ABSTRACT

Background Preterm birth at very low birth weight (VLBW, <1500g) has a multitude of consequences that extend to various aspects of adult life. Little is known about the long-term reproductive outcome of VLBW that survive to adulthood.

Aims To evaluate the reproductive outcome of VLBW infants who survive to adulthood (next-generation).

Study Design Retrospective cohort

Subjects Infants born at a single tertiary center between the years 1982–1997 who survived to 18 years of age (first-generation).

Outcome measures The number and the birth weight of offspring from adults born with VLBW were compared to those of other birth weight groups born in the same epoch: 1500–2499g, 2500–3799g (reference group) and ≥3800g. We calculated the ratio of actual compared to expected number of children in the next-generation for extreme birth weight parents, using the reference group as a control group and adjusting for birth year. Thereafter, we measured whether first-generation VLBW had an increased risk for a VLBW in the next-generation.

Results After exclusions, we identified first-generation 67,183 births, including 618 (9.2%) VLBW. There were 193 males and 184 female VLBW infants who survived to adulthood. Both female and male first-generation patients from the VLBW group had half the reproductive rate relative for the normal birth weight group. After adjusting for parental age, male and female VLBW survivors had no significant risk for a VLBW neonate in the next-generation, however, the overall number of are small and may limit any conclusion.

Conclusion VLBW children who reach adulthood may be at a significantly lower reproductive capacity.

Keywords

Very low birth weight, low birth weight, reproductive outcome, preterm birth, prematurity

Abbreviations

VLBW, Very Low Birth Weight

LBW, Low Birth Weight

Introduction

Prematurity is the leading cause of neonatal morbidity and mortality in both developed and developing countries. Advancement in antenatal and neonatal care over the past several decades has led to a consistent increase in long-term survival along with reduced morbidity of prematurely born babies around the world [1, 2]. The incidence of very low birth weight (VLBW, defined as birth weight of 1500g or less) has been rising as a consequence of increased maternal age, maternal morbidity, and multiple gestations. VLBW may be a result of preterm delivery, impaired fetal growth, or fetal malformations. Apart from the higher mortality rates of VLBW neonates, they are at risk for developing short- and long-term health problems due to anatomic and functional immaturity [3]. Nevertheless, the majority of the VLBW born infants survive to adulthood and as a group show an increased risk for long-term chronic health disorders including cardiovascular diseases [4-7], pulmonary diseases [8, 9], glucose intolerance [10, 11] and neurodevelopmental disorders [12, 13]. In spite of their increasing survival and the success in incorporating these newborns into the education and work systems, little information has been published on the long-term reproductive outcome of the VLBW infants once they reach adulthood.

The aim of our study was to investigate the long-term reproductive outcomes of males and females who were born at a VLBW. Towards this purpose, we evaluated the frequency with which these individuals, the first-generation have living offspring, and the risk that their own children, the next-generation will be born at VLBW, compared to a reference group of adults who were born with normal birth rate.

Materials and Methods

We conducted a hospital-based cohort study by linkage of the Shaare Zedek Medical Center (large tertiary medical center) birth certificate database of the children born between July 1982 and June 1997 (first-generation) with the birth- and death certificate registries of the Israeli Ministry of Health for live births in Israel between 2000 and 2015 (next-generation), based on the unique identification number assigned to each Israeli citizen. We included all members of the first-generation for whom a full data set was available, and who survived to at least age 18.

The study protocol was submitted to the Institutional Ethical (Helsinki) Committee and was exempted on the basis of an anonymous analysis (reference number 0212-15-SZMC, dated 04.02.16); Identifying numbers were erased after the data was linked.

Under Israeli law, each maternity center files a birth certificate for every live birth, which is the basis of updating the Israeli population registry at the Ministry of Internal Affairs. Each medical center submits reports directly to the Ministry of Health with information regarding all births (99% of births take place in a hospital). The birth registry includes standardized documentation for mothers and infants at each delivery, including maternal and paternal identification numbers, maternal geographic area of origin, years of formal education, maternal marital status, gestational age, gender, and birth weight (in grams). These records are sent on a monthly basis to the Israeli Ministry of Health and the data is regularly checked for accuracy at the Ministry. Data for this study was prospectively obtained through the longitudinal collection of records for children born in the Shaare Zedek Medical Center between July 1982 to June 1997 and in Israel between 2000 and 2015. Records with missing information were excluded.

For the purpose of the present study, first-generation children born from July 1982 to June 1997 at the Shaare Zedek Medical Center were categorized into groups according to their birth weight: the exposure group was VLBW, <1500g, and compared to the normal birth weight reference group (2500–3799g). Additionally, other birth weight groups first-generation were analyzed in comparison to the reference group; low birth weight (LBW) and high birth weight, <2500g and ≥3800g, respectively. For each patient in the first-generation during the study period, we matched all records of children born in Israel from 2000–2015 using the Ministry of Health database. The end of follow-up was December 31, 2015 or death due to all causes, whichever occurred first.

We hypothesized that, compared to the reference normal birth weight, VLBW that survive to adulthood would have lower reproductive outcomes. The primary aim was to evaluate the VLBW first-generation survivors' fecundity and to assess whether the first-generation VLBW had an increased risk of giving birth to a VLBW in the next-generation, in comparison to first-generation born at normal weight (reference group). The secondary aim was to compute the LBW and high birth weight fecundity and their next-generation birthweight, in comparison to those born at normal birth weight (reference group).

To evaluate fecundity, we calculated the ratio of actual vs. expected number of children (next-generation) for the first-generation, compared with 2500-3799g as the control group. Thereafter, we performed separate logistic regression models for first-generation fathers and first-generation mothers. Explanatory variables were the first-generation parental birth weight, and parental age at the next-generation birth. Due to the long period of the study (almost two decades) we considered it appropriate to adjust for the year of birth in order to control for differences that may had occurred in the population and therapies of the VLBW born infants. To evaluate the next-generation birthweight according to the first-generation birth weight, multivariate regression models were performed using the same explanatory variables. Odds Ratio (OR) and 95% confidence intervals (CI) are reported. All tests are two-tailed; P value below 0.05 was considered statistically significant. Analyses were carried out using SAS 9.3 (Cary, NC, USA).

Results

The study population consisted 67,304 live births between July 1982 and June 1997 in the Shaare Zedek Medical Center. Out of these neonates, 618 were VLBW and 54,336 were of normal birth weight. Overall 873 of the first-generation group were excluded due to missing data (121) or death before age 18 years (752 patients). The final cohort comprised 377 VLBW and 53,906 of normal birth weight (control). The survival rates to age 18 years were 61.0% and 99.3% for VLBW and normal birthweight neonates, respectively (Fig. 1). In the VLBW group, 184 females and 193 males reached adulthood, representing a survival rate of 61.3% and 60.7% for females and males, respectively (Table 1).

After adjustment for calendar birth year, comparing to the entire first-generation cohort of survivors, VLBW survivors had half the expected number of offspring compared with the control group of normal birth weight (OR=0.49, 95%CI 0.33-0.66, p<0.001) for female VLBW survivors (OR=0.52, 95%CI 0.30-0.74, $p<0.001$) for male VLBW survivors (Table 2).

According to the regression analysis presented in Table 3, the likelihood of a first-generation VLBW to become a parent to a next-generation VLBW was 1.31 (95%CI 0.18-9.47) for first-generation females and 2.36 (95%CI 0.33-17.2) for first-generation males, however not statistically significant. The odds ratios for next-generation offspring being LBW for first-generation LBW mothers and fathers were 1.94 (95%CI 1.72-2.21, $p<0.001$) and 1.44 (95%CI 1.18-1.76, $p=0.001$), respectively. Adults who weighed >3,800g at birth had significantly more offspring per person. In addition, they were significantly more likely to have offspring with high birth weight and significantly less likely to have a LBW offspring (Table 3).

Discussion

In this study, we found that adults born at a very low birth weight had significantly lower number of children, compared to adults who were born at a normal weight. Overall, the reproductive rate of both females and males who are VLBW survivors into adulthood is decreased by approximately 50% compared with parents of the normal birth weight group. Moreover, this risk presents a dose-response relationship with lower birth weight parents having a lower likelihood for an offspring at their next-generation compared to those born at normal birth weight. First-generation VLBW survivors had non-significant higher odds ratio for the delivery of a next-generation either VLBW. First-generation LBW survivors had a significantly increased risk for a next-generation LBW “trait” transmission. On the other side of the spectrum, those born at high birth weight had a higher likelihood for an offspring as compared to those born at a normal birth weight. Additionally, those born at a high birth weight had higher odds for a high birth weight offspring and lower odds for a low birth weight offspring.

Previously, a large population-based study, an overall of 1471 females and 1329 males who were born at a VLBW in Sweden between 1973–1983 were followed up to 2006 [14]. They reported that VLBW male and female neonates (birth weight 1000–1500g) who survived to the age of 13 years had hazard ratio of 0.83 (0.71–0.95, p=0.02) and 0.80 (0.72–0.89, p<0.001), respectively for having living offspring, respectively. No data on next-generation birth weight was given. A Swedish population registry-based study [15] followed 436 VLBW females born in the years 1973–1975until 2001. Compared to women born in the same period with normal birth weight, the VLBW adults had a likelihood of 0.74 (95%CI 0.60-0.91) for giving birth to a child, consistent with the experience of our study group. The Swedish study did not provide information on next-generation birth weight. First-generation newborns who had a high birth weight (≥3800g) had the highest reproductive yield with a high rate of "large trait" transmission to the next-generation.

In an analysis [16] of Norwegians born between 1967–1988, those born before gestational week 27 had an absolute reproduction rate of 25% in females and 14% in males compared with rates of 68% in females and 50% in males who were born at full term during the same period. In addition, preterm women, but not men, were at increased risk of having a preterm offspring. In a subsequent prospective cohort study [17] of the correlation between Danish women's gestational age and her fecundability, women who were born before gestational week 34 had a reduced adjusted fecundability rate compared to women born at the conclusion of a full-term pregnancy (OR=0.39, 95%CI 0.18-0.84). However, only 19/2814 participants were born at before gestational week 34. Hack et al. [13] compared 116 young adults born with VLBW to normal birth weight young adults and found that VLBW men had an equal probability (0.7, 95%CI 0.4–1.5) of having living (next-generation) offspring, while women had a reduced probability 0.4 (95%CI 0.2–0.9) for a live birth.

It is noteworthy that most of these analyses describe first-generation adults who were born three to four decades ago, during a different era in perinatal care. This era preceded the widespread use of antenatal corticosteroids for preterm birth along with postpartum use of surfactant [18], and many other practices have changed leading to a constant increase in the VLBW survival with less significant morbidity [2, 19, 20]. In the present study we adjusted for the year of birth of the first-generation in order to control for the change in the perinatal care. However, an unadjusted analysis showed similar trends. Indeed, if the results were different, then adjusting for an intermediate such as year of birth could produce biased results [21].

We may postulate on several explanations for the reduced reproductive outcome of adults who are VLBW survivors. First, this population is known to have a high rate of early morbidities of this population. Although they survive to adolescence and young adulthood, they may suffer from conditions such as cerebral palsy or blindness which limit their social functioning and independence, so they are less likely to date a romantic partner [22]. Second low fertility may be a result of insufficient or altered maturation of the hypothalamic-pituitary-gonadal axis, as evidenced by increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) seen for up to 3 months in girls born before the 34^{th} gestational week [23]. A similar elevation is also noted in luteinizing hormone (LH) and testosterone among boys born preterm [24]. Third, infertility may be “mechanical infertility” secondary to abdominal surgery, which is common in the VLBW population due to necrotizing enterocolitis and its complications

[25]. Reduced fertility is also noted among VLBW males who in many cases had a surgically corrected undescended testis [26, 27].

Although both VLBW and LBW first-generation adults had lower reproductive rates, significant odds for an offspring with LBW was observed for the LBW parents only. This intriguing observation could be the result of the smaller number of adults who were VLBW survivors in the study population as compared to the LBW survivors of the first-generation. Nonetheless, this could be a genuine reflection of the concept that preterm birth is a complex syndrome and its risk factors, etiologies and genetic clusters contribute to the risk of preterm gestational age at birth [28, 29]. Preterm births may be due to maternal health problems, gestational conditions, or may be spontaneous secondary to various etiologies at different gestational age. Nevertheless, the underlying cause remains unknown for a significant proportion of preterm births. Regardless of the primary circumstances leading to preterm birth, there is strong evidence that genetics plays an major independent role in preterm birth [30]. However, preterm birth does not clearly follow traditional monogenic or Mendelian patterns of inheritance, but rather clusters in families and is commonly due to de novo fetal mutations or epigenetic mechanisms [31, 32]. We may postulate that the LBW birth trait is transmittable and translated into pregnancy complications, while the birth of a VLBW infant might be an incidental non-repetitive phenomenon.

The apparent reproductive advantage of the newborns ≥3800g individuals and its transmission is difficult to interpret. High birth weight is related to multifactorial and hereditary morbid states such as maternal diabetes mellitus and obesity [33]. Nevertheless, it may reflect the tendency to late maternal age and improved socioeconomic status [34, 35].

Our study is not without limitations. [1] The most important limitation is the small numbers of VLBW individuals included in the study, thus limiting the significance of our results. Therefore, our results may be of limited value. Nevertheless, any information about VLBW may prove helpful to the parents and children. [2] Despite the overall limited number of LBW and VLBW in the first generation, we could not integrate all in a single group and perform more significant analyses since the neonatal course and adult life prognosis are significantly different among these birth weight groups. Due to this different "postnatal natural history" limitation, which is common to many studies, an international task force has been established to provide a platform for comparative evaluation of outcomes and present protocols for future studies on LBW and VLBW newborn.[1] [3] Several factors associated with reduced reproduction are not included the national birth registry; therefore, factors such as medical conditions and body mass in adults born with VLBW could not be analyzed. [4] Congenital and genetic abnormalities are known to be associated with VLBW were not excluded in this study. [5] We lack data on the proportion of VLBW survivors who attempted to conceive. [6] For “rare” outcomes such as VLBW, Odds Ratios estimate well the Risk Ratios, but this might not be the case for less rare outcomes such as 1500-2500 g or ≥3800 g infants, however the paper is intended to assess the VLBW, and therefore we used Odds Ratio for all outcomes [7] Ethnicity, socioeconomic status, and religious beliefs may have an impact on the age and motivation for reproductive outcome of the population included; however, we could not identify these trends from the available data.

The study also has strengths. [1] Data was extracted from mandatory national registries, which cover information on all citizens including alive/deceased status, and parenting.

[2] All mothers and infants in Israel benefit from equal and uniform health care coverage under the National Health Insurance Plan.

In conclusion, adults who had VLBW at their own births appear to have had fewer offspring compared with adults born at a normal birth weight during the study period. Additionally, the LBW did have higher odds for having LBW children compared to adults who had normal birth weight. This information should be available to caregivers and be considered in the care of VLBW who reach adulthood. Further studies of birth rates, and of the birthweight of children born to adults at extreme birth weights is warranted.

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Figure 1: study population categorized into birth weight groups

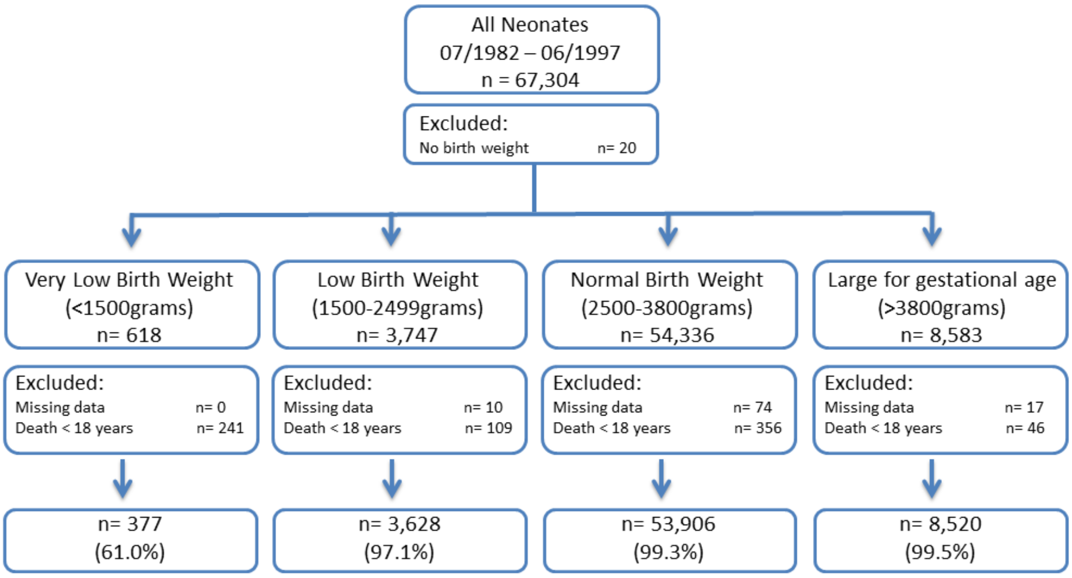

Table 1: First-generation birth weight and survival to adulthood according to gender

First-generation*	Birth weight (grams)	Total born (n)	Survivors to age >18 (n)	Survival (%)
All	All	67183	66431	98.9%
Female	<1500	300	184	61.3%
	1500–2499	2079	2033	97.8%
	2500–3799	27224	27081	99.5%
	≥3800	3159	3146	99.6%
	All	32762	32444	99.0%
Male	<1500	318	193	60.7%
	1500–2499	1658	1595	96.2%
	2500–3799	27038	26825	99.2%
	≥3800	5407	5374	99.4%
	All	34421	33987	98.7%

* Figures are after exclusion of cases with missing data

Table 2: Number of next-generation offspring and the adjusted odds ratio for offspring according to first-generation birth weight

First-generation	First-generation birth weight (grams)	Number of next-generation offspring (n)	Unadjusted number of offspring (n)	Adjusted ratio of actual vs. expected (95%CI) for a next-generation offspring[1]
Either	<1500	175	0.46	0.51 (95% CI 0.37-0.64, p<0.001)
	1500–2499	3497	0.96	0.84 (95% CI 0.81-0.88, p<0.001)
	2500–3799	63304	1.17	1.00[2]
	≥3800	9785	1.15	1.03 (95% CI 1.01-1.06, p=0.008)
Female	<1500	107	0.58	0.49 (95% CI 0.33-0.66, p<0.001)
	1500–2499	2316	1.14	0.85 (95% CI 0.80-0.89, p<0.001)
	2500–3799	36897	1.36	1.00[2]
	≥3800	4323	1.37	1.07 (95% CI 1.03-1.11, p<0.001)
Male	<1500	68	0.35	0.52 (95% CI 0.30-0.74, p<0.001)
	1500–2499	1181	0.74	0.78 (95% CI 0.72-0.85, p<0.001)
	2500–3799	26407	0.98	1.00[2]
	≥3800	5462	1.02	1.08 (95% CI 1.05-1.12, p<0.001)

CI, Confidence Interval

[1]Adjusted for first-generation birth year

[2]Survivors of the 2500–3799g birth weight are the control group.

Table 3: Regression analysis for the offspring (next-generation) birthweight according to parent birth weight (first-generation)

First-generation gender	**First-generation birth weight (grams)**	**Next-generation birth weight <1500 grams**			**Next-generation birth weight <2500 grams**			**Next-generation birth weight ≥3800 grams**		
		OR	**95% CI**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Female	<1500	1.31	0.18–9.47	0.787	1.43	0.75–2.76	0.279	0.44	0.18–1.09	0.077
	<2500	1.10	0.68-1.78	0.691	1.94	1.71-2.21	**0.000**	0.51	0.42-0.62	**0.000**
	1500-2499	1.09	0.67–1.79	0.726	1.97	1.72–2.25	**0.000**	0.51	0.43–0.62	**0.000**
	2500–3799	1.00	Reference		1.00	Reference		1.00	Reference	
	≥3800	0.96	0.64–1.45	0.861	0.68	0.58–0.80	**0.000**	2.47	2.28-2.68	**0.000**
Male	<1500	2.36	0.33–17.2	0.395	1.43	0.62–3.34	0.403	1.10	0.50–2.42	0.810
	<2500	2.01	1.20-3.37	**0.008**	1.44	1.18-1.76	**0.000**	0.77	0.62-0.95	**0.015**
	1500-2499	1.99	1.17–3.39	**0.011**	1.44	1.17–1.77	**0.001**	0.75	0.60–0.93	**0.011**
	2500–3799	1.00	Reference		1.00	Reference		1.00	Reference	
	≥3800	1.17	0.82–1.66	0.381	0.86	0.75–0.98	**0.022**	1.99	1.83–2.15	**0.000**

OR, Odds ratio; CI, Confidence Interval