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REVIEW

Extremely Preterm Birth Outcome: A Review of Four Decades of Cognitive Research

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Abstract Premature birth incidence and survival rates are increasing steadily due to advances in obstetric and neonatal intensive care. Those born at the limits of viability are highly at-risk of adverse neurocognitive function over their lifespan, leading to current controversy regarding aggressive resuscitation efforts for these extremely preterm children. However, data from earlier generation cohorts who were born in substantially different eras of neonatal intensive care cannot be relied on to predict outcome of today's newborn. Our review by the crucial variable of birth cohort year shows a changing developmental trajectory in which today's extremely preterm survivor is likely to have fewer severe medical complications, better neurological outcomes, and fewer adverse cognitive late effects. Such data further underscore the importance of concurrently considering medical, familial, socioenvironmental, and neurobiological factors in combination with individual neonatal intensive care center protocols when studying outcomes of the preterm child. This complex, interrelated range of factors directly affects the immature, rapidly developing premature brain. However, ongoing surveillance to detect subsequent delay or impairment and to apply interventional strategies early in the developmental course holds promise for further enhancement of functional outcome.

Keywords Extremely preterm birth · Cognitive function · Extremely low birth weight · Neurocognition · Neuropsychological tests · Neurodevelopmental outcome · Neurological outcome

Introduction

Steadily rising premature birth rates signify an escalating pediatric public health problem (Ashton et al. 2009). Survivors of early birth incur immediate medical morbidities as well as long-term neuromotor, neurocognitive, and behavioral impairments (Tyson and Saigal 2005). Adverse effects have been found across the preterm spectrum, from extremely preterm (<28 weeks gestation) to late-preterm (34–36 weeks) birth (Engle et al. 2007). Although moderate to severe impairments are well-documented following extremely preterm birth (Aarnoudse-Moens et al. 2009), even late-preterm birth may result in subtle and specific neurocognitive deficits (Baron et al. 2009b). Neonates born weighing <750 g or at <26 weeks, i.e., micropremature (MacDonald 2002), represent a rapidly increasing extremely preterm subpopulation at risk of high mortality and morbidity rates, and lifespan impairments (American College of Obstetricians and Gynecologists 2002). Therefore, aggres-

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sive delivery resuscitation efforts have not been universally endorsed for these earliest born neonates, although consensus has been reached to support intensive care for those born ≥26 weeks (Vavasseur et al. 2007).

Cohort birth year is a crucial variable to be considered when evaluating the literature since substantially different intensive care medical management was applied across different neonatal care eras. The course and subsequent outcome of extremely preterm neonates born since 2000 appears to be changing relative to earlier generation cohorts. Although data continue to be published regarding cohorts born and cared for in earlier decades, these data do not usefully guide resuscitation and treatment recommendations for today's neonate, or aid counseling of today's new parents regarding their child's future. Reports of fewer severe medical complications, better neurological outcomes, and less adverse cognitive late effects suggest a more optimistic prognosis is warranted for the neonate born today (Fawke 2007; Lorenz et al. 1998; Stjernqvist and Svenningsen 1993). Outcomes for the extremely preterm population, and whether they are changing, may be best appreciated by a review of studies published over the decades since inception of neonatal intensive care in the 1970s. Thus, the goals of this review are to: 1) provide a brief clinical context for discussion of extremely preterm birth, including basic terminology, incidence rates, and risk factors; 2) review effects of extreme prematurity on the immature but rapidly developing brain; 3) summarize reports of cognitive and neuropsychological outcome following extremely preterm birth by cohort birth year, extracting data on those born <26 weeks whenever possible; and, 4) describe intervention strategies that have begun to be applied to this at-risk population, concluding with suggestions for future directions. MEDLINE and PubMed were used to search the English literature for studies published since 1970 reporting on both mortality and disability in extremely preterm infants, i.e., those born <28 weeks gestational age or with a birth weight <1,000 g. Reference lists from literature retrieved were used to identify additional articles.

Preterm Birth Terminology, Incidence, and Risk Factors

Terminology

After a long history of inconsistent prematurity definitions (Lorenz et al. 1998), standard birth weight and gestational age designations now ensure classification uniformity (Engle 2004). Table 1 lists terms and definitions in standard usage. Although some report birth weight to be a reliable predictor of neonatal course and outcome (Cole et al. 2002), and others gestational age (Cooke 2005; Foster-Cohen et al. 2007; Saigal and Doyle 2008), neither birth weight or gestational age alone has been a sufficient predictor of outcome (Tyson et al. 2008). A complex array of medical and non-medical risk factors contributes to eventual function. Multifactorial methods may best aid identification of the most predictive factors, and more sophisticated decision parameters are needed (Tyson et al. 2008). Nevertheless, a clear inverse relationship exists between birth weight or gestational age and impairment, with greater disability incidence found with lower birth weight or earlier gestational age (Bhutta et al. 2002). Each additional week of gestational age or gram birth weight decreases the likelihood of impairment (Synnes et al. 1994) and improves functional outcome (MacDonald 2002), including of cognition (Fily et al. 2006; Piecuch et al. 1997).

Table 1 Preterm categories with corresponding birth weight and/or gestational age

	Birth weight	Gestational age
Postmature Birth		≥43 wks
Term Birth	≥2500 g	37–42 wks
Late-preterm Birth		34–36 wks
Low Birth Weight	<2500 g	
Low Gestational Age		<37 wks
Very Low Birth Weight	<1500 g	
Very Low Gestational Age		<32 wks
Extremely Low Birth Weight	<1000 g	
Extremely Low Gestational Age		<28 wks
Micropremature	<750 g	<26 wks

The neonate's size according to standardized age and growth curves is referred to as "appropriate for gestational age" (25–75th percentile) or "small for gestational age" (<10th percentile). The latter term has been used interchangeably with intrauterine growth delay and intrauterine growth retardation or restriction (Kok et al. 1998).

To account for ex-utero neurodevelopmental immaturity, preterm infants are routinely accorded a "corrected age", i.e., chronological age minus the number of weeks born before full-term (40 weeks) (Engle 2004). In clinical practice, age correction has generally been made only until around 24 to 30 chronological months based on older data. However, survival at current lower viability limits is associated with more immature brain development than for survivable birth in past decades. Therefore, researchers tend to endorse use of age correction further along the developmental spectrum (Anderson and Doyle 2003; Raz et al. 2009). Empirical evidence remains lacking for when age correction is no longer necessary.

Preterm Birth Incidence

There has been a 21% increase in rates of low birth weight incidence since 1980, and of birth <37 weeks since 1990 (Hamilton et al. 2006; Martin et al. 2008). Until the latest (2008) report indicating a 12.3% incidence of preterm birth, rates had risen to 12.8% in the United States. Of the most recent statistics for U.S. livebirths, 8.3% were at low BW, approximately 1% at <1,000 g, 0.3–0.4% at <750 g, and .002% at 24–25 weeks (Hamilton et al. 2009; Martin et al. 2005; Martin et al. 2008; Ment et al. 2006; Vavasseur et al. 2007). Ethnicity/racial group differences include that births <33 weeks and <1,500 g for African/African-American women are double those of other groups (Behrman and Butler 2007).

Medical Risk Factors

Although pregnancy complications may emerge early in gestation, preterm birth is often the unexpected consequence of sudden maternal or fetal distress. Modern obstetric practices and in-hospital prenatal care for at-risk pregnancies have improved newborn overall health and survival (Skrablin et al. 2002), but not all at-risk pregnant women have access to those factors that significantly reduce complications, such as prenatal care, antenatal corticosteroids, or hospitalization in a tertiary care facility with in-house neonatal specialists (O'Shea 2008). The combination of antenatal and postnatal factors that contributes most to optimal outcome remains to be determined.

Severity rates have lessened for several common adverse effects related to extremely preterm birth. A significant turning point was the introduction of surfactant in the mid-1980s, which improved neonatal lung function, decreased the incidence of disabling conditions, and greatly enhanced survival rates of those born ≤26 weeks (Ferrara et al. 1994; The Victorian Infant Collaborative Study Group 1997). Antenatal corticosteroids, prophylactic infection control, and better modes of ventilation were also introduced. Additionally, nutritional supplements while in intensive care have had a significant effect on early neurodevelopment and growth (Ehrenkranz et al. 2006). Medical care in the first hours of life appears especially critical, and attempts to develop indices that are predictive continue. For example, standardized illness severity scores assessing physiologic instability in the first 12 postnatal hours provided risk information regarding brain damage and neurodevelopmental dysfunction (Dammann et al. 2009). Length of hospital stay is another indicator of neonatal course severity, related to such common perinatal risk factors as bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, patent ductus arteriosus, retinopathy of prematurity, and neurological complications. As a consequence of many treatment and procedural advances, rates of cerebral palsy, hydrocephalus, deafness, blindness, seizures, and mental retardation have declined, but adverse late effects still occur at unacceptably high rates in those currently born (Lorenz et al. 1998). Along with these advances, assessment of brain lesion presence and severity has been enabled by routine imaging surveillance with head ultrasonography and increasingly sophisticated neuroimaging techniques (Flodmark and Barkovich 2002; Papile et al. 1978; Volpe 2008). Magnetic resonance imaging at term equivalent, though insensitive to subtle microstructure abnormalities, was found to predict neurodevelopmental outcome (Woodward et al. 2006). Even preterm children at low risk for neurodevelopmental deficits (born at 30–34 weeks gestation) had decreased regional cortical gray matter unilaterally at age 9 in the parietal lobe and bilaterally in the temporal lobe (especially of the middle temporal gyrus), which correlated strongly with intelligence score and smaller white matter volumes (Soria-Pastor et al. 2009)

Familial, Socioenvironmental, and Neurobiological Risk Factors

Familial factors such as parental literacy, educational achievement, occupation, socioeconomic status, maternal substance use, ethnicity/culture, family adversity, and parental/caregiver attitudes influence preterm birth outcomes (Collaborative Group on Antenatal Steroid Therapy 1984; Fily et al. 2006; Landry et al. 2006; Laptook et al. 2005; Stjernqvist 1992; Vohr et al. 2003a; Washington and Craig 1992). Maternal education is an especially strong predictor (Breslau et al. 2004; Kesler et al. 2004). Relatedly, a relatively homogenous population of 1996–1997 extremely low birth weight (ELBW; <1,000 g) infants that benefited from maternal prenatal health care in Finland had 11% intraventricular hemorrhage incidence (Mikkola et al. 2005), contrasting with 32% intraventricular hemorrhage incidence for a heterogeneous United States population born <25 weeks and <751 g between 1993 and 1999, that included those disadvantaged by low maternal education, poor prenatal care, and low socioeconomic status (Shankaran et al. 2004). While it remains unclear which combination of factors will best predict good cognitive outcome (McCormick et al. 2006; Msall 2005), later learning difficulties were found to be predicted better by socioenvironmental than perinatal medical risk factors (Aylward et al. 1989; Teplin et al. 1991), cognitive development was better predicted by early environmental factors than genetic factors (Koeppen-Schomerus et al. 2000), and higher socioeconomic status was advantageous (Kilbride et al. 2004).

Negative socioenvironmental risk factors include multiple gestation, which also lowers survival odds, and adverse

social conditions (Kesler et al. 2008; Castro et al. 2004; Marlow et al. 2005). The latter has been associated with poorer behavioral, attentional, and adaptive functioning (Chapieski and Evankovich 1997), and effects may be identified early (Delobel-Ayoub et al. 2006).

Male gender is a significant risk factor for brain maturational and neurobehavioral dysfunction (Brothwood et al. 1986; Fily et al. 2006; Hille et al. 1994; Kesler et al. 2008; Tyson et al. 2008; Vohr et al. 2003b). Imaging studies support these findings. Preterm children had smaller gray and white matter cerebral volumes than all controls, and white matter volumes were not significantly different between preterm and term females. However, preterm males were especially vulnerable to adverse effects on white matter development compared with term males (Reiss et al. 2004), and preterm males had greater hippocampal volume reduction than controls (Lodygensky et al. 2005). Furthermore, higher female than male representation in a majority of clinical studies likely reflects higher female survival rates or less attrition in female cohorts.

Neonatal Intensive Care Unit Factors

Neonatal intensive care unit factors have been understudied but account for significant variance across preterm studies (Vohr et al. 2004). Disparities in neonatal intensive care unit complication rates, survival rates, and long-term outcome are affected by preferred delivery method, inborn-outborn proportion (outborns disadvantaged by transport time), care level (tertiary or less specialized), preterm patient volume, and neonatal specialist staffing patterns (Bartels et al. 2005; Doyle 2004; Hakansson et al. 2004; Hoekstra et al. 2004; International Neonatal Network 2000; Tommiska et al. 2007). Medical complication rates vary greatly across neonatal intensive care units, including for crucial complications of intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, and retinopathy of prematurity (Daniel et al. 2003; McCormick 1994; Msall et al. 2004). Improvements to the neonatal intensive care environment that have had a positive effect on acute care and eventual outcome continue to be introduced, such as waterbeds, dimmed light, reduced sound levels, and private rooms (Gross et al. 2005; Jobe 2004; Maayan-Metzger et al. 2002), but are not uniformly similar across neonatal intensive care units. Furthermore, while parent satisfaction about the child's adaptive and behavioral function is measurable (Hille et al. 2001; Szatmari et al. 1990), physician attitude is not easily quantified despite its importance in determining the care provided to borderline viable infants (see Hakansson et al. 2004 for North and South Sweden care practices and outcome differences). Overall, an institution's outcome statistics require cautious interpretation based on care practices. For example, survival rates and outcomes of a neonatal intensive care unit that aggressively resuscitates a high volume of medically severe neonates is not easily compared with those of a neonatal intensive care unit that provides less aggressive care for infants born <26 weeks or <750 g, whose survival rates and outcomes may be inflated because their survivors were born at later gestational age or with heavier birth weight.

Unintended negative consequences may result when neurodevelopmental risk is weighed against medical gain (O'Shea et al. 2007). For example, systemic corticosteroid use introduced to reduce prematurity associated complications remains controversial. In an animal study, cholinergic neurons were more vulnerable to later learning challenges after prenatal dexamethasone treatment (Emgard et al. 2006), and in human studies, postnatal corticosteroid use was associated with poor early growth and negative cognitive effects (Wood et al. 2003). Studies caution about potential negative psychological effects detectable by the preschool years (Barrington 2001; Short et al. 2003; Yeh et al. 2004), although not all agree (Gross et al. 2005; Lodygensky et al. 2005; Meyer-Bahlburg et al. 2004; Trautman et al. 1995; Wilson et al. 2006). Conclusions based on preschool performance parameters need further longitudinal studies that extend outcome measurement further along the maturational course, consider the broad range of risk factors inherent to this population, and examine rate of maturational development to resolve these concerns.

In summary, the range and complexity of risk factors affecting neuropsychological outcome in extremely preterm children confounds attempts to interpret this large literature consisting of diverse cohort demographic and medical characteristics. In addition to medical, developmental, and psychosocial variables, differences in neonatal intensive care unit practices and environment appear to have a substantial impact on later outcome.

Effects of Prematurity on the Developmentally Immature Central Nervous System

Neurological status and stage along the brain developmental continuum are important risk factors (Jenkins et al. 2009). A full-term infant brain is very different from the maturation-dependent preterm brain whose growth has been interrupted at a critical neurodevelopmental stage. There are both general and specific consequences of the impact of preterm birth on brain development that may affect psychological function over the lifespan. Multiple immature body systems are present in a preterm child, but central nervous system (CNS) in-utero and ex-utero effects are especially predictive of later neurocognitive

impairment (Patra et al. 2006; Piecuch et al. 1997; Selzer et al. 1992).

In-utero Effects

Prevalent in-utero cortical and neuronal effects include disproportionately enlarged frontal and parietal gray matter volumes, and smaller temporal and subcortical region volumes (Kesler et al. 2004; Kesler et al. 2006) related to enhanced apoptosis or excitotoxic damage of susceptible immature neurons (Bhutta and Anand 2001; Edgin et al. 2008). A higher likelihood of brain and lateral ventricular volume alterations has been associated with supratentorial lesions, including of sensorimotor and parieto-occipital regions (Peterson et al. 2003). Abnormalities also involve the hippocampus (Gimenez et al. 2004; Gimenez et al. 2008; Isaacs et al. 2000; Thompson et al. 2008), and cerebellum, including hemorrhagic cerebellar injury (Limperopoulos et al. 2005) and abnormal cerebellar growth (Allin et al. 2001). Immature cerebrovascular systems compromise cerebral blood flow autoregulation, supply, and perfusion, including to cerebral white matter (Volpe 2008). This leaves the developing brain vulnerable to hypoxic ischemic injury and white matter progenitor cell damage, as well as gray matter maldevelopment (Allin et al. 2004; Back et al. 2007; Khwaja and Volpe 2008). Hypoxic ischemic injury involves metabolic cascades in response to ischemia and reperfusion, contributing to oligodendrocyte progenitor cell (myelin precursor) damage due to these cells' heightened vulnerability to oxidative stress early in development (Ferriero 2004; Volpe 2008). Additionally, immature astrocytes appear vulnerable to injury at early stages in development, which further compromises white matter development related to hypoxic ischemia (Sen and Levison 2006). Disturbances of axonal maturation and cell-to-cell interaction secondary to diffuse periventricular white matter damage (Barrett et al. 2007; Volpe 2005) have the additional effect of resulting in smaller thalamic and lentiform nucleus volumes (Gimenez et al. 2006; Srinivasan et al. 2007). The consequences of diffuse white matter degradation also involve cortical, basal ganglia, and cerebellar abnormalities (Counsell et al. 2003; Kesler et al. 2006). Notably, white matter injury appears to be the most common brain abnormality in preterm infants, and a major predictor of smaller volumes along with gestational age (Martinussen et al. 2009).

Another in-utero complication that may lead to preterm birth is intrauterine infection. e.g., chorioamnionitis or maternal infection. Cytokines and their receptors, found in central nervous system cells, are important for brain development and function. They influence inflammatory response as well as neuron and glial cell development. Elevated levels of proinflammatory cytokines in amniotic fluid, cord blood, or neonatal blood indicate the presence of a systemic fetal inflammatory response. A persistent neuroinflammatory response may result when the inflammation signal is transmitted across the blood-brain barrier (Malaeb and Dammann 2009). This has been associated with intraventricular hemorrhage, white matter damage, and cerebral palsy (Tauscher et al. 2003; Yoon et al. 1997). When associated with hypoxic events, cytokines negatively affect functional outcome such as of early psychomotor development (Hansen-Pupp et al. 2008). High concentrations of such specific cytokines as interleukin-1-beta, interleukin-6, and interleukin-8 have been associated with abnormal neurodevelopment at 6 months, 12-months, and 30 months of age (Bartha et al. 2004; Okazaki et al. 2006; Rezaie and Dean 2002).

Brain development proceeds according to a complex plan that unfolds in response to intrinsic and extrinsic factors, and the timing of events is critical (Stiles 2008). The second half of gestation is an active period of cell migration, neuronal differentiation, synapse formation, and glial cell proliferation (de Graaf-Peters and Hadders-Algra 2006). Oligodendrocyte progenitor cells in the periventricular white matter and microglia are in activated stages of development during this period and are more vulnerable to injury (Volpe 2008). Similarly, neurotransmitters and neuromodulatory substances affect development in different ways at different stages in brain development; gamma-aminobutyric acid, an inhibitory neurotransmitter, has an excitatory role until the last trimester and glutamate receptors are over-expressed in regions of the developing brain susceptible to injury. Consequently, mechanisms and effects of neurological insults differ between preterm and term infants (Back 2006; Dyet et al. 2006; Ferriero 2004; McQuillen and Ferriero 2004; Okereafor et al. 2008). For example, while severe hypoxic ischemia preferentially damages deep gray matter in preterm and term neonates, perirolandic involvement is more frequent in term neonates. Less profound insult tends to result in intraventricular hemorrhage and periventricular white matter injury in preterm neonates while term neonates have a greater likelihood of parasagittal watershed territory infarcts (Huang and Castillo 2008).

Ex-utero Effects

Preterm birth perturbs the trajectory of cerebral development into adolescence, with preterm children showing both less gray matter reduction and less white matter gain over time compared with term controls, and relative sparing of the perirolandic cortex and structures supplied by the posterior circulation (Ment et al. 2009). Abnormalities in perirolandic gyri magnetic resonance signal intensity may indicate degree of myelination and development of nerve

cells, and be a marker of degree of brain maturation (Korogi et al. 1996). Although conventional imaging findings may be subtle or absent in the acute stage in neonates (Huang and Castillo 2008), the effects of severe hypoxic ischemia are apparent in deep gray matter nuclei, cortices, hippocampi, and cerebellum when these infants reach later childhood and adulthood. Ex-utero neonatal neurological complications include hypoxic ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, periventricular hemorrhagic infarction, ventriculomegaly, and white matter dysgenesis (Papile et al. 1978; Volpe 2008); their prevalence inversely related to gestational age (Hamrick et al. 2004). Of these, severe intraventricular hemorrhage and periventricular leukomalacia have been strongly associated with neurodevelopmental impairment (Laptook et al. 2005; Sherlock et al. 2005). Severe intraventricular hemorrhage occurs in approximately 25% of very low birth weight infants (Inder and Volpe 2000), and 0.3–0.4% of those born with extremely low birth weight (Hack et al. 2000a; Martin et al. 2005), and leads to smaller subcortical gray matter volumes (Kesler et al. 2004). Periventricular leukomalacia occurs in 5–15% of very low birth weight infants. When severe, periventricular cystic lesions develop, often in occipital and frontoparietal white matter (Flodmark and Barkovich 2002). Although the incidence of severe insult has declined consequent to the many medical advances, poor outcomes still may result after lower grade insults (Patra et al. 2006). Intraventricular hemorrhage and periventricular leukomalacia have been good predictors of cerebral palsy, other neurological complications, and neurobehavioral dysfunction (Dammann and Leviton 2006; Inder and Volpe 2000; Stjernqvist and Svenningsen 1990). For example, an increased incidence of cerebral palsy, hearing impairment, maladaptive daily living skills, and cognitive deficit for 600–1,250 g survivors with intraventricular hemorrhage at age 8 years contrasted with intact neurological, intellectual, and educational outcomes in 92–94% of those who had no intraventricular hemorrhage (Vohr et al. 2003b).

Such extensive cortical and subcortical regional dysmorphologies and volumetric changes negatively affect neurocognition long-term (Martinussen et al. 2009; Nosarti et al. 2002; Peterson et al. 2000). This is exemplified by report of executive, visuospatial, and language dysfunction in adolescents with smaller lateral cerebellar and white matter volumes (Allin et al. 2005), and language dysfunction in association with posterior corpus callosum thinning (Nosarti et al. 2004). Furthermore, areas of smaller white and gray matter volume mediated these cognitive impairments (Nosarti et al. 2008). The finding of white matter loss in the centrum semiovale and posterior periventricular regions in preterm adolescents is intriguing as a potential explanation for the frequently observed effects on processing speed and nonverbal/spatial function (Soria-Pastor et al. 2008). Additionally, preterm adolescents with low birth weight had both smaller total brain size and smaller specific brain volumes, particularly of the thalamus and cerebellar white matter (Martinussen et al. 2009). More optimal neurodevelopmental and neuropsychological outcomes have been reported in recent cohorts when neonatal neurological complications were mild or absent (Ahronovich et al. 2007; Baron et al. 2009a; Edgin et al. 2008; Wilson-Costello et al. 2007).

Neurocognitive Outcome by Birth Year

The profound cognitive morbidities of extremely preterm and micropremature birth have been documented across international studies (Hack and Fanaroff 1999; Marlow et al. 2005; Shankaran et al. 2004; Vanhaesebrouck et al. 2004; Wood et al. 2000). Yet, prediction of clinical course on an individual basis has been limited. Reports of unexpected intact outcome in individual children born <500 g (Coccia et al. 1992; Gidley Larson et al. 2010), as well as well-documented highly variable neurocognitive competence across cohorts with similar medical characteristics, underscore how difficult it is to predict outcome reliably. Cohort studies have been relied on but cross-center methodological and demographic differences make it difficult to generalize findings. Moreover, cohort selection bias effects may overestimate adverse cognitive outcomes, as data may be obtained principally for children whose parents have concerns about their child's development and are thus more likely to continue to participate in follow-up care and assessments (Castro et al. 2004).

Studies that reported cognitive outcomes of extremely preterm children are listed in Table 2, along with summary findings. Table 2 presents a summary of data extracted from studies of extremely preterm cohorts born from 1977 to 2005. Studies are listed chronologically by cohort birth year, with number of subjects, country, age at testing, and inclusion birth weight or gestational age indicated. Studies employed various cognitive metrics to evaluate cognitive function; these findings are summarized under "Cognitive Outcome", followed by some additional reported outcomes. Individual studies provide more detailed information regarding outcomes. Outcomes by decade are summarized below for the broad patterns that were found.

Pre-1980 Births: The Pre-surfactant Era

Preterm birth before 1980 occurred in an era of exceptionally high mortality rates. It was not until 1986 that pulmonary surfactant was introduced, a substance that improves neonatal lung function, reduces the incidence of severely disabling conditions, and improves survival

Table 2 Extremely preterm and micropremature birth cognitive outcomes by cohort birth year

	Birth year	N/Country	Age at study	GA/BW	Cognitive measures	Cognitive outcome	Other findings
(Saigal et al. 2000)	1977–1982	40/Canada	12–16 years	501–1000 g	WISC-R	52.5% IQ <84	WRAT-R Reading=79
					WRAT-R	22.5% IQ <70	WRAT-R Spelling=77
						<750 g IQ=86	WRAT-R Arithmetic=70
(Riley et al. 2008)	1981–2000	159/UK	1 year	22-25 wks	Griffiths	Mean DQ:	
		1981–1985 (n=25)				1981–1985: 105	
		1986–1990 (n=36)				1986–1990: 106.1	
		1991–1995 (n=40)				1991–1995: 103.9	
		1996–2000 (n=58)				1996–2000: 94.9* (*Griffiths revision)	
(Hack et al., 1994)	1982–1986	68/USA	6 years	25.7 wks	KABC	21% MPC <70	9% CP
				<750 g	VMI		25% severe visual ↓
					VABS		27% academic ↓
					CBCL		37% behavioral ↓
					WJ		
					NP+		
(Taylor et al. 1998)	1982–1986	68/USA	5–9 years	<750 g	CBCL, TRF		48% attention ↓
					CNT, MTA		
					UND, SSRS		
					WJ, VABS		
(Taylor et al. 2000)	1982–1986	60/USA	11 years	25.7 wks <1000 g	KABC	Mean MPC=83.5	23% behavioral ↓
						37% MPC <70	
(Taylor et al. 2004)	1982–1986	48/USA	16 years	<750 g	WISC - III	33% IQ <70 or	IQ >70 group: visuomotor,
					WAIS - III	↓neurosensory	memory, executive ↓
					CANTAB		
					NP+		
(Hille et al., 2007)	1983	24/Netherlands	19 years	25–26 wks	Computer IQ		16.7% moderate/severe cognitive and neurosensory↓
					Neurosensory		35.7% moderate/severe activities and participation↓
					Neuromotor		39.9% moderate/severe ↓ in overall outcome
(Synnes et al. 1994)	1983–1989	129/Canada	18 months	23–25 wks	Bayley	15.5% MDI <70	34% CP
							36% ↓
							18% sensorineural ↓
(Kilbride et al. 2004)	1983–1990	25/USA	3 years	<801 g	S-B-4	Mean IQ=85	PPVT=83
			5 years		WRAT	48% IQ <84	PMQ=79;
					Language	44% IQ 68–83	75% <84
					Motor		At age 5:
							Reading=81
							Spelling=69
							Arithmetic=74
							(Severe sensorimotor, CP, IQ <68 excluded)
(Emsley et al. 1998)	1984–1994	66/United Kingdom	19 months -10 years	23–25 wks	Griffiths	14% DQ <70	19% CP
				725 g			17% speech delay
							5% clumsy, learning, behavioral ↓

							56% disability (28% mild, 16% moderate, 13% severe)
(Stjernqvist and Svenningsen 1999)	1985–1986	61/Sweden	10 years	<29 wks	WISC-III	Mean IQ=94	6% CP
					VMI		8% major neurological handicap
					CBCL		32% behavior problems
							20% ADHD
							VMI=93
(Bowen et al. 2002)	1985–1990	82/Australia	8 years	<28 wks or <1000 g	SB-IV	74%≥85	
(Hoekstra et al. 2004)	1986–1990	147/USA	8 years	23–26 wks	CBCL		62% normal
				<1000 g	TRF		23 wks>severe than 24–26 wks
					Neuro exam		23 wks: 33% normal
							24 wks: 55% normal
							25 wks: 67% normal
							26 wks: 65% normal
(Farooqi et al. 2007)	1990–1992	86/Sweden	11 years	23–25 wks	CBCL		>internalizing symptoms, attention, social, thought problems than controls
					TRF		85% no major adjustment problems
					Self-report		
(Piecuch et al., 1997)	1990–1994	86/USA	12 months – 4.5 years	24 wks	Bayley	24 wks	24 wks
				668 g	S-B	28% WNL	11% CP
					McCarthy		28% nondisabled
				25 wks		25 wks	25 wks
				790 g		47% WNL	20% CP
							47% nondisabled
				26 wks		26 wks	26 wks
				842 g		71% WNL	11% CP
							63% nondisabled
(Agustines et al. 2000)	1990–1995	28/USA	30 months	24–25 wks	Bayley	24 wks 11% MDI≥85	
						34% MDI 84–71	
						33% MDI≤70	
						34% normal PDI	
						25 wks	
						50% MDI≥85	
						25% MDI 84–71	
						25% MDI≤70	
						50% normal PDI	
(Conom et al. 2006)	1990–2002	239/USA	24 months	22–27 wks<1000 g	Bayley I & II	22% MDI & PDI >84 41% MDI >84	
						72% MDI >69	
						10% MDI & PDI <50	
(Anderson and Doyle 2004)	1991–1992	298/Australia	8 years	<26 wks (n=73)	WISC-III		14% CP
				<750 g (n=54)	ROCFT BRIEF Tower of London		<750 g <750–999 g for EF: spatial conceptualizati on, visual reasoning, spatial organization;

Table 2 (continued)

	Birth year	N/Country	Age at study	GA/BW	Cognitive measures	Cognitive outcome	Other findings
							23–25 wks compared to 26–27 wks: poorer spatial conceptualization
(Hack et al. 1996)	1990–1992	114/USA	20 months	500–750 g	Bayley	20% MDI <70	10% CP
(Bohin et al. 1999)	1991–1993	55/Unitd Kingdom	18–24 months	23–25 wks	Griffiths		54.5% "entirely normal"
							12% chance normal survival to 2 years if <26 weeks
(Taylor et al. 2006)++	1992–1995	219/USA	8 years	26.4 wks<1000 g	KABC	35% MPC ↓	42% NEPSY ↓
					NEPSY		44% motor ↓
					W-J		28–33% W-J ↓
					VABS Motor		38–48% adaptive/socialization ↓
(Sutton and Bajuk 1999)	1992–1993	239/Australia	12 months	23–27 wks	Griffiths	11% major intellectual ↓	
(Neubauer et al. 2008)	1993–1998	135/Germany	4–6 years	<1000 g	KABC	43% normal	9% CP
			10 years		WISC (German)	39% mild ↓ 18% major ↓	15% IQ <70
(Shankaran et al., 2004)	1993–1999	246/USA	18–22 months	22–24 wks <751 g	Bayley-II	33% MDI >84 41% MDI >84	30% CP
						46% MDI <70	
						36% PDI <70	
(Hintz et al. 2005)	1993–1996 1996–1999	366/USA (Epoch 1)	18–22 months	<25 wks 501–1000 g	Bayley Neuro exam	Epoch 1: 43% MDI≥85 40% MDI <70;	Epoch 1: 23% CP 21% unimpaired 28% neurosensory↓ 55% neurodevelopmental↓
		473/USA (Epoch 2)				Epoch 2: 29%MDI≥85 47% MDI <70;	Epoch 2: 21% CP 21% unimpaired 22% neurosensory↓ 58% neurodevelopmental↓
(Adams-Chapman et al. 2008)	1993–2002	6161/USA	18–22 months	401–1000 g	Parent interview Bayley II	31% MDI <70 22% PDI <70	40% neurodevelopmental ↓ 14% CP 11% vision ↓; 2% hearing↓ 86% neurodevelopmental ↓ in infants with IVH and shunt
(Vohr et al. 2005)	1993–1994	665/USA (Epoch 1)	18–22 months	22–26 wks	Bayley	Epoch 1: 41.8% MDI <70 31.6% PDI <70	Epoch 1: 20.1% CP
	1995–1996	716/USA (Epoch 2)				Epoch 2: 18.7% CP 38.5% MDI <70; 31.8% PDI <70	Epoch 2: 18.7% CP
	1997–1998	910/USA (Epoch 3)				Epoch 3: 37.2% MDI <70 26% PDI <70	

(Wolke et al. 2008)	1995	241/United Kingdom	6 years	≤25 wks	KABC	IQ=82	PLS-3=89.6; 15.6%<-2SD
					Griffiths	40.6%<−2 SD	
					NEPSY		
					PLS-3		
					PAT		
(Wood et al. 2000)	1995	283/United Kingdom & Ireland	30 months	22–25 wks	Bayley	MDI=84	18% CP
						30% MDI <70	36% normal development
						PDI=87	24% severe ↓
(Marlow et al. 2005)	1995	241/UK & Ireland	6 years	22–25 wks	KABC	MPC=82.1 (score=39 if <40)	13% CP
					Griffiths	48% no disability	21% cognitive ↓compared to norms
					NEPSY		41% cognitive ↓compared to classmates
Johnson et al. 2009	1995	219/UK & Ireland	11 years	22–25 wks	KABC	MPC=83.7	17.4% CP
					Neuromotor exam	23 wks=82.9	40% cognitive ↓compared to classmates
						24 wks=79.6	
						25 wks=86.1	
(Rijken et al. 2003)	1996–1997	46/Netherlands	2 years	23–25 wks	Bayley-I		78% “adverse outcome”
							55% “definitely abnormal”
(Steinmacher et al. 2008)	1996–1997	67/Germany	5 years	22−25 wks	Neuro exam	12% MPC <51	12% severe CP
					KABC		18% severe disability:
					CBCL		43% no ↓
					NEPSY		57% regular schools
(Mikkola et al. 2005)	1996–1997	102/Finland	5 years	22–26 wks	WPPSI-R	IQ=94	19% CP
				mean=595 g	NEPSY	19% retarded/not tested	12% cognitive ↓
(Raz et al. 2009)	1996–2001	40/USA	4–5 years	23–26 wks	WPPSI-R	23–24 wk IQ=89	7.5% CP
				(>1000 g *n*=4)	PDMS	25–26 wk IQ=102	63% special education (23–24 wks)
					PLS-3		18% special education (25–26 wks)
							Motor Quotient (23–24 wks)=84.8
							Motor Quotient (25–26 wks)=93.6
(Larroque et al. 2008)	1997	446/France	5 years	24–28 wks	Neuro exam	MPC=90	18% CP (24–26 weeks)
					KABC (*N*=373)	38% <85	14% CP (24–28 weeks)
						19% <70	49% minor to severe disability
							22% moderate to severe disability
(Delobel-Ayoub et al. 2006)	1997	274/France	3 years	24–28 wks	SDQ		24% high total difficulties score
(Fily et al. 2006)	1997	<10/France	2 years	24–25 wks	Brunet-Lézine	24–25 wk DQ=86; (11 points<32 wks group)	
(Baron et al. 2009a)	1998–2001	16/USA	6 years	23–25 wks	DAS	GCA=98.19	0% CP
					Digit Span		4% GCA<70
					TEA-Ch		*WNL*: attention, working memory, phoneme analysis, selective attention, verbal fluency, VMI, BASC-2, BRIEF
					Corsi Blocks		1–2 SDs<mean: dexterity, spatial
					Purdue Pegs		memory, visual search
					VMI		No mean score ≤2 SD

Table 2 (continued)

	Birth year	N/Country	Age at study	GA/BW	Cognitive measures	Cognitive outcome	Other findings
					Fluency		
					CTOPP:elision		
					BASC-2		
					BRIEF		
Gargus et al. 2009	1998–2001	3150/USA	18–22 months	<1001 g	Bayley II	Unimpaired (n=850)	CP by impairment group:
						MDI=97.6	0% - unimpaired
						Mild Impairment	6.4% - mild
						MDI=83.4 Moderate/Severe Impairment	31.9% - moderate/severe
						MDI=60.8	
(De Groote et al. 2007)	1999–2000	77/Belgium	3 years	22–26 wks	Bayley-II-NL	MDI=81 (n=62) PDI=73 (n=62)	25% CP
						56% <85 (n=62)	
(Wilson-Costello et al. 2007)	2000–2002	161/USA	18–20 months	500–999 g	Bayley-II	57% MDI≥85 21% MDI <70	5% CP
(Baron et al. 2009b)	2004–2005	39/USA	3 years	<1000 g <26 wks (n=14)	DAS-II Purdue Pegs	82.1% GCA≥85 using corrected age:	
					VMI	<1000 g GCA=98.7	
					Fluency BASC-2	<26 wks GCA=95.2	
					BRIEF-P		

g grams; *wks* weeks;↓ impairment; *EPT* extremely preterm; *CP* cerebral palsy; *MDI* mental development index; *PDI* psychomotor developmental index; *DQ* developmental quotient; *GCA* General Conceptual Ability; *MPC* mental processing composite; *IQ* intelligence quotient; *NP+* additional neuropsychological measures; *Bayley* Bayley Scales of Infant Development; *VMI* Beery Test of Visual-Motor Integration; *CANTAB* Cambridge Neuropsychologial Test Automated Battery; *CBCL* Child Behavior Checklist; *CTOPP* Comprehensive Test of Phonological Processing; *CNT* Contingency Naming Test; *DAS* Differential Ability Scales; Griffiths, Griffiths Scales of Mental Development; *KABC* Kaufman Assessment Battery for Children; *MTA* Microcomputer Test of Attention; *PDMS* Peabody Developmental Motor Scale; *SSRS* Social Skills Rating Scale; *SDQ* Strengths and Difficulties Questionnaire; *PAT* Phonological Abilities Test; *PLS-3* Preschool Language Scale; *TRF* Teacher Report Form; *TEA-Ch Sky* Test of Everyday Attention for Children Sky Search subtest; *UND* Underlining Test; *VABS* Vineland Adaptive Behavior Scale; *WISC-R* Wechsler Intelligence Scale for Children-Revised; *WPSSI-R* Wechsler Preschool and Primary Scale of Intelligence-Revised; *WRAT-R* Wide Range Achievement Test-Revised; *WJ* Woodcock Johnson.

++ See also (Hack and Fanaroff 1999)

+++ See also (Jeyaseelan et al. 2006)

(Halliday 2008), especially for those born at 23–27 weeks (Ferrara et al. 1994; The Victorian Infant Collaborative Study Group 1997). Aggressive resuscitation efforts were not yet endorsed. Marginally viable birth weight in these early years was defined as around 1,500 g, quite a different cut-point than current viability boundaries of 400 g and 23 weeks. Neuropsychological evaluation was not conducted routinely. Instead, subjective clinical impressions, broad measures of neuromotor efficiency, and standardized infant neurodevelopmental tests, or general intelligence tests at school age, were the principal functional outcome measures in studies of survival, medical complication incidence rates, and functional outcomes.

Before 1980, surviving extremely preterm infants often had severe medical and psychological complications (Hack and Fanaroff 1989; Roth et al. 1993; Saigal et al. 2006; Vohr and Garcia Coll 1985). For example, 28% of those surviving birth <1,000 g in 1960–1972 had major neurological or sensory deficit, 72% fell below grade level at age 10, and 64% required special education (Nickel et al. 1982). High rates of microcephaly, ophthalmological problems, growth retardation, cerebral palsy, and neurosensory impairment were reported in the few (19%) who survived birth <1,000 g in 1976–1979; of these, 27% subsequently had IQ <85 and 64% had academic problems (Lefebvre et al. 1988). Poor neurocognitive and behavioral outcomes extended to adolescence in those born <750 g in 1977–1982 (Saigal et al. 2000), and in those born <1,000 g and <33 weeks in 1979–1980 (Stewart et al. 1999). Good outcomes were rarely reported. However, an outlier Australian study found adolescents born <32 weeks in 1970–1980 performed within normal limits on tests of attention, memory, perception, visuomotor skill, or executive function, suggesting only minor neuropsychological consequences of very preterm brain damage were present in this cohort (Rushe et al. 2001).

1980–1989 Births: Transition to Surfactant Treatment

Birth in the 1980s was a time of transition from the "pre-surfactant era" of high mortality and disability incidence (Lumley et al. 1988), to the "surfactant era" of rising survival rates. Mortality and severe neurodevelopmental disability data from 42 mostly pre-surfactant studies of birth ≤26 weeks or with birth weight ≤800 g published between 1969–1997 were reviewed. Mental retardation was reported in about 14% of survivors, 22–24% had major disability, and disability prevalence reached 52% (Lorenz et al. 1998). Since aggressive resuscitation efforts for the smallest and earliest born were often not endorsed, extremely preterm survival was less assured. Consequently, mean birth weight and gestational age were greater in these reports than in cohorts born in subsequent decades (Hansen and Greisen 2004; Teplin et al. 1991). Substantial negative effects persisted in these years. Of those born <1,000 g in 1983, only 13.5%, and 3.5% of those born at 25–26 weeks, survived to 19 years in one cohort; of these, 36–39% experienced moderate to severe impairment (Hille et al. 2007). For birth in 1983–1989, survival and morbidity rates improved for each successive birth week from 23 to 25 weeks; survival rate increased from 16% to 53%, morbidity decreased from 67% to 32%, and mental developmental index scores <−2SD at 18-months corrected age decreased from 10% to 1%. A single major impairment was present in 36%, and multiple deficits in 38% (Synnes et al. 1994).

Intellectual Outcome

The intelligence quotient (IQ), a principal psychological outcome index in the 1980s, was often reported to be below average in extremely preterm children. A meta-analysis of reports for 1980–2001 births after age 5 found mean cognitive performance directly proportional to birth weight and gestational age (Bhutta et al. 2002); only five case-control studies had reported cognitive and behavioral data for births <1,001 g, and all five were pre-1987 (pre-surfactant) cohorts (Hall et al. 1995; Portnoy et al. 1988; Saigal et al. 2000; Taylor et al. 2000; Teplin et al. 1991). At one center, mean IQ <85 was reported for 39% of those born <1,500 g in 1982–1986 and pre-surfactant, and 50% of those born <750 g (Hack et al. 1994; Taylor et al. 2000; Taylor et al. 2004); at 11 years of age, those born <750 g had persistent low average-to-average IQ, and mean scores below 750–1,499 g preterm children (Taylor et al. 2000).

Educational Outcome

Greater attention was directed toward assessing educational impairments in extremely preterm children during this decade. Swedish extremely preterm children born in 1985–1986 who had average IQ at 10 years also had learning disabilities, behavioral problems, and attentional disorder (Stjernqvist and Svenningsen 1999). In 1984, children born <1,000 g had a mean IQ of 90.4 compared with 102.5 for controls; 15% had cognitive deficits or met criteria for learning disability, and 52% received support services compared with only 16% of controls (Hall et al. 1995). One fourth of a 1985–1990 cohort (26%) was disabled at 8 years (10% severe), 27% were below grade level in reading or mathematics, and 43% required special education services. Only 30% were at grade level without academic support. Of the 74% children who had IQ≥85 and no neurosensory deficit, i.e., "non-disabled", 48% functioned below grade level and 25% received academic

support (Bowen et al. 2002). Of those born ≤800 g in 1982–1987 and who were neurologically normal with average intelligence (VIQ or PIQ≥85), 65% met LD criteria at 8–9 years compared with 13% of controls (Grunau et al. 2002). Thus, deficits were commonly found, even in association with average IQ.

Mid-1980s Trends

An early trend toward improved outcome emerged in the mid-1980s. An Australian study reported fewer severely disabled children at 5 years in those born in 1985–1987 compared with their 1977–1982 cohort (Doyle et al. 1994). Notably, it was suggested that the emergence of a positive impact of nationalized health care patterns as well as medical advances, such as surfactant, had a positive impact on extremely preterm outcomes. Several reports emerged from countries that provided comprehensive prenatal and postnatal care, and socioenvironmental supports such as teacher consistency and parental counseling. Nevertheless, their extremely preterm children were not insulated from deficit. For example, 50% of Swedish extremely preterm children born <29 weeks in 1985–1986 survived to 10 years, 92% without major neurological disability. However, their mean IQ and visuomotor scores, which were within the normal range, fell significantly below controls; 38% were below grade level, 32% had behavioral problems, and 20% were diagnosed with attention-deficit/hyperactivity disorder. Of a subgroup born 500–900 g at 24–30 weeks, 80% had normal growth and development at 1 year but 17% had neurological abnormalities, 8.7% had post-hemorrhagic shunted hydrocephalus, and 13% had vision deficits (Stjernqvist and Svenningsen 1999).

1990–1999 Birth: Rising Survival Rates Post-surfactant

Survival rates increased for children born at the limits of viability following the introduction of surfactant, and as other medical advances became available. For example, survival rates rose from 2% to 35% for those born at 23 weeks, 17% to 58% for those born at 24 weeks, and from 35% to 85% for those born at 25 weeks (Hack and Fanaroff 1999). A survival rate of 73% was reported for those born at 26 weeks at another center (Tommiska et al. 2007). Yet, extremely preterm birth after 1990 did not confer substantial advantage over birth in the 1980s with respect to overall functional outcomes. High rates of neuromotor, neurological, neuropsychological, and behavioral impairments continued to be reported well into the 1990s (Anderson and Doyle 2003; Daniel et al. 2003; Delobel-Ayoub et al. 2006; Hack et al. 2000b; Taylor et al. 2006; Vohr et al. 2000), especially for children born <750 g or <26 weeks (De Groote et al. 2007; Mikkola et al. 2005; Rijken et al. 2003). As lower gestational age survival rates increased, a negative impact on morbidity was observed. In a 1982–1988 pre-surfactant cohort, only 23% survived birth <750 g compared with 43% of this center's 1990–1992 cohort, but 20% of each cohort had a mental developmental index <70 at 20 months (Hack et al. 1996).

Disability and Educational Outcomes

A review of four international cohorts born in this decade found more than 50% of preterm survivors required special education or repeated a grade by age 8 to 11, and only 44–62% had IQ >84 (Saigal et al. 2003). A 38% disability rate in 1984–1989 survivors increased to 68% in 1990–1994 survivors, attributed to increased survival of those especially fragile children born at 23–24 weeks (Emsley et al. 1998). Report of health and educational needs of a 1992–1995 cohort at age 8 compared with controls noted elevated rates of cerebral palsy (14%), vision impairment (10%), and motor impairments (47%), and low IQ (i.e., <85; 38% v. 14% controls), academic limitations (37% vs. 15% controls), and poor adaptive function (69% vs. 34% controls) (Hack et al. 2005). Notably, this study's control group's higher than expected impairment rates highlighted the variability inherent in many control populations, and reinforces cautions to consider methodology and cohort characteristics stringently.

A Focus on Longitudinal Study

In the 1990s, attempts were made to determine longitudinal course and outcomes in later childhood. Neurofunctional assessment at 12 months of extremely low birth weight infants born in 1996–2001, along with magnetic resonance imaging status and chronic lung disease, predicted cognitive function at 36 months (Gianni et al. 2007). Children born <26 weeks in 1995 had a mean mental developmental index of 84 and a psychomotor developmental index of 87 at 30 months; 49% had cognitive or neurologic disability and 23% were severely disabled (Wood et al. 2000). At 6 years of age, 80% of this cohort was disabled (34% mildly, 24% moderately, and 22% severely). A 21% cognitive impairment rate increased to 41% when classmates, not normative data, were the comparison group. It was concluded that severe disability at 30-months strongly predicted developmental problems at 6 years, with 86% remaining moderately to severely impaired (Marlow et al. 2005).

Less dire outcomes characterized some birth cohorts in this decade. When 1990s extremely low birth weight survivors in Denmark were compared with 1980s very low birth weight survivors at 4–5 years, it was found that greater survival of the smallest in the 1980s and 1990s

occurred without increased intellectual deficit, even though the 1990s cohort had lower mean birth weight (Hansen and Greisen 2004). Also, children born at 23–25 weeks in Sweden between 1990 and 1992 who had been evaluated at 36 months corrected age were studied again between 10 and 12 years and compared with controls on behavioral, emotion, social competency, and adaptive function measures. Parents and teachers reported more internalizing behavioral problems (anxiety/depression, withdrawn, and somatic) along with attention, thinking, and social problems. Child self-reports showed a trend toward increased depression symptoms. Teachers rated extremely preterm children less well adjusted than controls. However, a majority, 85%, were mainstreamed without adjustment problems (Farooqi et al. 2007).

Neuropsychological Measures Introduced

Studies of children born in the 1990s began to extend measurement beyond broad neurodevelopmental or general intellectual instruments to include neuropsychological tests. An early 1990s cohort demonstrated poorer performance compared with controls on all neuropsychological measures at 12 years, and severe brain injury and unfavorable social factors were the most important predictors of adverse cognitive outcomes (Luu et al. 2009). In a 1996–1997 extremely low birth weight cohort from Finland, 26% were normally developing at 5 years but 9% were impaired in all five assessed neuropsychological domains; 20% had major disabilities, 19% had minor disabilities, and 61% had no functional developmental abnormalities although subtle abnormalities were suggested. The overall extremely low birth weight group mean IQ was 96±19 and cerebral palsy rate was 14% whereas in the 22–26 weeks subgroup mean IQ was 94±19 and cerebral palsy rate was 19% (Mikkola et al. 2005).

Executive function and attention, broad capacities subsuming more specific subcomponents essential for overall cognitive development and adaptive efficiency, came under increased scrutiny post-1990 (Carmody et al. 2006). Preterm associated white matter pathology, prefrontal cortical dysfunction, and fronto-subcortical neural network disruption presumptively underlie executive deficits (Anderson et al. 2005; Chen and Desmond 2005; Edgin et al. 2008). Studies began to examine the stepwise development of executive subcomponents in normal children and adolescents using measures that ranged in degree of required cognitive control (Conklin et al. 2007; Luciana et al. 2005). In preterm studies, at-risk very low birth weight and extremely low birth weight survivors performed poorly on working memory, verbal fluency, set shifting, interference suppression, inhibition, and behavioral regulation measures, despite average range intelligence (Bohm et al. 2004; Caravale et al. 2005; Harvey et al. 1999; Vicari et al. 2004). A prospective longitudinal study of young high-risk preterm children with white matter abnormality detected by magnetic resonance imaging at term equivalent found poor inhibitory control and mental inflexibility persisted from 2 to 4 years of age, even after controlling for IQ, socioeconomic status, and medical variables (Edgin et al. 2008). Australian extremely preterm survivors born in 1991–1992 also exhibited executive dysfunction, even after adjustment for sociodemographic variables and when those with substantial sensorineural impairment were excluded from analyses (Anderson and Doyle 2004). However, in a Danish national cohort at 5 years, case-control group differences were not found for memory and executive measures after controlling for IQ, suggesting a global cognitive impact of preterm birth (Hoff Esbjorn et al. 2006). The accumulating literature suggests that early executive dysfunction detection is both possible and necessary to permit timely diagnosis and intervention for fundamental capacities.

As neuropsychology clinical practice and research methods become increasingly sophisticated the opportunities to address more specific hypotheses about neurocognitive function are possible. Clinical assessments need to more effectively adapt strategies used in research to clinical assessment paradigms in order to examine more specific functions than general intelligence and broad achievement. A long history of reliance on global measures will necessarily be strengthened by more fine-tuned longitudinal studies of the development of specific neuropsychological domains in these at-risk children. Simultaneously, assessment of parental and environmental factors that contribute to the very young child's growth and development need to be considered in such long-term studies. Establishing the foundational importance of thorough assessment should benefit these children as they mature and enter adolescence and young adulthood.

Post-2000 Birth: An Era of Tentative Optimism

Opinion persists that the long-term adverse effects of preterm birth cannot be lessened despite medical advances that have substantially improved survival (Tommiska et al. 2007; Tyson and Saigal 2005). However, reports of more optimal outcome have begun to be reported for recent births. Extremely preterm survival rates continue their upward trend post-2000, along with variable reports about medical complications and associated long-term morbidities. A reduction of adverse neurodevelopmental outcome has not always been found in conjunction with increased survival rates (O'Shea et al. 1997; Riley et al. 2008), but reduced morbidity was reported for infants born at 22–27 weeks gestational age in 1999–2000 (Markestad et al. 2005), and in 1990–2000 (Washburn et al. 2007). While

post-2000 extremely preterm birth has not yet dramatically changed expectation for poor outcome (De Groote et al. 2007; Tyson and Saigal 2005), gradual gains have been noted for young survivors. In a 1988–2001 extremely low birth weight multicenter cohort who survived to NICU discharge, 27% had unimpaired outcomes at 18–22 months (Gargus et al. 2009). Identification of those factors that contribute most to successful long-term outcome remains a primary concern. Decisions about when to aggressively resuscitate the borderline viable infant remain individualized and care center-specific, with few published guidelines (Batton 2009; Kaempf et al. 2006).

Although post-2000 extremely preterm data allow for reserved optimism, comparisons with older cohort studies remain limited as recent survivors are still too young for researchers to appreciate their full outcome. Besides earlier reports, such as those that found 85% of a Swedish extremely low birth weight cohort had normal range cognitive development at 4 years of age (Stjernqvist and Svenningsen 1995), age-appropriate neurodevelopmental and cognitive outcomes are only just beginning to be reported, e.g., at 18–20 months (Wilson-Costello et al. 2007), and at early school age (Baron et al. 2009a). The extremely preterm survival rates in the former study increased from 49% to 68% to 71% for birth in 1982–1989, 1990–1999, and 2000–2002. Major neurologic and sensorineural impairment rates and mental developmental index scores <70, decreased for their 2000–2002 cohort at 20 months of age, i.e., 28%, 35%, to 23%. Better outcome was attributed to increased Cesarean delivery, increased antenatal steroid use, decreased postnatal steroid use, decreased intraventricular hemorrhage incidence, less sepsis, and a lowered moderate to severe cerebral palsy rate (Wilson-Costello et al. 2007). The significant decline in severe intraventricular hemorrhage may have particular relevance, as low intraventricular hemorrhage incidence but high incidence for other risk factors was present in the 1998–2001 cohort that had low average-to-average function in most respects, and no impaired scores (i.e., <−2 SD) (Ahronovich et al. 2007; Baron et al. 2009a). Reduced neonatal complication incidence is not sufficiently explanatory of favorable outcomes and more fine-grained analyses of both antenatal and postnatal factors are expected to lead to a more comprehensive understanding of risk and outcome of extremely preterm birth in future decades (Eichenwald and Stark 2008).

In summary, an examination of outcome studies by birth decades reveals the effects of progressively improving intensive care, with slight but consistent change in a positive direction beginning to be documented (Table 2). Nevertheless, cohort variability and the absence of a uniform metric to assess disability necessarily limited cross-study comparisons in this review. In the future, meta-analytic techniques should be applied to compare temporal trends in outcomes and to evaluate methodological quality, with particular emphasis on effect sizes.

Intervention and Future Directions

Prevention of preterm birth is the principal means of reducing mortality and morbidity (McCormick 1994). Yet, preterm incidence rates are rising steadily (Behrman and Butler 2007). Consequently, there is a need for strong advocacy, proactive measures, and enhanced interdisciplinary collaboration among obstetrics/gynecology and neonatology practitioners, geneticists, immunologists, endocrinologists, and others to improve preterm risk assessment strategies and to devise appropriate interventions (Lamont 2003). Progress in antenatal and neonatal intensive care is evident in improving medical outcomes, and decreased mortality and severe morbidity rates. Molecular and cellular mechanisms associated with neonatal brain injury risk and injury prevention are the subject of intense study, which aids formulation of a rationale for developing specific strategies (Back et al. 2007). Early identification and management of cerebral circulation and autoregulation problems that increase the risk of ischemia in preterm neonates may prevent damage to white matter precursor cells by replenishing anti-oxidant defenses and preventing free radical generation, and protective agents may enable excitotoxic pathways to prevent oligodendrocyte precursor cell damage (Back et al. 2007; Khwaja and Volpe 2008).

Targeted intervention strategies uniquely suited for at-risk preterm neonates are likely to evolve with greater understanding of brain development, and of the mechanisms and progression of injury in the immature brain. Plasticity, the capacity for reorganization associated with an immature brain, becomes a fundamental consideration (Stiles 2008), along with the potential for greater vulnerability to brain injury (de Haan and Johnson 2003; Johnston 2009). Specific interventions are needed to support reparative processes as well as preventive strategies. Such studies will likely include analysis of biomarkers and interactions with other risk factors (Ferriero 2009).

Early postnatal intervention is crucial to ensure more optimal outcomes, particularly for mental development (Spittle et al. 2007). A stimulating home environment and early intervention lessened cognitive deficit in preschool very low birth weight (VLBW; <1,500 g) children, while increased deficit was found in those from less stimulating homes (Weisglas-Kuperus et al. 1993). Interventions can begin within the neonatal intensive care unit. Adaptation of the neonatal care environment prior to term using the Newborn Individualized Developmental Care and Assess-

ment Program (NIDCAP) enhanced brain structure and function, and may promote the preterm infant's self-regulatory capacity, leading to more optimal overall outcome (Als et al. 2003). Efforts to optimize preterm infant management through individualized developmentally informed approaches has encouragingly improved neurocognitive function (Westrup et al. 2002) and enhanced brain development, as documented with diffusion tensor imaging (Als et al. 2004). At 1 year, children born at <32 weeks and enrolled in a family centered developmentally supportive intervention program had a mean mental developmental index 10 points higher than those not enrolled, although psychomotor developmental index scores did not differ (Kleberg et al. 2002). Positive effects of this program were also reported for children at 3 years and born very low birth weight in 1992–1993 (Kleberg et al. 2000) and at age 18 months for children born in 1999–2004 (Peters et al. 2009), although not all centers have been able to demonstrate the effectiveness of this type of intervention (Maguire et al. 2009).

Concurrent with learning more about specific neuropsychological developmental processes and their susceptibility to disruption after early birth, timely and targeted interventions need to be devised and applied as preventive as well as remedial measures. It is concerning that those with mild-to-moderate disability and adverse social risk do not access those early intervention resources as consistently as those more impaired (Roberts et al. 2008), since it is these children who likely will benefit greatly from such treatments. Furthermore, enrollment in early intervention may be inconsistent, despite availability of services (Wang et al. 2009).

Cognitive rehabilitation strategies adapted for the cognitive late effects of childhood cancers that also affect cerebral white matter development and result in neuropsychological impairment are showing promise in addressing attention and cognitive processing deficits. These may be applicable to children born extremely preterm (Butler and Copeland 2002; Butler et al. 2008; Mulhern et al. 1992). Strategies that promote self-regulatory capacities and preserve the integrity of emerging neuropsychological capacities hold promise, as do structured "follow-along" intervention programs that customize support to the family and social and educational environments. Ongoing care post-neonatal unit discharge may be especially critical for both the preterm child and stressed family (Drotar et al. 2006; Kaaresen et al. 2006). The potential efficacy of pharmacological strategies has yet to be studied through clinical trial investigations. As more is learned about the unique vulnerable periods in development, interventions will need to be devised and implemented according to specific windows of opportunity. Multi-faceted approaches that integrate medical, cognitive, familial, and psychosocial needs within a community context will be required.

Intervention programs will also need to include an educational component to aid parents and educators in understanding the unique developmental needs of this vulnerable population. As more children survive into preschool and adolescence, educational systems need to be prepared to provide the types of interventions required to support optimal progress and overall adjustment.

Conclusions

A review of research on extremely preterm birth cognitive outcomes since the 1960's to the present reveals that those extremely preterm children born post-2000 are more likely to demonstrate greater cognitive strengths than those survivors born in earlier eras of prenatal and neonatal intensive care. However, even children who have average general intelligence remain at risk for subtle to more profound neuropsychological and behavioral problems that will impact academic and personal functioning over their lifespan. Guarded optimism about the outcomes of today's neonate appears appropriate, although discrepancies are seen across NICUs related to complex interrelated factors. It is necessary to identify those factors that promote resilience and best guide future intervention and prevention efforts. Access to ongoing care, follow-up surveillance, and interventional treatments appear critical. The vast literature on this population needs to be interpreted with an appreciation of the complex systemic interactions among biological, medical, social, familial, cultural, and environmental factors, and their influence on the dynamic and adaptive maturational process of brain development. Assessment strategies need to be more theory-driven and developmentally referenced, addressing specific neurobehavioral domains and subdomains of functioning. Furthermore, more consistent and comprehensive methods for describing overall outcome are needed so that interventions can be targeted appropriately and findings across studies can be directly compared. These assessment methods would need to address the impact of disability on overall functioning in the context of specific environmental and personal factors. The International Classification of Functioning (ICF) model has been suggested as a useful way of understanding the spectrum of issues affecting a child's overall adjustment and adaptation (Msall and Park 2008). Greater use of sophisticated imaging techniques integrated with knowledge about developmental stage holds great promise to better inform about the developing child and the effects of too early birth on brain structure and function. These findings in turn will serve to guide advances in prevention and rehabilitation efforts.

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