approximately 85%, severe neurodevelopmental handicaps are discovered in 12-32% of these infants (Peterson et al., 2000). While survival rates continue to increase, there is much research being done to assess the long-term developmental affects of premature birth. This article will briefly address the influence of FVF and multiple births on preterm birth as well as the significance of gestational age and birth weight. Also, a review of literature details the impact on brain development as well neurological and behavioral impairments associated with preterm and very preterm birth. INFLUENCES ON PRETERM BIRTH IVF and Multiple Births The impacts of IVF on multiple births lend further complication to the already delicate experience of the premature infant. While some studies show no statistically significant differences between IVF and spontaneous twin pregnancies (Bernako et al., 1997 and Olivennes et al., 1996), others suggest that IVF compounds premature birth complications. Bryan (2003) has found several examples that correlate the tendency toward prematurity and low birthweight in FVF twins. She has noted increased risk of perinatal mortality and long term morbidity in preterm IVF deliveries compared to those that are spontaneously conceived. Furthermore, there is a three to seven-fold higher incidence of cerebral palsy (CP) in premature twins compared to single births. The rate of incidence of CP increases with the level of multiple births and is highest in surviving children whose co-twin or triplet died in utero. Olivennes et al. (1996), however, concludes that the relationship between age and parity plays a more significant role among premature IVF babies than does the use of IVF itself. Gestational Age In general, Goldberg and DiVitto (1980) found that those preterm infants born younger and smaller experience the most frequent and severe complications and are most likely to suffer subsequent impairments. Fetuses of 24 weeks gestational age are now viable. The brain is yet a "thin shell of tissue surrounding the cerebral ventricles, and virtually all of the normal cortical and subcortical architecture has yet to be established" (Peterson et al., 2000, p. 1940). It is around 35-36 weeks that there are very important changes in behavioral and neurophysiological organization (Goldberg &DiVitto, 1980). Prior to this age, the presence of physiological stress can severely disrupt the maturational processes that lay down the foundational architecture of the brain. When severe stress is present, the region of the brain affected is greatly influenced by the timing of the Stressor. Any subsequent abnormalities in a premature infant's brain structure

may lead to the presence of long-term cognitive defects (Peterson et al., 2000). A study of healthy preterm infants at varying gestational ages found that gestational age is a significant influence on the behavior of the infant. In this study, Mouradian, Als and Coster (2000) used the Assessment of Preterm Infants' Behavior (APIB) assessment to provide detailed measures of behavioral differentiation and modulation, including infant thresholds that range from stable behavioral organization to disorganization, to assess autonomic, motor, state, and attention subsystems. Also measured were infant self-regulation, specific behavioral cues and reflex behaviors. The authors compared 42 newborns born at 40 weeks, 37 weeks or 34 weeks of gestational age. They found significant differences in autonomic modulation, attention and the ability to orient, motor maturity, and self-regulation as well as a pattern of decreased behavioral organization with decreased gestational age. Overall, the most pronounced behavioral differences were seen in those infants born at 34 weeks as well as a surprising difference in those born at 37 weeks versus 40 weeks. The researchers found there to be a continuum of development with even the last few weeks making a tremendous difference in behavioral development. As expected, those infants born at term or close to term displayed a more differentiated level of functioning than those born at 34 weeks across multiple variables. Mouradian et al. propose that this may have occurred due to a difference among groups in cortical organization, particularly of the frontal and prefrontal regions. Anderson and Doyle (2003) also found that both gestational age and birth weight had significant influence on the outcome of preterm infants. The infants were assessed at ages 2, 5, and 8. They found that, at school age, infants with birth weights of 500-749 g had significantly lower scores on some cognitive and academic tests than those children born at birth weights of 750-999 g. Also, those with gestational ages of 23-25 weeks had lower cognitive and academic scores than those born at 26-27 weeks. Furthermore, there are several areas where the impact on preterm infants seems to be the most long lasting. Along with gestational age and birth weight, these include: brain development; neurological development, which includes perceptual, motor and cognitive impairments; and behavior problems. The following literature review will explore these areas in more depth. BRAIN DEVELOPMENT A study conducted by Ajayi-Obe et al. (2000) explains that the most growth in cortical connections occurs after 25 weeks of gestational age. They claim that 68% of survivors born before 25 weeks have debilitating morbidity. Since infants experience the most growth in cortical connections and complexity after 25 weeks, the cerebral cortex of extremely preterm infants observed at a corrected age of 38-42 weeks showed less cortical surface area and demonstrated less complexity than infants born at term. The authors speculate that, "Since deficits acquired during critical periods of brain development may be permanent, these results suggest a neural substrate for the neurocognitive impairment that is frequent among such preterm infants" (p. 1165). Furthermore, although neuronal migration is primarily completed by 25 weeks, glial migration and the growth of cortical connections continue after this time which greatly increases the surface area of the brain. Infants born during this time of rapid brain growth are exposed to many threats including: infection, chronic hypoxia, and under nutrition. Ajayi-Obe et al. found that although cerebral-tissue volume did not differ significantly between term-corrected and term infants, there were significant differences within the specific brain regions. They found that despite rapid coherent growth, cortical surface area and whole cortex convolution index in preterm infants was significantly less than in term controls. Also, they concluded that motor impairment is associated with white-matter damage and even in the absence of white matter damage; the normal increase in cortical surface area and complexity might be impeded. Later research by Peterson et al. (2000) showed impaired development in the cortex, ventricles, basal ganglia, amygdala, hippocampus, and corpus callosum in preterm infants. While brain volume has been shown to be comparable to term infants, regional brain volumes suggest that preterm birth leads to long-term impairments in cerebral development that may in turn be responsible for cognitive deficits. Peterson et al. found impairments concentrated in the motor portions of the cortex, corpus callosum, and basal ganglia and hypothesized that this could account for the predisposition to cerebral palsy and other motor disturbances in preterm children. A further study conducted by Peterson et al. (2003) measured regional brain volume in 10 preterm infants who were scanned at near term

age and then re-evaluated at age 8. They found that there were significant differences between term and preterm infants in the subregions of cortical gray matter and cerebral ventricles. All of the cortical gray matter regions were found to be significantly smaller in the preterm group when assessed according to head circumference. The use of head circumference as a variable also showed impact on parietooccipital, sensorimotor, and inferior occipital cortices. These regions were significantly smaller in the preterm infants while other regions were of fairly average size. They discovered that assigning subregions was very important in confirming their hypothesis about regional specificity of abnormal brain development in preterm infants along with the potential of these abnormalities to predict impaired developmental outcomes. Using a cross-sectional analysis of preterm children at 8 years of age, the authors also noted that while differences often appeared slight in the preterm newborns as opposed to the fullterm babies, by 8 years of age, reductions in premotor, sensorimotor, and midtemporal regions were more prominent. Another study that looks at the risk associated with cerebral ventricular dilatation is that of Grasby, Esterman and Marshall (2003). They found that cerebral ventricular dilatation usually occurs following intraventricular-periventricular hemorrhage (IV-PVH). IV-PVH has been found in approximately 25% of preterm infants weighing less than 1500 g and is considered to be a consequence of impaired absorption of cerebrospinal fluid from arachnoid villi coated with fibrin. The authors note that several prospective studies have found that the IV-PVH associated hemorrhage into the brain's white matter contributes significantly to neonatal mortality and long-term neurodevelopmental impairments. Ventricular dilatation results in diffuse axonal injury and reduced myelin formation, which may result in secondary brain injury as well as leading to adverse neurodevelopmental outcomes. A further risk to brain development in the preterm infant is intraventricular and periventricular hemorrhage and hypoxic-ischemic damage. Stewart et al. (1999) assessed 105 infants born before 33 weeks and examined them at 1, 4, 8, and 14-15 years of age. MRFs conducted at 14-15 detected many more abnormalities than in the fullterm control group. Ventricular dilatation and atrophy of the corpus callosum were found to be commonly associated with each other and with other lesions. These symptoms were noted to be markers of hypoxic-ischemic damage while white matter lesions in the majority of children confirmed brain damage in preterm infants predominantly occurs in the white matter. Atrophy of the corpus callosum, however, was interpreted to indicate poor interhemishperic interaction. Overall, the brain abnormalities found in these adolescent children were found to express themselves in behavioral abnormalities rather than the more common neurological impairments associated with preterm birth. NEUROLOGICAL OUTCOMES While there is evidence that very low birth weight infants are at increased risk of severe motor, perceptual, cognitive and behavioral disorders, minor neurological problems are also significantly higher among this group than among full-term infants. Minor neurological problems can include motor, perceptual, or cognitive difficulties (Torrioli et al., 2000). Despite reports in the 1970s that 80-90% of infants less than 1500 g were surviving without serious handicaps, it is now known that there is a risk that by school age, very low birth weight (VLBW) children will have poorer cognitive function and academic performance than normal birth weight children. Learning problems have been found to persist into adolescence and are even apparent in children with normal intelligence and no neurologic impairment. Goldberg and DiVitto (1980) found that a delay in motor skills is especially marked in the second half of the first year. They propose that this may be due to the length of inactivity the infant experienced in the NICU, which would further inhibit muscle development. They also saw discrepancies in academic skills compared to term children as well as difficulty with visual and spatial skills, greater incidence of behavioral problems, and more reading disabilities. Wocadlo and Rieger (2000) examined the skill differences in 5-yearold preterm children who were not cooperative with developmental testing at age 3. They found that minor neurological dysfunction was significantly higher for uncooperative children and also showed that children who were uncooperative at age 3 continued to show refusal to complete tasks at age 5. The authors felt that this suggested differences in visual-spatial organization, visual short-term memory, minor neurological signs and continued behavioral difficulties compared to the cooperative group. The presence of minor neurological impairments was correlated with later

academic difficulties while also predicting lower IQ scores, specifically around 7.5 years of age. Children with higher levels of minor neurological dysfunction (MND) were more likely to show significant discrepancies between Verbal IQ and Performance IQ scores. They found that only 14% of the children with a higher MND score were in their expected class placement in school suggesting greater risk for later learning difficulties. The preterm children in this study showed poor psychomotor organization and poor visual-perceptual organization, which are two of the factors used to identify symptoms of nonverbal learning disabilities. These deficits result in difficulties adapting to novelty, social competence, emotional stability, and activity level. A study by Hack et al. (2002) looked at the outcomes in young adulthood for very low birth weight infants. They evaluated 490 VLBW infants and compared them to 366 normal birth weight controls born during the same time period and then re-evaluated them at the age of 20. They found that while marital status and sociodemographic status did not differ significantly, VLBW adults had significantly higher rates of chronic conditions than controls that may have been attributable to higher rates of neurosensory impairment and subnormal height. IQ scores were also significantly lower in the VLBW adults than those of the control group, and there was also a higher incidence of subnormal or borderline IQ. Also, fewer VLBW participants had graduated from high school or obtained a GED by age 20 and 40% of the VLBW participants had repeated a grade. Furthermore, there were fewer VLBW men enrolled in post-secondary studies and of those enrolled; only 16% were in a four-year program. Even when restricted to looking at those VLBW participants without neurosensory impairment or subnormal IQ, there were significant differences in grade repetition, educational attainment, and current enrollment in post-secondary studies. Although rates of smoking did not differ significantly, VLBW participants reported significantly lower use of alcohol and marijuana (primarily among the women). Finally, fewer VLBW men had been in contact with the police and fewer VLBW women reported having intercourse, being pregnant, or delivering live born infants. The authors speculate that the low risk taking behavior of the VLBW participants may be due to increased parental monitoring. Delayed language is another neurological impairment frequently found in preterm infants. Based upon her literature review, Cusson (2003) found that despite the common belief that preterm infants will "catch up" in development by the time they reach their second birthday, delayed language development has pervasive and long-lasting effects. Language disorders are caused by damage to the nervous system or from general brain dysfunction. Cognitive or developmental impairments can result in a language delay or disorder, which puts children at continued risk for developmental delays, poor school performance, and poor social adaptation. Cusson further identified preterm infants as being less socially interactive and more difficult to engage. Mothers of preterm infants were found to have fewer synchronous interactions with their infants. "They work harder to engage their infants, play fewer games, and receive less gratification" (p. 405). She goes on to theorize that because maternal responsiveness is linked to infant development and especially language development, a decrease in maternal responsiveness is problematic since preterm infants are already at risk for developmental delay. Furthermore, infants who are known to have developmental delay are often also affected by impaired cognitive maturation and impaired social relationships. In her own study, Cusson found that language was delayed an average of 3-5 months. The factors that influenced language development were: length of hospital stay; birth weight; Apgar scores; infant irritability and state regulation at discharge; and, as previously mentioned, maternal sensitivity. There is much research focused on the long-term neurological impairments associated with preterm birth. While many studies have compared preterm children at various stages in development in an effort to determine where the most impact occurs and possible early prevention opportunities, there appears to be no easy way of predicting the success or long-term impairments of each preterm infant. Goldberg and DiVitto (1980) found that although a 26 week old infant weighing less than 1000 g may show no sign of developmental setbacks and may progress more quickly than full term babies, we may also see a preterm infant of more than 30 weeks gestation weighing more than 1300 g that may have considerable developmental disadvantages and over time, seems to be falling further behind in development instead of catching up. BEHAVIOR PROBLEMS Preterm infants, especially those of very low birth weight, have

been shown to have a higher incidence of behavioral disorders some of which include differences in emotional maturation, hyperactivity, motor control and ability to accomplish a task (Torrioli et al., 2000). Anderson and Doyle (2003) evaluated 298 VLBW infants with whom they did a follow-up study at age 8. Compared to controls, very preterm children scored significantly lower on full-scale IQ tests as well as verbal comprehension, perceptual organization, freedom from distractibility, and processing speed. The VLBW children also performed less well on reading, spelling, and arithmetic and displayed more attentional difficulties, internalizing behavioral problems, and immature adaptive skills than the normal birth weight controls. These infants also displayed more hyperactivity, somatic complaints, and atypical behavior as well as less developed social and leadership skills. Further behavioral studies indicate that young children acquire skills to cope with stressful situations and that behavioral differences in response to stressful or new situations have been linked to differences in social and cognitive development at later ages (Wocadlo &Rieger, 2000). In their study that re-evaluated non-cooperative preterm children, Wocadlo and Rieger found that the non-cooperative preterm infants demonstrated less autonomy and did not cope as well with stressful situations. They hypothesized that is perhaps due to environmental circumstances such as single parenthood or social disadvantage. Furthermore, parenting stress has been linked to poorer developmental scores as well. Preterm infants at a corrected age of 3-6 months have been rated by caregivers to be less adaptable, more intense, more negative in mood, less predictable, less persistent, and more passive than full term babies (Hughes, Shults, McGrath &Medoff-Cooper, 2002). The most significant variations occurred in regards to adaptability, which has been linked to hospitalization for more than 60 days, and persistence/attention span at 12 months. CASE STUDY As a method for integrating this paper with personal experience, I interviewed a friend who is raising the surviving twin of an extreme preterm birth. In order to respect the trauma and hardship that this family has faced, this family shall remain anonymous. This is their story. After struggling with endometriosis after the birth of her first child in 1999, this woman became pregnant via IVF in early 2001. She was aware early on that she was pregnant with fraternal twins, a girl and a boy. Her pregnancy had been normal until, at 22 weeks of pregnancy, she began spotting. She went immediately to the hospital whereupon she learned that she was dilated to 6 cm and one of the amniotic sacks was bulging. She was given terbutaline, was put on bed rest-lying upside down to alleviate any pressure on her cervix-and it was thought that she would deliver that night. She, as well as the babies, remained stable for two weeks until she had a major hemorrhage and became fully dilated. With a vaginal birth, her daughter was born at 24 weeks gestation, weighing 477 g (1 lb. 1 oz). The baby was breathing on her own immediately following the birth and was able to do so for the first 10 minutes of life. She received an Apgar score of 9; she was vigorous, had good muscle tone, good color, and was crying. It was suspected that there was significant stress during the pregnancy, perhaps due to several factors such as the age of the mother, the presence of twins, as well as her diagnosis of endometriosis. As a result, the baby was more advanced at the time of birth and resembled a baby of 28 weeks gestation rather than 24. In fact, the doctors felt that her demeanor was almost inappropriate for her age as they had never seen a 24-week-old baby do as well as her. The baby received cranial ultrasounds at days 3 and 7 and then every week thereafter. They found no brain lesions or other abnormalities. She demonstrated good kidney function and her lung capacity was good considering her gestational age. She had been intubated approximately 10 minutes after birth but her ventilator settings were kept very low. For the first month of life, the baby's parents were not able to hold her. They were able to have skin contact with her through the incubator and were encouraged to do so by the nurses. Overall, the family had very positive things to say about the doctors and nursing staff in regards to the way they were treated and the operation of the NICU. The doctors kept the family involved in all of the decisions and were very sensitive in their approach. The nurses talked to the infant prior to doing medical procedures and it was reported that one nurse often told her stories. Also, only the family was allowed inside the NICU and the environment was kept subdued to keep stimulation to a minimum. They used dim lighting and everyone was restricted to using a whisper when talking near the incubator. When the baby was old enough, volunteers would sign up to hold her

and rock her each day. Although still in critical condition, two months after her birth, the baby was successfully breathing on her own without support or additional supplements. She received physical therapy and was worked with vigorously to develop a feeding pattern (which, I was told, typically develops in the womb around 32 weeks gestation). It took one month to teach the baby to swallow and it was quite some time before she was able to take regular feedings without gagging. Also, because she was off the ventilators so quickly, the physical therapist made the baby a special doughnut-shaped pillow, which they used for positioning the baby's head so that she did not develop the characteristic "cone-shaped" head that occurs in preterm infants because of the restriction to side-to-side positioning. The family learned that by using the pillow the baby's head would thus develop a normal round shape, which would facilitate brain development. The young baby was released from the NICU after four months, weighing only 4 1⁄2 pounds. The family's true test began when they arrived home with their premature baby. The mother mentioned that nothing had prepared her for taking care of an extremely preterm infant. In the NICU and while first at home, the baby slept continuously. This shifted, however, once the baby reached birthing age and was finally "born". At this time, she cried 16 hours a day for the first year of her life. They were not prepared for the intensity of caring for a premature infant with an underdeveloped nervous system. Through California Children Services they were visited by an Occupational Therapist who was able to teach the parents how to, sometimes, soothe their infant. If nothing else, this person was able to validate the parents' feelings of exhaustion and helplessness. Furthermore, the baby had chronic colds, now believed to be caused by the RSV vaccine that she received once a month until she was 13-14 months old. When they stopped giving her the vaccine, her health improved and she began sleeping through the night. She has been sick only once since discontinuing the use of the vaccine. Although blindness is often a risk for premature infants, so far, her eyesight is perfect. She also continues to show no noticeable brain abnormalities and appears to have appropriate brain development based upon her corrected age. Her development is delayed based upon the Bailey exam. She is currently 26 months old and functions as a 16 month old. She is walking independently and is beginning to talk. In regards to the second fetus, following her daughter's birth, the placenta and umbilical cord were left intact and the mother received a cerclage in hopes of holding the pregnancy until at least 32 weeks. Two weeks after the birth of the first child, at 26 weeks, her placenta ruptured and she was forced to have an emergency C-section. Her baby boy's lungs were not fully developed and he lived for only 8 hours. EVALUATION Based on the literature reviewed and the suggested outcomes for an infant born at 24 weeks, this young girl has surprisingly encountered minimal difficulties. Her success could be due to many variables. First of all, the sensitivity of the nursing staff and doctors was tremendously important. It is also possible that she received exceptional care in comparison to other infants in the NICU because of her special circumstances. She was the smallest baby that has been born at this particular hospital and it was indicated that the length of her stay was considerably longer than other infants in the NICU at that time. Also, several aspects of the family were extremely significant. The mother of the child has worked previously as a nurse in the pediatric intensive care and therefore has extensive knowledge and understanding of her daughter's condition. She currently works as a public health nurse where she works with families in low-income or stressful situations similar to her own experience. For her clients, she helps them establish occupational and physical therapy for their infants and helps connect them with the resources they need to deal with their particular parenting challenges. The father is an occupational therapist who works with developmentally disabled children. Based on their professional backgrounds, the parents knew to begin their daughter in occupational therapy immediately; in this case, one week after her discharge. Another important factor is that they were fortunate to be able to hire a nanny to help with the care of the baby. In the beginning, they had a caretaker from 8pm to 8am five nights a week and then moved to having a caretaker during the day for the baby's first two years of life. Because of the baby's excessive crying tendency toward overarousal, this would be a tremendous asset to the family. The strength of the parent's relationship was also important. The mother shared that losing one child and the extreme stress of caring for their extremely preterm infant was very challenging to their marriage. However,

because of the depth of their relationship and their willingness to do intensive grief counseling, their relationship has remained strong despite their many challenges. Furthermore, the family has an extensive external support network. Finally, the sheer determination of this young child to live cannot be overlooked. Her family was adamant that no heroic measures were used to keep her alive and it's an amazing test to her will and the skill of those who worked with her in the early months of her life that she is still here with us today. Despite her apparent success thus far in development, one cannot underestimate the trauma that she has endured. She is truly an inspiration. SUMMARY The research presented here has shown the difficulty of predicting the success of individual preterm infants. There are many variables that influence brain, neurological, and behavioral development. Some of these include maternal sensitivity, economic status of the family, length of hospital stay, gestational age, and birth weight. Overall, the studies demonstrate that even when severe handicaps are not present, the infant is at risk for minor brain abnormalities that often produce cognitive deficits that influence IQ and school performance. The studies also indicate that minor neurological impairments were often present in adolescence despite normal evaluations during infancy. Preterm children were found to have impaired visual and spatial skills, reading disabilities, delayed language, as well as other difficulties. The review of literature also showed that behavioral development was also affected by preterm birth. Studies showed that preterm children are often more intense, they tend to have delayed emotional maturation, and may have difficulties coping with stress. Overall, further long-term research is needed that can follow the development of preterm babies throughout a significant portion of their development to track when the most significant impairments tend to occur. Due to the range of risks associated with preterm births, it is imperative to continue to examine the different sociological variables that compound the risks of preterm infants. Finally, although this review did not touch on the stress of the parents caring for premature infants, based upon the case study presented, the need to create or strengthen programs within the hospital and community to transition the parents into the role of caring for their infant with special needs in the home seems imperative. References REFERENCES Ajayi-Obe, M., Saeed, N., Cowan, P.M., Rutherford, M.A., &Edwards, A.D. (2000). Reduced development of cerebral cortex in extremely preterm infants. The Lancet, 356(9236), 1162-1165. Anderson, P. &Doyle, L. (2003). Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. The Journal of the American Medical Association, 289, 3264-3272. Bernasko, J., Lynch, L., Lapinski, R., &Berkowitz, R. (1997). Twin pregnancies conceived by assisted reproductive techniques: maternal and neonatal outcomes. Obstetrics &Gynecology, 89(3), 368-372. Bryan, E. (2003). The impact of multiple preterm births on the family. BJOG: an International Journal of Obstetrics and Gynaecology, 110(Suppl. 20), 24-28. Cusson, R. (2003). Factors influencing language development in preterm infants. JOGNN, 32(3), 402-409. Goldberg, S. &DiVitto, B. (1983). Born too soon. San Francisco: W.H. Freeman and Company. Grasby, D.O., Esterman, A., &Marshall, P. (2003). Ultrasound grading of cerebral ventricular dilatation in preterm neonates. Journal of Paediatrics and Child Health, 39, 186-190. Hack, M., Flannery, D., Schluchter, M., Cartar, L., Borawski, E., &Klein, N. (2002). Outcomes in young adulthood for very-low-birth-weight infants. The New England Journal of Medicine, 346(3), 149-157. Hughes, M., Shults, J., McGrath, J. &Medoff-Cooper, B. (2002). Temperament characteristics of premature infants in the first year of life. Journal of Developmental and Behavioral Pediatrics, 23(6), 430-435. Mouradian, L., Als, H., &Coster, W. (2000). Neurobehavioral functioning of healthy preterm infants of varying gestational ages. Journal of Developmental and Behavioral Pediatrics, 21(6), 408-416. Olivennes, F., Kadhel, P., Rufat, P., Fanchin, R., Fernandez, H., &Frydman, R. (1996). Perinatal outcome of twin pregnancies obtained after in vitro fertilization: comparison with twin pregnancies obtained spontaneously or after ovarian stimulation. Assisted Reproductive Technology, 66(1), 105-109. Peterson, B., Anderson, A., Ehrenkranz, R., Staib, L., Tageldin, M., Colson, E., Gore, J., Duncan, C., Makuch, R., &Ment, L. (2003). Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics, 111(5), 939-948. Peterson, B., Vohr, B., Staib, L., Cannistraci, C., Dolberg, A., Schneider, K., Katz, K., Westerveld, M., Sparrow, S., Anderson, A., Duncan, C., Makuch, R., Gore, J., &Ment, L. (2000).

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