Seminars in Fetal & Neonatal Medicine (2006) **11**, 127—137

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Seminars in FETAL & NEONATAL MEDICINE

Young adult outcomes of very-low-birth-weight children

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KEYWORDS
Prematurity;
Very-low-birth-weight;
Extremely low birth weight;
Adult outcomes

Summary Information on the young adult outcomes of the initial survivors of neonatal intensive care has been reported from the United States, Canada, Australia, Great Britain and other European countries. The studies have varied with regard to whether they were regional or hospital-based, their birth-weight group and gestational age, rates of survival, socio-demographic background, and measures of assessment and types of outcome studied. Despite these differences the overall results reveal that neurodevelopment and growth sequelae persist to young adulthood. Very-low-birth-weight young adults have, with few exceptions, poorer educational achievement than normal-birth-weight controls, and fewer continue with post-high-school study. Rates of employment are, however, similar. There are no major differences in general health status, but the young adults demonstrate poorer physical abilities, higher mean blood pressure and poorer respiratory function. There is no evidence of major psychiatric disorder, although anxiety and depression are reported more often. The young adults report less risk-taking than control populations. They report fairly normal social lives and quality of life. When differences are noted they are usually due to neurosensory disabilities. Longer-term studies are needed to evaluate ultimate educational and occupational achievement. It will also be important to assess the effects of preterm birth, early growth failure and catch-up growth on later metabolic and cardiovascular health.
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Introduction

Prior to the 1950s, when few preterm infants survived, the majority of survivors to adulthood who were born with very low birth weight (VLBW, <1.5 kg) were described as having average development and normal function.[1,2] However, neonatal therapies introduced between 1950 and 1960, such as the overuse of oxygen and antibiotics to prevent infection, resulted in poorer outcomes with high rates of neurosensory deficits, including cerebral palsy, blindness and deafness.[3] There were significant improvements in the survival of VLBW infants and a decrease in the rates of neurodevelopmental sequelae after the introduction of modern methods of neonatal intensive care in the 1960s.[4] By the 1970s, 80—90% of VLBW children were reported to be free from serious handicap during early childhood; however, other problems became evident during the school-age and adolescent years. They included poorer cognitive

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1744-165X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.siny.2005.11.007

function and academic performance when compared to normal-birth-weight (NBW) controls. This was evident even among VLBW children who were free of neurologic handicaps and had normal intelligence.[5] The associated school learning problems resulted in higher rates of special education assistance and grade repetition for VLBW children. Chronic health problems were also more prevalent and included those associated with cerebral palsy, asthma, and visual and hearing impairments. The health problems also led to functional limitations, among them restriction in physical activities, inability to participate in sports, and visual difficulties. The majority of VLBW children also experienced poorer growth attainment, although some catch-up growth occurred during childhood. Additional problems evident during the school age and adolescent years include behavioral problems: mainly hyperactivity and attentional weaknesses, but also shyness and withdrawn behavior, difficulty in social skills, and anxiety and depression. These developmental, behavioral and health problems led to concern as to how the increasing numbers of VLBW infants, who survived as a result of neonatal intensive care in the 1970s and 1980s, would function as they approached adulthood.

Predictors of the poorer outcomes of VLBW survivors during childhood and adolescence include social and/or environmental risk factors, together with the biologic risk factors: male sex and complications of prematurity, specifically periventricular hemorrhage and/or periventricular leucomalacia (PVL), chronic lung disease, infection, and subnormal brain growth. Neuropathologic and magnetic resonance imaging (MRI) correlates of brain injury include PVL and lesser degrees of brain damage. Also relevant to the adult outcomes of VLBW infants is the current interest in the origins of adult disease during early life. Based on epidemiologic studies, it has been hypothesized that adaptations made by the fetus or young infant when undernourished may have long-term effects on health and result in mental illness, hypertension, atherosclerosis, diabetes, central obesity and death due to cardiovascular disease in middle age.[6] Subjects who grow rapidly and demonstrate catch-up growth are considered at greatest risk for the medical complications.[7] However, socioeconomic (SES) conditions, life style and environmental factors both in childhood and adulthood may be as important in causing adult disease as factors in utero or in infancy.[8]

The initial survivors of neonatal intensive care born in the 1970s reached young adulthood in the mid-1990s. Since that time, increasing numbers of studies have reported on their health and overall functioning as young adults. This paper reviews current knowledge concerning the outcomes of VLBW children who have survived to adulthood as a result of the modern methods of neonatal intensive care.[4]

Considerations in the evaluation of adult outcome studies

Considerations in evaluating the adult outcomes of neonatal intensive care include the variation in the countries of origin of the participants, their birth-weight subgroup, sociodemographic status, sample size, as well as the types of outcomes studied and the methods used (see Tables 1 and 2). Some reports include data extracted from national databases,[9] others are regional,[10,11] and others hospital-based.[12–15] Some include only males and only singleton births.[9] Others include multiple births which are prevalent among VLBW cohorts.[10,12] Some studies include a physical and neurologic examination and/or face-to-face interviews of the subjects and their parents,[10,12–14] whereas others undertook telephone interviews,[16] mail surveys,[15] or used school records.[17] Differences also pertain to the mean birth weight and gestational age of the adult participants, the type of neonatal care provided, as well as the year of birth, the age and rates of follow-up, and the method of selection and maintenance of the normative control populations. In most studies, the loss to follow-up tends to be greater among the subjects of lower sociodemographic status (SES).[11,12,18] Loss to follow-up is also greater among the control populations than among VLBW study subjects.[12,13,15] The control populations who are followed are thus usually of higher SES than the VLBW populations.[2,12,13,17,19,20] This difference in SES may bias the results against the VLBW subjects, although most studies adjust statistically for SES in the analyses of outcomes.

With the exception of one study,[19,20] all of the studies have been specific for birth weight rather than gestational age, and include either VLBW or extremely-low-birth-weight (ELBW <1 kg) survivors. Early studies, especially those of children born in the 1960s, included low-birth-weight (LBW <2.5 kg) children.[2,21–24] Because of the birth-weight rather than gestational-age cut-off, the LBW, VLBW and ELBW populations which have been studied include an increased proportion of subjects who experienced intrauterine growth failure and are thus small-for-gestational-age (SGA). This may influence outcomes, especially those concerning long-term growth.[25] Furthermore, some studies exclude children with major congenital malformations[12] or neurosensory impairments[11,15,17,18] and/or those who attended special schools,[15] whereas others include all the survivors, including those with congenital malformations.[1,16,19,20]

Review of late adolescent and young adult studies of VLBW children

Studies of various aspects of late adolescent and young adult outcomes of VLBW children born during the years 1971 and 1986 have been reported from the United States,[12] Canada,[10,11,13,26] England,[15,17] Australia,[14] Denmark,[16,18,27] Norway[28] and Sweden.[9] Table 1 describes the populations and methods of the various studies, and Table 2 lists the outcomes studied.

Neurosensory impairments

VLBW subjects

Rates of cerebral palsy range from 5 to 8%.[9,12,16] Hack et al. reported an overall rate of neurosensory impairment (cerebral palsy, blindness or deafness) of 10%.[12] Among singleton VLBW males, Ericson and Källén reported that 7% had severely reduced vision, 12% refraction errors, and 8% severe hearing loss.[9]

Table 1 Adult outcome studies of extremely low birth weight (ELBW, <1 kg) and very low birth weight (VLBW, <1.5 kg) infants

	Year of birth	Population studied	Age (years)	Type of study	Live birth (*n*)	Survived (*n*, %)[a]	Followed (*n*, %)	NBW controls recruited (*n*)	NBW controls followed (*n*, %)	Study measures
United States										
Hack et al.[12]	1977–1979	VLBW	20	Hospital	419	312 (64)	242 (78)	366	233 (64)	Testing and questionnaires
Canada										
Grunau et al.,[11] Rogers et al.[32]	1981–1986	<800 g	17–19	Regional	250[c]	98 (39)	53/79[b,d] (67)	42	31 (74)	Testing and questionnaire/interviews
Lefebvre et al.[13]	1976–1981	ELBW	18	Hospital	351[c,e]	82 (23)	59 (72)	79	44 (56)	Testing and questionnaire/interviews
Saigal et al.[10]	1977–1982	ELBW	23	Regional	397	166 (42)	147 (89)	145	131 (90)	Questionnaire/interviews
United Kingdom										
Cooke[15]	1980–1983	VLBW	20	Hospital	–	138	79 (57)[f]	163	71 (44)[f]	Mailed questionnaire
Pharoah et al.[17]	1980–1981	VLBW	20	Regional	399	219 (55)	51 (56)	167	158 (95)[g]	Results of GCSE
Australia										
Doyle et al.[14]	1977–1980	ELBW	20	Hospital	159	60 (38)	44 (73)	–	–	Testing
Denmark										
Bjerarger et al.[16]	1971–1974	VLBW	18-20	Hospital	249[c]	110 (45)	85 (77)	110	85 (77)	Telephone interview
Dineson and Greisen,[27] Hansen et al.[18]	1980–1982	VLBW	18–20	Hospital	150[c]	114 (76)	92 (90)	114	69 (60)	Telephone interview
Sweden										
Ericson and Källén[9]	1973–1975	VLBW	18–19	National[h]	–	288	260 (90)	–	Population	Testing
Norway										
Halvorsen et al.[28]	1982–1985	ELBW, <28 weeks	18	Regional	81	52 (64)	46 (88)	46	35 (76)	Testing and questionnaires

NBW, normal birth weight; GCSE, General Certificate of Secondary Education.
[a] Survival to young adulthood.
[b] 59 had IQ tests.
[c] Admitted to neonatal intensive care unit (NICU).
[d] Neurosensory intact.
[e] 198 live births and 153 admitted to NICU from community.
[f] Children who attended mainstream school.
[g] Includes 37 new controls.
[h] Singleton men in National Service Registry.

Table 2 Adult outcome studies of extremely low birth weight (ELBW, <1 kg) and very low birth weight (VLBW, <1.5 kg) infants

	Included neurologic impairment	Test of IQ	Test of academic achievement	Education attained	Post-high-school study	Employment	Health	Physical ability	Growth	Blood pressure	Risk-taking	Behavior	Quality of life	Other
United States														
Hack et al.[12]	+	+	+	+	+	+	+	−	+	+	+	+	−	−
Canada														
Grunau et al.,[11] Rogers et al.[32]	−	+	+	−	−	−	−	+	−	+	−	+	−	
Lefebvre et al.[13]	+	+	+	+	+	−	+	−	−	−	−	−	−	−
Saigal et al.[10]	+	−	−	+	+	+	+	+	+	+	−	+	+	+[c]
United Kingdom														
Cooke[15]	−[a]	−	−	+	+	+	+	−	+	−	+	+	+	−
Pharoah et al.[17]	−[b]	−	+	+	−	−	−	−	−	−	−	−	−	−
Australia														
Doyle et al.[14]	−	−	−	−	−	−	−	−	+	+	−	−	−	+[d]
Denmark														
Bjerarger et al.[16]	+	−	−	+	+	+	+	−	−	−	+	+	+	−
Dineson and Greisen,[27] Hansen et al.[18]	−	−	−	−	−	−	+	−	−	−	−	−	+	−
Sweden														
Ericson and Källén[9]	+	+	+	+	+		+	+	+	−	−	−	−	−
Norway														
Halvorsen et al.[28]	+	−	−	−	−	−	+	−	−	−	−	−	−	+[d]

[a] Included only children who attended mainstream school.
[b] Excluded neurosensory or educationally subnormal children and those with disabilities.
[c] Family impact.
[d] Respiratory function.

ELBW subjects

Both Lefevre et al. and Hack et al. (who examined the subset of ELBW subjects in their VLBW cohort) reported overall rates of neurosensory impairment of 12%.[13,29] Saigal et al. reported a rate of neurosensory impairment of 28%, with 37% of the subjects having problems with visual function and 4% late retinal detachment.[30]

Intelligence and academic achievement

VLBW subjects

The VLBW subjects reported by Hack et al. in the USA had significantly lower IQ scores than NBW subjects (mean IQ: 87 versus 92, $P < 0.001$) and higher rates of subnormal (<70, 7% versus 2%) and borderline IQ (70–84, 42% versus 31%), all $P < 0.05$.[12] The odds ratio for having a subnormal IQ (<70) was 4.0 (95% CI 1.3–12.2). The young adults also had lower scores on tests of academic achievement, including letter/word identification and applied problems.[12] These results remained significant when adjusted for social risk and gender, and when subjects with neurosensory impairments were excluded. There were no gender differences in these outcomes. The VLBW men reported by Ericson and Källén in Sweden similarly tested at a significantly lower level than the rest of the population on tests of IQ (OR 4.5, CI 3.4–6.0).[9] In Denmark, nonhandicapped VLBW subjects reported less satisfactory school performance in mathematics, foreign language, general learning ability and ability to concentrate than NBW controls.[16]

ELBW subjects

Among ELBW young adults in Canada, Lefevre et al.[13] reported a mean IQ of 98 versus 106 for the NBW controls after adjusting for parental SES ($P < 0.005$); 19% versus 2% respectively had an IQ score <85 ($P < 0.05$). In the subset of ELBW young adults in the cohort of Hack et al. the mean IQ was 81 versus 92 for the NBW controls ($P < 0.001$). ELBW subjects similarly performed more poorly on tests of academic achievement.[29] The subjects of birth weight <800 g studied by Grunau et al. who did not have neurosensory problems or subnormal IQ had significantly lower IQ scores than the NBW controls with lower scores on the arithmetic ($P < 0.001$) and reading ($P < 0.05$) subtests of academic achievement, but not in spelling ability.[11] There were no gender differences reported in IQ or academic achievement.

Educational attainment, current enrollment in college, and work status

VLBW subjects

In the study by Hack et al., significantly fewer VLBW than NBW participants had graduated from high school or obtained a General Education Diploma (GED) by the age of 20 years. VLBW subjects who graduated from high school did so at a later age than the controls (mean 18.2 versus 17.9 years, $P < 0.001$). VLBW men had poorer educational outcomes than the NBW controls in that fewer were enrolled in 4-year college programs, but more were working ($P < 0.01$). In contrast, VLBW and NBW females did not differ in educational or work status. Rates of unemployment did not differ significantly among either male or female subjects when compared to their NBW controls. These outcomes were similar when the 35 VLBW and four NBW subjects with neurosensory impairments and/or subnormal IQ (<70) were excluded from analyses.[12]

In the United Kingdom, Cooke—who excluded children who had attended special schools—similarly reported that more VLBW subjects had left school at a younger age than the NBW controls (age 16 versus 17 years, $P < 0.001$). Fewer had university degrees (23% versus 58%, OR 0.21, 95% CI 0.11–0.44), more were in paid work (56% versus 44%, OR 2.1, 95% CI 1.07–3.94), and fewer were full-time students (23% versus 51%, OR 0.28, 95% CI 0.14–0.58).[15] Pharoah et al. excluded children who had clinical disabilities or were in special schools because of blindness, deafness or a subnormal IQ, but still found that VLBW young adults had lower total mean scores ($P = 0.050$) on the British General Certificate of Secondary Education (GCSE) test, as well as significantly lower mean scores per examination subtest ($P < 0.05$).[17] In Sweden, significantly more of the VLBW men had left school early and thus had lower levels of educational attainment (OR 1.6, 95%CI 1.2–2.2),[9] but in Denmark there were no significant differences between the VLBW and NBW subjects in the percentage of subjects who had completed high school (33% in each group), had a university level of education (8% versus 12%), who were employed in job apprenticeships (52% versus 45%), or were unemployed (7% versus 9%).[16]

ELBW subjects

Lefevre et al. reported that 56% ELBW versus 65% NBW subjects ($P < 0.05$) who were at least 18 years old had obtained a school diploma (i.e. graduated from high school).[13] Of the ELBW subgroup in the cohort of Hack et al., 38% versus 53% were enrolled in a post-high-school educational program (NS), but significantly more of the ELBW subjects were enrolled in community/technical/trade schools (28% versus 13%), and fewer were in a 4-year college (10% versus 40%). There was a significant sex by birth weight interaction, with no male ELBW subjects enrolled in a 4-year college as compared to 44% of the NBW males. However, the male subjects who were not in colleges were working. Furthermore, the rates of unemployment did not differ between groups (14% versus 13%).[29] In contrast, Saigal et al. found no differences between groups. At age 23 years, 15% ELBW versus 11% NBW had not completed high school; 5% versus 14% had completed university education, while one-third (32% versus 33%) were still pursuing post secondary education; 47% versus 52% had permanent employment, of whom there were no differences in job status or in mean annual income. The only significant difference was the proportion of subjects who were unemployed (26% ELBW versus 15% NBW, $P < 0.05$). When the subjects with neurosensory disabilities were excluded the differences were not significant.[10]

The overall poorer educational achievement and lesser enrollment of the VLBW subjects in college reported by Hack and others is of concern, as this predicts lower ultimate educational and occupational achievement and thus lower future earning ability for both VLBW and ELBW survivors.

Chronic illness, health status, physical ability and respiratory health

VLBW subjects

In the cohort of Hack et al., with the exception of neurosensory impairments (10% versus 0.4%, $P < 0.001$), the overall rates of chronic medical and psychiatric conditions did not differ significantly between groups (21% versus 16%); 8% VLBW versus 6% NBW had asthma (NS) and 2% versus 1% had bipolar disorder. There were no differences between the VLBW and NBW subjects on the CHIP-AE, a measure of health status in satisfaction with health, self-esteem, physical and emotional discomfort, and physical limitations. VLBW subjects, however, reported less physical activity, more long-term surgical disorders, and more psychosocial disorders. When the subjects with neurosensory impairments, subnormal IQ and other chronic conditions were excluded, the differences in physical activity remained significant, but the differences in long-term surgical conditions and psychosocial disorders were no longer significant. Thus, with the exception of those with neurosensory impairments, VLBW subjects report a health status similar to that of NBW controls.[31] Cooke, who included only subjects who had been in mainstream school, thus excluding those with major neurosensory disabilities, found that more VLBW subjects were taking a regularly prescribed medication, most commonly for asthma. There were no differences in the reports of health status between the total VLBW and NBW populations on the SF36 Health Survey in the domains of role limitation due to physical or emotional health, social functioning, mental health, energy and vitality, pain or general health perception. The only significant differences pertained to lower physical functioning, and among males both an overall lower general health perception and lower physical functioning ($P < 0.05$).[15] Ericson and Källén also found a significant reduction in muscular strength (OR 2.7, 95% CI 2.1–3.5) and physical work capacity (OR 3.3, 95% CI 2.2–5.1) in the VLBW young men that they studied.[9] In all studies, the deaths reported after the period of early childhood are similar to those of controls.

ELBW subjects

Saigal et al., like Cook, found no differences in current health status on the SF-36 Health Survey between ELBW and NBW subjects. There were also no differences in the utilization of health-care resources with the exception of home care ($P < 0.05$). Saigal et al. also reported significantly poorer physical functioning exemplified by more problems with coordination, weaker hand-grip measurements, and lower perceived physical ability and physical self-confidence.[30] Rogers et al. examined the aerobic capacity, strength, flexibility and activity of unimpaired ELBW subjects compared to NBW controls in Grunau's cohort of adults with birth weight <800 g. ELBW subjects reported poorer sports participation and demonstrated poorer aerobic capacity, a lower physical activity level and poorer coordination and maintenance of rhythm and cadence. However, despite these deficiencies, the ELBW subjects were satisfied with their level of physical fitness.[32]

Halvorsen et al. in Norway examined respiratory health and function among <28-week and/or <1000 g birthweight subjects. They found that more ELBW than NBW subjects had a current history of asthma and need for asthma inhalers (20% versus 2% and 17% versus 2%, respectively). Pulmonary function tests revealed significantly reduced airflow, increased airway resistance, and increased evidence of bronchial hyperresponsiveness to metacholine among ELBW subjects. These were related to the severity of neonatal chronic lung disease.[28] Northway et al. had previously reported the deleterious effect of chronic lung disease on pulmonary function in 18-year-old LBW subjects born between 1964 and 1973. Similarly to the study of Halvorsen et al., those who had had bronchopulmonary dysplasia ($n = 18$) had significantly poorer pulmonary function—including airway obstruction, airway hyperactivity and hyperinflation—when compared to both preterm subjects who had not had bronchopulmonary dysplasia or to NBW controls.[33] Doyle et al. compared the respiratory function of 20-year-old ELBW subjects who smoked as compared to those who did not smoke, and found higher rates of asthma among smokers as compared to non-smokers as well as poorer lung function; however, he did not compare the lung function of the ELBW to that of an NBW control population.[34]

Thus, with the exception of an increase in neurosensory impairments (see above) which result in the need for more surgical interventions, VLBW and ELBW young adults have a fairly normal health status. However, they both report and demonstrate on examination poorer physical strength and abilities and, in some studies, evidence of higher rates of asthma.[15,28] Residual effects on respiratory function and susceptibility to the effects of smoking are evident.[28,33,34]

Growth attainment

VLBW subjects

Hack et al. found that although males and females had similar rates of intrauterine and neonatal growth failure, VLBW females later demonstrated greater catch-up growth than VLBW males such that by 20 years of age the females did not differ significantly from their NBW controls in weight, height, or body mass index (BMI). At age 20 years, 21% of the VLBW females were overweight (BMI 25–29.9) and 15% were obese (BMI >30), rates similar to their NBW peers. VLBW males, in contrast, remained significantly smaller than their controls in weight, height, and BMI. Predictors of 20-year weight attainment among VLBW females included black race and chronic illness, specifically asthma. Among both males and females height was predicted by maternal height and birth-weight *z*-score (a measure of intrauterine growth), but only in males was height predicted by the severity of neonatal illness.[25] Ericson and Källén reported a significantly lower weight, height and BMI for VLBW males as compared to the general population of males recruited to the Swedish army.[9] Cooke reported a significantly lower height for both male and female young adults, a lower weight for males, but no differences in BMI for males or females. The VLBW females, however, had higher BMI than the NBW controls (24.4 versus 23.4, NS).[15]

Other reports pertaining to long-term growth include those of bone mineral content and head size.[26,35] A study of

growth and bone mineralization in 25 Canadian VLBW subjects at age 16–19 years (30% follow-up rate) revealed them to be shorter than controls. Weight and BMI, however, did not differ significantly between groups. The VLBW subjects had a significantly lower whole-body mineral content, but it was appropriate for their size.[26] Brandt et al. in Germany examined the effects of early postnatal nutrition on brain growth and found that infants born small-for-gestational age (SGA) who demonstrated catch-up of head size by age 12 months ($n = 27$) had a significantly larger head circumference at age 23 years compared to those who did not catch up in head size ($n = 19$), although there was no effect of early nutrient energy intake on adult IQ.[35]

ELBW subjects

Doyle et al. examined weight and height attainment among neurologically normal ELBW subjects. By age 20 years weight did not differ from normative growth. Height attainment was significantly below the norm (z-score of 0, i.e. 50th percentile), although it was consistent with parental height. However, the subjects were relatively heavy for their height. Doyle et al. did not examine gender differences in growth attainment.[14] Saigal et al. found that although catch-up growth occurred between infancy and adulthood, both ELBW males and females had significantly lower weight, height and head circumference than their NBW controls at age 23 years. In contrast to the findings of Doyle et al., their weight and height attainment was significantly less than that of their parents, although their BMIs did not differ from those of their parent or of their NBW controls. These differences remained significant even when the neurologically impaired subjects were excluded.[36] Halvorsen et al. found their ELBW subjects to have a significantly lower height than NBW controls, although weight and BMI did not differ between groups.[28] Rogers et al. reported that 17-year-old neurologically intact subjects with birth weight <800 g had significantly lower weight, height and head circumference than controls.[32]

These results reveal that VLBW and ELBW subjects are at a disadvantage in growth attainment in adulthood. The males tend to be more affected than females. The fact that males remain smaller than their peers may have social implications. The catch-up growth, especially of weight, may predispose both males and females to develop metabolic and cardiovascular disease in later life.[7]

Blood pressure

VLBW subjects

Hack et al. reported a higher mean systolic blood pressure for VLBW than NBW subjects (114 versus 112 mmHg ($P = 0.047$). This occurred predominantly among females (110 versus 107 mmHg, $P = 0.03$; males 118 versus 117 mmHg, $P = 0.66$). Diastolic blood pressure did not differ between groups (females, 73 versus 72 mmHg; males, 74 versus 73 mmHg). The rates of hypertension did not differ significantly between groups. In multiple regression analyses adjusting for maternal education and race, VLBW status had an independent effect on systolic blood pressure in females but not in males. Results of multivariate analyses adjusting for maternal education and race revealed that intrauterine growth did not have a significant effect on systolic blood pressure in female or male subjects. However, among females, intrauterine growth had an effect on diastolic blood pressure ($P < 0.05$).[37] Doyle et al. examined the blood pressure of 145 VLBW subjects who were at least 18 years old and found that they had a significantly higher mean systolic and diastolic blood pressure than the NBW controls. In addition, significantly more of the VLBW subjects had an ambulatory systolic blood pressure above the 95th percentile.[38] Two older studies of the blood pressure of LBW preterm births also reported a significantly higher mean systolic blood pressure among preterm survivors in adulthood.[39,40] However, no association between intrauterine growth failure and systolic blood pressure has been demonstrated in any of the studies,[37–40] suggesting that the higher blood pressure demonstrated among VLBW subjects is related to other factors, including maternal blood pressure (i.e. genetic effects) and adverse neonatal experiences such as type of nutrition, complications of prematurity, stress, and antenatal and neonatal therapies. This increase in systolic blood pressure among preterm subjects which persists into young adulthood may, however, have implications for cardiovascular health later in adult life.

ELBW subjects

The only report is that of Saigal et al. who found no differences in systolic or diastolic blood pressure in their ELBW cohort.[30]

Behavior and psychopathology

VLBW subjects

Hack et al. administered the Achenbach young adult self and parent reports of behavior after adjusting for social risk. VLBW females reported significantly more internalizing problems (i.e. symptoms of anxiety, depression and withdrawal) than NBW females, as well as higher rates of internalizing above the borderline clinical cut-off suggestive of clinical depression. Parents of VLBW women tended to agree with the internalizing symptoms reported by their daughters in that they reported significantly more anxious/depressed and withdrawn problems than parents of NBW control women and higher rates of internalizing above both the borderline and clinical cut-offs. In addition, parents of both VLBW men and women reported that their children had significantly more thought problems as compared to parents of NBW controls.[41,42] A separate questionnaire administered concerning the presence of attention deficit and hyperactivity disorder (ADHD) did not find differences in the self-report of the inattention, hyper-impulsive or combined inattention subtypes of ADHD behavior between male and female VLBW subjects and their respective NBW controls. Parents of VLBW men, however, reported significantly higher mean scores for inattention for their sons than parents of controls ($P < 0.05$), but not higher rates of ADHD according to clinical criteria.[41] Cooke did not find overall differences between VLBW and NBW subjects on the Hospital Anxiety and Depression Scale (HADS), but VLBW females were significantly more likely to have an anxiety state.[15] In contrast, Bjerarger et al. found no differences in mental health between VLBW subjects and

controls.[16] The only report of the presence of psychosis pertains to that of an abstract by Rifkin et al. which noted two cases of schizophrenia among 60 VLBW 20-year-old young men in London but no cases among 80 VLBW women born in the years 1966–1977.[43] Bipolar disorder was reported by 2% of Hack et al.'s VLBW subjects or their parents versus 1% of the NBW controls (not significant).

ELBW subjects

On the Achenbach parent child report Grunau found subjects with birth weight <800 g to have more internalizing ($P < 0.003$), externalizing ($P < 0.005$) and total problems ($P < 0.001$) than NBW controls, which resulted in significantly more problems above the clinical cut-off in internalizing, externalizing and total problems. Parents also reported significant differences in social competence, more withdrawal ($P < 0.05$), social ($P < 0.01$), thought ($P < 0.01$) and attention ($P < 0.001$) problems, and more delinquent ($P < 0.01$) and aggressive ($P < 0.05$) behavior. The problems were greater in the comparisons of males than of females. However, there were no differences in attention using a repetitive computer task.[11] Saigal et al., in contrast, found no differences on the mean depression scores of the CES-D depression scale or in self esteem.[10,44]

Factors predisposing to the development of adult psychopathology which are prevalent among preterm children include poorer cognitive and motor function, learning disability, need for special education, and chronic health problems. It is thus not surprising that the little information available on the behavioral outcomes of VLBW children reveals increased signs of anxiety and depression, especially among females, and among males more attention problems. Retrospective epidemiologic studies have suggested a relationship between perinatal risk and adult psychiatric disorder, including affective disorder and schizophrenia. The relatively small numbers of VLBW subjects studied, the fact that they have only reached young adulthood, and the lack of formal psychiatric interviews preclude any conclusion in this regard.

Social and sexual functioning, risk taking and contact with the law

VLBW subjects

Hack et al. reported significantly less risk-taking—including drug and alcohol abuse and sexual activity—among VLBW subjects, as well as fewer threats to achievement such as delinquent behavior and association with or influence from peers who abuse drugs or alcohol or are sexually active. These differences were primarily due to differences among women and remained significant even when subjects with neurosensory impairments, subnormal IQ, or other chronic conditions were excluded. The parents similarly reported lower rates of alcohol use for the VLBW young adults.[12] There were no significant differences between VLBW and NBW subjects in rates of conviction for a crime or incarceration, being held in jail (including overnight) or in juvenile detention. Fewer VLBW subjects had ever had contact with the police, a difference mainly attributable to the males who had less contact related to truancy (5% versus 14%, $P < 0.05$), or drug or alcohol use (13% versus 29%, $P < 0.01$). VLBW females reported significantly lower rates than controls in sexual activity, pregnancy and childbirth. These included ever being in a steady relationship (46% versus 68%), dating (91% versus 98%), petting heavily (71% versus 86%), having intercourse (66% versus 78%), pregnancy (29% versus 42%), abortion (10% versus 20%) or live birth (14% versus 24%). These differences remained significant when subjects with neurosensory impairments and/or subnormal IQ were excluded. Among males, there were no reported differences in sexual activity or female impregnation.[12] Bjerarger et al. found no differences in alcohol or drug use.[16] Cooke reported that VLBW subjects consumed alcohol less frequently than NBW controls (OR 0.21, 95% CI 0.06–0.075) and smoked cannabis less (OR 0.31, 95% CI 0.12, 0.64). Similar to Hack et al., he also found no differences in smoking between groups. Cooke reported that VLBW participation in social activities was similar to that of controls, with the exception that VLBW subjects frequented pubs less (OR 0.27, 95% CI 0.1–0.72). VLBW adults were more likely to be living at home with their parents (OR 2.52, 95% CI 1.10–5.37) and less likely to be living away from home with their peers, particularly if they were females (OR 0.05, 95% CI 0.01–0.41). There were no differences in the proportion of subjects who had experienced sexual intercourse, the frequency of intercourse, or previous or current relationships. Pregnancy rates were similar. There were also no differences between groups in the rates of involvement with police.[15]

ELBW subjects

Saigal et al. also reported significantly less alcohol and marijuana use and less contact with the police compared to NBW controls. Rates of convictions and incarcerations did not differ. Similar proportions were married (10% versus 7%), living together (13% versus 18%) or had children.[10,44] There was also no difference in the proportion who had left the parental home (42% versus 53%); however, 2.7% versus no NBW were living in group homes. Peer, partner and family relationships were similar, including the mean number of close friends and involvement in clubs and social activities (28% versus 31%) or community service or volunteer work (32% versus 37%). They rated their satisfaction with life similar to that of the controls. A lower proportion of the ELBW subjects were sexually active (62% versus 87%, $P < 0.001$).[44]

Thus, with few exceptions pertaining to subjects with neurosensory and functional disabilities, the VLBW and ELBW subjects report that they have social lives similar to those of NBW controls. They furthermore report less risk-taking, including alcohol and illicit drug use. The rates of criminality do not differ from those of NBW controls.

Quality of life (QOL)

VLBW subjects

Bjerarger et al. examined four basic human needs to assess quality of life: elemental biologic needs, warm relationships, a meaningful occupation, and diverse and exciting experiences. These were rated for their presence (objective), and then the subjects were asked whether the needs were important for their well-being (subjective). Non-handicapped VLBW subjects had similar objective and subjective scores compared to the NBW controls. However, handicapped subjects scored significantly lower on both

objective and subjective quality of life.[16] Dinesen and Greisen studied a similar Danish population 10 years later and found that, due to societal changes, objective quality of life had increased for both VLBW and NBW populations, but more for the NBW controls. During this time the survival of VLBW children had increased from 48% to 81%, and smaller children had survived, with the result that the objective QOL was poorer for the non-handicapped VLBW than 10 years earlier, although the differences between the VLBW and NBW groups remained non-significant. Handicapped subjects continued to rate significantly lower than controls.[27] Cooke in Liverpool, England, reported similar self-reported QOL for VLBW and NBW subjects.[15]

ELBW subjects

Saigal et al., who had previously reported on QOL at age 12—16 years, similarly found that although the self-reported health status at age 23 years of the ELBW subjects was significantly poorer than that of the NBW controls, with sensory problems, cognition and a higher proportion of multiple attributes affected, the ELBW rated their health-related quality of life to be fairly high, despite disabilities, and not to differ from that of the NBW controls.[45]

Gestational-age-based outcomes

The only study of gestational-age-based young adult outcomes published to date is that of Tideman and colleagues who reported on the outcomes of 39 of 46 Swedish 19-year-old subjects born in 1976 and 1977.[19,20] The preterm population, which included those with major congenital malformations, had a mean birth weight of 2034 g and a mean gestational age of 32.5 weeks. The results of the study revealed that although the preterm subjects had significantly poorer school grades compared to term-born controls at age 16 years, by age 19 years these differences had become insignificant. There were also no differences in tests of IQ or history of attention deficits at age 19 years. The preterm subjects reported significantly more somatic health problems but similar rates of mental health problems. They also rated their self-esteem and quality of life similar to that of the term-born controls.[20]

Conclusions

The diverse results of the adult follow-up studies summarized in this review provide a societal life-time perspective of the consequences of preterm birth for VLBW and ELBW young adults who survived as a result of methods of neonatal intensive care introduced in the 1960s and 1970s. Although there are differences between studies, the results reveal that the neurodevelopmental and growth-related sequelae of very low and extremely low birth weight persist into young adulthood. VLBW and ELBW subjects have, in general, poorer educational achievement than NBW controls, and fewer continue with post-high-school study. Rates of employment are, however, similar. There are no major differences in general health status, but when tested the young adults demonstrate poorer physical abilities, higher mean blood pressure and poorer respiratory function. There is no evidence of major psychiatric disorder, although anxiety and depression are reported more often, especially among females. There is also no evidence of increased contact with the law or criminal activity. In contrast, ELBW and VLBW survivors report lower rates of risk-taking than controls. They lead fairly normal social lives and report a quality of life similar to that of NBW controls. When differences are noted they are usually among subjects who have neurosensory disabilities. The effects of disability may be less evident in countries that provide sufficient resources to disabled people.[10,16]

Very few of the studies have, to date, examined the predictors of the adult findings. However, when examined, SES is found to play a major role, especially in the determination of the cognitive and educational outcomes. It has previously been shown that over time sociodemographic factors predominate in determining long-term outcomes, as biologic factors play a lesser role.[46] However, perinatal brain and lung injury will most probably continue to influence the longer-term outcomes of recent VLBW and ELBW survivors. Allin et al. have performed MRI studies of the brains of 32 VLBW survivors in the age range 17—33 years and describe diffuse abnormalities of the gray and white matter. These brain abnormalities are postulated to be a consequence of the interaction between perinatal brain injury and normal processes of brain development.[47] They may potentially have longer-term effects with aging. The catch-up growth and increase in BMI noted in most of the growth studies, together with an increase in systolic blood pressure, are also of concern as they may predispose to type 2 diabetes and cardiovascular risk.[6,7] To gain information in this regard it will be important to maintain the cohorts and continue to follow the survivors into mature adulthood and longer.[48] From a clinical health-care point of view it is also important to transition all VLBW and ELBW survivors into to adult care as they approach late adolescence in order to optimize continuation of the care of existing chronic health problems, and for preventative physical and mental health care.[49,50]

Practice points

- Neurodevelopmental disability persists into adulthood.
- Lower educational achievement.
- Similar rates of employment.
- Suggestion of increase in anxiety and depression.
- Fairly normal social activities and quality of life.
- Suboptimal growth attainment despite catch-up growth.

Research directions

- Longer-term follow-up is needed.
- Study of educational and occupational attainment.
- Study of independent living ability.
- Study of blood pressure, cardiovascular risk and insulin resistance.

Acknowledgements

This work was supported by grants (RO1 HD34177 and M01 RR00080, General Clinical Research Center) of the National Institutes of Health.

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