AMERICAN UNIVERSITY OF ARMENIA

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Case Control Study Aimed at Revealing Risk Factors of Low Birth Weight in Yerevan City

A research grant proposal

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Abstract

Low birthweight (LBW) is among the leading causes of infant mortality. While the factors associated with LBW are well studied in developed countries, little information is available on its causes in developing countries. In particular, the relative or independent contributions of established LBW risk factors are not well examined in transitional countries like Armenia. Meanwhile, a better understanding of LBW causes in developing countries is essential for designing specific cost-effective interventions aimed at reducing LBW rates. With increasing incidence of LBW in Armenia, exploring the causes of LBW has become an important task for Armenian health care authorities. This paper proposes conducting a case-control study that will reveal the contribution of selected risk factors to the incidence of LBW in the city of Yerevan, Armenia's capital. The paper describes main LBW risk factors, discusses their relevance in Armenia, and explains study's methodology and analytical plans. Once the study is completed, its results can be used by the Armenian Ministry of Health, international aid agencies, non-profit organizations, and other parties in devising effective policies aimed at decreasing infant morbidity and mortality in developing countries. The study will also contribute to the current knowledge on LBW risk factors.

Specific Aims/Objectives

The goal of this study is to assess the contributions of known LBW risk factors in the city of Yerevan. The objective of the study is to assess the independent effects and interactions of selected LBW risk factors. Specific objectives of the study are to test the hypotheses that, (1) mother's primary and secondary smoking, (2) caffeine consumption during the pregnancy, (3) short inter-pregnancy intervals, and (4) insufficient weight gain during the pregnancy increase the risk of LBW.

Background

Low birthweight constitutes a major public health problem worldwide, and is one of the determinants of neonatal and infant death [1, 2, 3]. The World Health Organization refers to LBW as infants born with weight of less than 2500 grams [4]. They are classified into two groups depending on their weight: very low birth weight (VLBW), (newborns weighing 500 to 1499 grams), and moderately low birth weight (MLBW), (newborns weighing 1500 to 2499 grams) [5, 6]. Low birthweight is a result of preterm birth, impaired fetal growth (intrauterine growth restriction), or a combination of both pathophysiologic conditions [7]. Preterm birth refers to cases when the gestational age of the fetus is less than 37 weeks; intrauterine growth restriction refers to cases of birth weight below the 10^{th} percentile for gestational age. Preterm birth is considered to be more important in affecting infant mortality rates [8]. The relationship between LBW and infant mortality has been documented in numerous studies [9, 10, 11]. Research conducted in the United States shows that, during their first year of life, white MLBW infants have 4 times, and VLBW infants have 84 times greater risk of dying compared to the infants born with normal birthweight. In addition, during their neonatal period, white MLBW infants have 6 times, and VLBW infants have 160 times greater risk of dying than the infants born with normal birthweight [12, 13]. Other studies conducted worldwide confirm these findings [14, 15, 16].

Studies showed that LBW affects childrens' health even beyond their first year of life. The most common medical conditions found in LBW children after the first year of life are asthma, upper and lower respiratory infections, and ear infections [17]. It has been shown that, compared to the children born with a normal birth weight, the LBW children are more often hospitalized for above-mentioned medical conditions and surgeries related to adenoids, tonsils, and orthopedic problems [18]. Research also shows that older children who had had LBW are at a higher risk of developing neuro-developmental disorders and learning disabilities compared to the normal birthweight (NBW) children [19]. Finally, the consequences of LBW can be found among adults, as *Newnham* showed an association between the LBW and adult hypertension [20].

Based on the above findings, one can conclude that the problem of LBW has implications for public health services in that the hospitalization rates and average length of stay of LBW infants in the hospitals are higher compared to NBW infants. Hence, treating LBW infants costs more. According to *Lewit et al.*, in addition to medical costs, the LBW cost components include special education, early intervention, and other support services consumed disproportionately by LBW children. Other often overlooked components of the LBW costs are the time and money that parents of sick LBW babies devote to their care [21].

Finally, the problem of LBW has implications on the family function. Past studies showed that the bonds between mothers and critically ill infants may be disrupted, which results in an inappropriate parental behavior such as overprotectiveness or physical abuse [22]. Research conducted by *Singer et al.* shows that, during the neonatal period of VLBW infants, their mothers are likely to experience psychological distress [23].

Preliminary Studies on LBW Risk Factors

Low birthweight is a result of two pathophysiologic conditions: prematurity and intrauterine growth retardation (IUGR) [24]. In the pathophysiology of premature birth, the uterine contractions are believed to play a major role. They are affected by a number of factors, including endocrine changes in mother's body, fetal cortisol, estrogene, and progesteron. Structural and biochemical reorganizations of the myometrial muscle are also thought to affect uterine contractions. However, the mechanisms by which these factors induce uterine contractions are still unclear [25]. It is believed that, infectious diseases, stress, hypertension, and other conditions influence the hormonal changes and the state of the myometrium. Analysis of etiologic factors done in the past revealed premature rupture of fetal membranes and maternal-fetal problems as other causes of premature birth [26].

The factors causing IUGR are many and include placental defects, hypertension, pulmonary disease, infectious diseases, cigarette smoking, and excessive coffee consumption [27]. These factors affect the health and nutritional status of the pregnant, reduce the delivery of oxygen and nutrients to the fetus, and cause metabolic stress. Under this condition, the fetus exerts an anti-insulin response that is thought to be regulated by catecholamines. As a result of this response, the fetuses fat stores, muscle mass, and glycogen stores are being depleted, which results in fetal growth restriction. Despite an extensive amount of research, the exact mechanisms causing IUGR have not been confirmed [28].

As it was stated earlier, there are various conditions associated with LBW (causing either IUGR or preterm birth). They can be classified as **genetic** (e.g. race, congenital anomalies, constitutional characteristics), **demographic** (e.g. mother's age, socioeconomic status), **nutritional** (e.g. weight gain during pregnancy), **medical** (e.g. infections), **behavioral** (e.g. cigarette smoking), and **related to health care services** (e.g. quality of prenatal care).

Race

Numerous studies have shown that LBW rates are higher among black neonates than among whites [29, 30]. Although it is asserted that race has an independent effect on the LBW, its effect may have been confounded by other factors [31]. For instance, it is known that the average educational attainment, health care utilization patterns, socioeconomic status, and health behavior vary across racial groups. Since the above-mentioned factors are related to the LBW, they disproportionate prevalence across racial groups may be the underlying cause of disparity in LBW rates.

Mother's Age

It is known that among primiparous women (*bearing first child*) of age groups below 20 and above 35 the LBW deliveries occur more often than in other age groups. A review of international studies by *Makinson* shows a strong association between mother's young age and the risk of LBW [32]. Similarly, older age of primiparous mothers has also been found as a risk factor for LBW [33]. For instance, a case-control study conducted in Israel showed that, babies born from women aged over 35 years had significantly higher incidence of LBW ($p = 0.001$), prematurity (< 37 weeks, $p = 0.02$), and intrauterine growth retardation ($p = 0.001$) than babies born from mothers aged 35 and younger. [34].

As it was the case with race, researchers argue that the effect of age on LBW is not independent. Some studies suggest that the high incidence of LBW deliveries among very young mothers is explained by the fact that the latter had been exposed to other LBW risk factors, such as low socioeconomic status, low education, poor nutrition, and low body mass index. It is not clear, however, what contributes to the high risk of LBW deliveries among mothers over 35. Most studies hypothesize that physiological changes in the uterus account for that phenomenon. According to *Stein and Susser*, older mothers have a "social advantage" but are "biologically disadvantageous" compared to the younger mothers. The authors mention higher rates of chromosomal anomalies, pre-eclampsia, and diabetes as factors modifying effect of older maternal age on incidence of preterm births [35].

Socioeconomic Status

Among most commonly used indicators of social status are education, occupation, family income, and unemployment [36, 37]. Past research has established associations between the above-mentioned factors and LBW [38,39]. For example, in a cross-sectional study, *Karim et al.* found that LBW deliveries were more common among mothers with low income and low educational attainment [40]. *Lekea-Karanika et al.* found that LBW was associated with maternal occupation and father's education among primigravidae, and mother's education and place (region) of residence among miltigravidae [41].

Stress

There is evidence that mother's stress during pregnancy is associated with LBW incidence [42, 43]. When measuring the impact of stress on LBW, physical and psychological stress need to be differentiated. Studies assessing the effects of physical stress show that, infants born to mothers who worked during the third trimester of pregnancy had lower average birth weight, compared to those whose mothers did not work during the pregnancy. Similarly, *Berkowitz* asserts that mothers, who stood while working during the pregnancy delivered greater number of IUGR babies than those who did not work [44]. On the contrary, in a prospective study *Klebanoff et al.* showed that prolonged periods of standing (≥ 8 hours per day) were *only* associated with a modest increase in the risk of pre-term delivery (adjusted OR = 1.31), while heavy work or exercise (≥ 12 hours per day) was not associated with preterm delivery (adjusted OR = 1.04) [45]. In a longitudinal study *Homer et al.* found that working women who experienced high levels of physical exertion during pregnancy had higher rates of low birthweight delivery (adjusted RR = 5.1, 95% CI = 1.5, 17.7) [46]. Other studies [Cardiff British survey] showed that there was no negative effect of the employment on the birth weight. Moreover, the proportion of growth retardation was higher among infants whose mothers were unemployed.

Studies assessing the effect of psychological stress on LBW yield conflicting results. *Orr et al.* found association between psychological stress and adverse health outcomes [47]. Using standard reliable questionnaires that measured episodic and chronic stress, strain (response to stress), and pregnancy-related anxiety, *Wadhwa et al* found that, independently of biomedical risk, each unit increase of prenatal life event stress was associated with a 55.03 gm decrease in infant birth weight and a significant increase in the risk of low birthweight (odds ratio 1.32). It was also found that each unit increase of prenatal pregnancy anxiety was associated with a 3-day decrease in gestational age at birth [48]. On the other hand, *Sheehan* found that economic stress, family stress, social support, or its absence have no direct influence on low birth weight [49]. It should be noted that the conflicting results of the vast number of studies assessing effect of psychosocial stress on LBW are partly due to their limitations, such as small sample size, recall bias, absence of common ascertainment of stress, and lack of control for confounders.

Number of Previous Live Births

There is a negative association between the number of previous births and the risk of LBW. Most studies indicate that there is a positive association between the number of mother's previous deliveries and infant's mean birth weight [50]. However, they speculate that the effect of parity on LBW may be modified by other risk factors. For instance, one study found that among primiparous mothers, the effect of smoking and age on the LBW risk is greater compared to multiparous mothers [51]. Since primiparous mothers are likely to be of younger age, they may differ from older multiparous mothers by their height, pre-pregnant weight, nutrition, exposure to smoking, utilization of prenatal care, social status, and thus, have greater exposure to LBW risk factors. Those factors need to be controlled for when estimating the individual effect of parity on LBW.

Interpregnancy Interval

The effect of interpregancy interval on LBW is determined by different mechanisms, among which hormonal and nutritional factors are the most important ones. Short interpregnancy interval is considered an independent risk factor for LBW. Using multivariate analysis, *Shults et al.* found that, compared to those having interpregnancy intervals of 13-24 months, mothers having interpregnancy intervals 1-3 months had an adjusted odds ratio of 1.6 for delivering a small for gestational age (SGA) baby [52]. Studies in which confounders were controlled, found that interpregnancy intervals less than 6 months increase the risk of LBW [53]. On the other hand, other studies found an association between short interpregnancy intervals (≤ 8 months) and preterm birth, but not with low birth weight [54].

Mother's Body Mass Index

Studies conducted in the past have shown an association between maternal prepregnancy weight and the size of the newborn [55]. According to one study, women with low pre-pregnant body mass index (BMI < 20) had 1.8 times increased risk of delivering a LBW baby (95% CI: 1.32-2.43), compared to women whose pre-pregnant BMI was 20 and above. It was also found that short maternal height (< 150 cm) was associated with a significant LBW risk (1.47; 95% CI: 1.03-2.12). Another study by *Deshmukh et al.* found that among other factors maternal height (OR-2.78) and body mass index (OR-2.02) were associated with LBW [56]. Similarly, *Amin et al.* found association between maternal height and weight and LBW [57].

Weight Gain During Pregnancy

Physiological weight gain during pregnancy is normally between 10 and 16 kg, and represents 20% of the body's pre-pregnancy weight [58]. The increase in pregnant's weight is usually lower during the first trimester and higher during the second and third trimesters. Studies have found a correlation between poor weight gain and LBW. In an American study of two cohorts, it was found that low weight gain during pregnancy (defined as <-0.1 kg/wk for the 1st trimester and <0.3 kg/wk for 2nd and 3rd trimesters) was associated with an increased risk of intrauterine growth retardation [59]. Similarly, a case-control study conducted by *Lawoyin* showed that, when compared to mothers of NBW babies, mothers who delivered LBW babies gained significantly less weight during the 3rd trimester of term pregnancy [60].

Anemia

It has been established that iron deficiency anemia in pregnancy is a risk factor for preterm delivery and low birthweight. Study by *Lawoyin* showed that mothers of preterm LBW babies had significantly lower hemoglobin levels compared to mothers of NBW babies; however, no difference was found in hemoglobin levels of term LBW and NBW mothers. Similarly, a cohort study conducted in India detected anemia as a significant risk factor for LBW (OR=4.84) [61]. Another study conducted by *Scholl and Reilly* found that early maternal anemia (one that is present before midpregnancy) increased the risk of preterm delivery; however, maternal anemia occurring during the later stages of pregnancy was not associated with the risk of preterm delivery [62].

Hypertension

Pregnancy-induced hypertension (classified as gestational hypertension, preeclampsia, or severe preeclampsia-eclampsia) may increase the risk of LBW. A matched case-control study in Argentina showed that gestational hypertension, preeclampsia and eclampsia increased odds of giving birth to small for gestational age infants (OR = 7.08; 95% CI: 3.07-18.6), LBW (OR = 1.8, 95% CI: 1.24-2.60), and

VLBW infants (OR = 2.14; 95% CI: 1.13-4.19) [63]. Several other studies revealed maternal hypertension as a risk factor for LBW. For instance, a retrospective study of birth certificates by *Fang et al.* showed a strong association between the hypertension and LBW both among whites (3.58, 95% CI = 3.39-3.79), and blacks (1.99, 95% CI = 1.93-2.06) [64]. Another large retrospective cohort study of 16,936 births in China failed to establish an association between gestational hypertension (adjusted OR 1.56 [1.00-2.41]), but found an increased risk for LBW among mothers with preeclampsia and severe preeclampsia (adjusted OR 2.65 [1.73-4.39] and 2.53 [1.19-4.93]) [65]. Thus, the majority of studies yield similar results in that pregnancy hypertension, eclampsia, and preeclampsia increase the risk of LBW [66, 67].

Poor Obstetric History

Numerous studies have shown a relationship between LBW and previous miscarriages, induced abortions, stillbirths and history of hemorrhage during a prior pregnancy. For example, a cohort study conducted in Scotland showed that a history of prenatal death and spontaneous abortion was associated with the risk of LBW [68]. A population-based study conducted in Greece revealed that, mothers who had previously experienced miscarriages, induced abortions, or stillbirths were at higher risk of delivering LBW babies compared to mothers without any previous fetal loss (RR = 1.65, 1.81 and 3.59 respectively) [69]. Similarly, results of a case-control study conducted by *Paz et al.* showed that among other adverse pregnancy outcomes, low birthweight was associated with previous fetal loss [70].

Despite a fairly large number of studies suggesting an association between the LBW and poor obstetric history, there are several published papers suggesting that none exists. [71, 72]. *Basso et al* suggested that lack of control for confounders could yield conflicting results or overestimate the effect of induced or spontaneous abortions on LBW. In their study, the authors assessed risk of LBW and growth retardation in two cohorts: women with poor obstetric history (women having a livebirth preceded by a spontaneous abortion) and a sample of women who had given two consecutive livebirths (reference cohort). The results showed that the abortion cohort had higher risks low birthweight (OR = 1.76, 95% CI: 1.5-2.1) and intrauterine growth retardation (OR = 1.50, 95% CI: 1.4-1.6) [73].

Other studies that claim to have controlled confounders found little or no association between the LBW and induced previous abortions. For example, an analysis of perinatal data in an Australian territory by *Algert et al* found unadjusted risks ratio (RR) of small for gestational age in singleton births following induced abortion of 1.2 (95% CI : 1.1,1.2), but after adjustment for 11 potential confounders the RR was even closer to one [74]. A similar finding was observed by *Mandelson et al* [75].

Infections

Studies show that infections during pregnancy increase the risk of LBW. In a case control study, Schultz et al. found that, after controlling for potential confounding variables the OR for giving birth to LBW infants was higher among women who had genitourinary tract infections (OR = 4.0, 95% CI 2.3; 7.0). The association was present for infections occurring both during pregnancy and at the time of delivery [76]. Similarly, *Chaim et al.* showed an association between LBW and bacterial vaginosis, the most prevalent form of vaginal infection of reproductive age women [77]. A case-control study conducted in Canada showed that Gonococcal infection as well as other STDs is independently increasing the risk of LBW [78].

Smoking

Most studies show smoking during pregnancy increases risk of LBW [79]. Studies assessing effects of passive smoking yield conflicting results. A cohort study conducted in Sweden showed that, after controlling for confounding factors such as age, height, weight, nationality, education, passive smoking in early pregnancy increased woman's risk of delivering a small-for-gestational-age infant (odds ratio [OR] = 2.7). The study also showed an interaction of maternal smoking and passive smoking in increasing the risk of delivering small-for-gestational-age infants [80]. On the other hand, in a case control study *Chen et al.* found no association between passive smoking and the risk of term small-for-gestational age infants [81].

Prenatal Care

Early prenatal care may have a beneficial impact on the growth and development of the fetus through prevention and timely treatment of complications of pregnancy such as toxicosis, hypertension, and diabetes [82]. Through prenatal care behavioral risk factors for LBW may be detected and their exposure reduced. Among those risk factors, which can be modified, are smoking, insufficient food consumption, intensity of work during the pregnancy [83].

Two main factors, adequate prenatal care and first prenatal visit, play a major role in prevention of LBW. *Kramer* notes that that the risk of delivering a LBW baby is lower among mothers who applied early for prenatal care [84]. The author clarifies that many studies assessing the effect of prenatal care have limitations, such as lack of control of gestational age as a confounder (mothers of preterm infants had less time to apply to prenatal care), as well as health status of the pregnant (those who are sick could have applied for a prenatal care earlier).

Risk of LBW is thought to be associated with the number of mother's prenatal visits. In fact, the more contacts a pregnant woman has with health workers who are lessening the effects of risk factors, the better will be the outcome of pregnancy. In some studies, the effect of prenatal visits on birth outcome was analyzed together with the effect of first prenatal visit. Lack of control over confounders is among the limitations of those studies (gestational age). Thus, the studies did not allow precise estimates of the separate effect of the number of prenatal visits on the risk of LBW.

Quality of Prenatal Care

Many publications showed a relationship between the quality of prenatal care and risk of preterm birth or intrauterine growth retardation. It has been shown that the adequate and intermediate (compared with inadequate) prenatal care was significantly associated with a lower risk of low birthweight. The low risk remained after adjusting for maternal age, maternal body mass index, social class, marital status, cigarette smoking, pregnancy weight gain, and complications of pregnancy. Therefore, the quality of prenatal care has an independent effect on risk of LBW.

Based on the literature review conducted above, the principal LBW risk factors can be listed in the table below:

Principal LBW Risk Factors

Genetic and constitutional factors	Medical risks in current pregnancy
Race	Multiple pregnancy
Height of mother	Infections
Mother's prepregnancy weight	Nutritional factors
Gender of the newborn	Weight gain during the pregnancy
Demographic and psychosocial factors	Energy consumption and physical activity
Age of mother	Medical risks predating pregnancy
Socioeconomic status	Diabetes
Marital status of mother	Chronic hypertension
Mother's psychological and physical stress	Behavioral and environmental risks
Obstetric factors	Smoking
Number of previous live births	Caffeine and alcohol consumption
Intervals between pregnancies	Health care risks
History of abortions	First prenatal visit
Previous LBW child	Number of prenatal visits
	Absent or inadequate prenatal care

Relevance of LBW Risk Factors in Armenia

The population of Armenia has unique demographic, socioeconomic and cultural characteristics. One of demographic peculiarities of Armenian population is its ethnic homogeneity: approximately 94% are Armenian. Therefore, race as a LBW risk factor is not relevant for Armenia, since the country's population is entirely made up of one race.

Virtually the whole population of the country is literate (99%) and has access to mass media [85]. Although in the past Armenian women rarely smoke, during the last decade the number of smoking women was on the rise. Although no accurate information is available, sociologists estimate that the rate of increase of smoking women is higher in Yerevan compared to the regions. In an unpublished report, *Vardanian* states that every 5th woman in Yerevan smokes at least 1 cigarette a day [86]. Vardanian further confirms that the Armenian women exhibit low alcohol consumption behavior. It can, therefore, be presumed that the smoking, but not alcohol consumption may be a relevant LBW risk factor in Armenia.

Armenian population is characterized by low levels of social and economical life, high unemployment, and poverty. According to World Bank, Armenia's GDP per capita was $2,233 (compared to the US $31,500). Although country's GDP has been increasing during last 10 years, so does the income gap of the population [87]. According to World Bank human development reports, the ratio of average income in highest 20% to the one in lowest 20% has increased more than four-fold from 1991 to 1995. These facts support the speculations that LBW rates will differ among high and low income groups. Thus, mother's socioeconomic status may well be considered a relevant risk factor for Armenia.

Armenia has a high abortion rate - 2.7 abortions per woman [88]. Connected with this, the incidence of adverse pregnancy outcomes is expected to be high among Armenian women. Therefore, poor obstetric history should be accounted for, when studying the risk factors of LBW.

Due to constantly increasing prices and stagnant, unpaid, or decreasing salaries, many food products have become unavailable or unaffordable for large portion of Armenian population, and both food security and food safety are major concerns. The people widely consume many foods (especially imported) that do not meet nutrition and safety standards are widely consumed. The situation analysis of children and women in Armenia conducted mainly by the government, UNICEF and Save the Children showed that the nutrition status of many women of reproductive age is not appropriate [89]. Therefore, when studying LBW risk factors in Armenia, contribution of nutritional factors to be considered.

Armenian NGOs have reported on the poor condition of prenatal services. There has been a considerable increase in the incidence of anemia in pregnant women in recent years, as well as deficiencies in breast-feeding, and other related health problems. As a result of socio-economical difficulties, the number of women attending prenatal clinics has dropped. According to the statistics of the Armenian Ministry of Health, the percentage of pregnant women under the supervision of prenatal clinics has been decreasing. Consequently, the prenatal services face difficulties in organizing preventive examinations among high-risk pregnant. As a result, incidence of pre-eclampsia and eclampsia cases increased significantly from 2.3% in 1980 to 7.1% in 1993 [90].

Because of increasing prevalence of risk factors related to prenatal care, pregnant's health status, and obstetric history, their contributions in causing LBW must be assessed.

Problem of LBW in Armenia

In Armenia, the rate of LBW had been increasing from 5.7% of all live births in 1980 to 8.0 % in 1995. In 1996, the Ministry of Health adopted registering infants born with birth weight from 500-1000 grams and because of that change the rate of the LBW increased up to 8.4% [91]. According to specialists of the Armenian Ministry of Health, LBW rates will continue to increase in years to come [92]. Precise information on LBW burden in Armenia is not available, but statistics on developing countries suggests that 33-40% of infant deaths in developing countries (population attributable risk) can be attributed to LBW [93]. According to UNICEF's "The State of the World's Children 1998" report, LBW children have higher risks of impaired cognitive development and malnourishment in later childhood. The problem of LBW is associated with substantial financial costs and often causes emotional pain and suffering to children and their families.

It is obvious that with the increasing rates of LBW, the magnitude of problems associated with it will also increase. Therefore, there is an urgent need for answers to basic and fundamental questions regarding prevention of LBW. In order to prevent LBW in Armenia, its main modifiable risk factors need to be understood. Additionally, the interrelationships between biological mechanisms and social, psychological, and cultural factors need to be investigated. Results of the research would be critical in developing interventions aimed at lengthening inter-pregnancy intervals, modifying behavior, and promoting adequate weight gain during pregnancy.

In their joint report "Situational Analysis of Maternal and Child Health of Armenia" Ministry of Health and UNICEF state that the issue of LBW needs to be investigated. This paper proposes conducting a study examining risk factors of LBW in the city of Yerevan. The vast majority of studies conducted on LBW are of a prospective type, have long duration and are expensive. Meanwhile, case-control studies conducted in the past proved to be cost-effective and had significant results [94]. The proposed case-control study is relatively low-cost, does not bear risk for participants, and will contribute to existing scarce literature on LBW retrospective studies.

Methodology of the Study

Overview of the concept

Case-control studies compare characteristics of a group of subjects having the disease of interest (case group) to at least one group of subjects without the disease. During the study, attribution of various factors to the disease is examined by comparing the frequencies of its occurrence of the factor between both groups [95].

Through simple techniques these frequencies are converted into odds ratios (OR), which are approximate estimates of relative risks and rate ratios used in cohort studies. Odds ratios are expressed as follows:

$$\text{OR} = \frac{\text{Number of cases with disease}}{\text{Number of cases without disease}} \times \frac{\text{Number of controls without disease}}{\text{Number of controls with disease}}$$

In order to improve comparability of the groups, controls may be selected to be matched to the cases for some characteristics. In these cases, subjects are analyzed in pairs of cases and controls, and the OR is calculated as a ratio of the number of case-control pairs in which only the case has disease, to the number of pairs in which only the control has the disease.

The case-control study is the least expensive and most readily performed type of investigation. It is a useful tool when a rare disease is studied.

Selection of cases and controls

Data collection will be conducted at all ten maternal hospitals of Yerevan. Cases will be selected among singleton infants with birth weight < 2500g born at the hospitals during the period August 7, 2001 - March 14, 2003. Birth registration books, where each birth is recorded, and information on newborn's weight is present, will be used for identifying cases. In order to increase statistical power, for each LBW infant two controls will be selected from the same hospital. The controls will be identified using the same registration book. Although the cases and controls will not be matched by their date of birth, during the selection of controls those born during the same week as the case will be considered first. If, for a given case there will be no control born during the same week, controls born next week will be considered. An infant will be eligible for being a control if s/he was born within three days before or after the case, had a birthweight equal or above 2500g. If there are more than two infants eligible to be controls for a particular case, all will be enumerated and two will be selected by simple random sampling. Considering the rarity of the incidence of the LBW, the situation when a case lacks controls will be rarely observed.

Inclusion criteria for cases and controls

The cases and controls must be singleton infants, born within three days of the visit of the research team member, during the period August 7, 2001 - March 14, 2003. The cases and controls must be alive at the time of the interview. Mothers of cases and controls must have lived in Armenia at least one year prior to the birth of the case.

Exclusion criteria for cases and controls

Pregnancy of mother of a case or a control should not be associated with abruptio placenta, placenta praevia, and multiple pregnancy. Neither the case nor the control should have any congenital anomaly.

Sample size calculation

The sample size calculation will be done using the formula used for case-control studies.

$$n = [z_a \sqrt{2\overline{p}\,\overline{q}} + z_b \sqrt{p_1 q_1 + p_0 q_0}\,]^2 / (p_1 - p_0)^2$$

Where:

$$p_1 = p_0 R / [1 + p_0 (R - 1)]$$

$$\overline{p} = 1/2(p_1 + p_0) \qquad \overline{q} = 1 - \overline{p}$$

$$q_1 = 1 - p_1 \qquad q_0 = 1 - p_0$$

p_0 is estimated exposure rate (proportion exposed) among controls

R is the relative risk of corresponding to the smallest increase or decrease in risk of interest.

Z_α and Z_β are the values for α and β errors respectively.

Assuming that the lowest proportion of the population exposed to any of the independent variables is 0.1, a sample of 668 cases and 1336 controls will be needed to achieve an 80% power and a minimum detectable odds ratio of 1.5. Empirically assuming a response rate of 70%, needed numbers of cases and controls can be calculated, and are 955 and 1909 respectively.

The table with alternative values for minimum detectable odds ratio and proportion of population exposed is below:

	Min. detectable OR	p-0 (exposure rate in general population)									
		0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
# cases	1.25	4448	2379	1702	1374	1188	1074	1005	965	947	950
# controls		8896	4758	3404	2748	2376	2148	2010	1930	1894	1900
Total		13344	7137	5106	4122	3564	3222	3015	2895	2841	2850
# cases	1.5	1235	**668**	484	395	345	316	298	290	287	291
# controls		2470	**1336**	968	790	690	632	596	580	574	582
Total		3705	2004	1452	1185	1035	948	894	870	861	873
# cases	1.75	604	330	242	199	176	162	155	152	152	155
# controls		1208	660	484	398	352	324	310	304	304	310
Total		1812	990	726	597	528	486	465	456	456	465
# cases	2	371	205	151	126	112	104	101	99	100	103
# controls		742	410	302	252	224	208	202	198	200	206
Total		1113	615	453	378	336	312	303	297	300	309

The period of selection of cases and controls will last as long as the necessary sample size is achieved and planned number of mothers is recruited. Considering that (1) the incidence of LBW in Armenia is approximately 80 per 1000 live births; (2) there are approximately 38,000 live births per year in Armenia; (3) cases of LBW are equally distributed all over Armenia; and (4) population of Yerevan represents approximately 1/3 of Armenia's population, it is estimated that during 12 months there will be approximately 1000 live LBW births in all ten maternity hospitals in Yerevan. Since some cases will be excluded from the study, it may take a slightly longer time to obtain the necessary 955 cases. It is expected that data collection will last approximately 14 months. The total number of controls is estimated to be 1909. These numbers are calculated for achieving statistically significant results (with 95 % confidence intervals) and a power of 80%, considering that the response rate of participants will be approximately 70%.

Data collectors trained to select cases and controls, and to conduct interviews will visit each hospital twice per week, on Mondays and Thursdays and select cases and controls during the visits. After the cases and controls are selected, and a satisfactory medical condition of their mothers is ascertained by the staff doctors, mothers will be approached by data collectors and asked to participate in the study. The objectives of the study will be explained to mothers of cases and controls, and written consent forms will be prepared for those who agrees to participate in the study. The mothers will receive no incentives for participation.

The participants (mothers of the cases and controls) will be interviewed using a pre-tested standard structured questionnaire. The questionnaire will contain questions on demographics, socioeconomic status, education, parity, and smoking status of participants and their family members. Information on anthropometrics of mother and infant, duration of the pregnancy, pathologic conditions, and prenatal care will be obtained from medical records.

It is estimated that the questionnaire will contain 17 close-ended questions. Each interview is estimated to last approximately 10 minutes. The time for review of medical records and data abstraction for each participant is estimated to be approximately 25 minutes.

Potential difficulties and limitations of the proposed procedures

Although it is unlikely that the mothers and the newborns will be discharged within less than three days after the birth, it is theoretically possible that the mother of the case or control will not be present at the hospital at the time of the interview. In that case, her home address will be determined and a team member will visit her to interview at home.

It is possible that the medical records of study subjects will not be available. In case if the proportion of the subjects with no medical records will be more than 10%, the information obtained from the records will not be analyzed.

Some medical records may be incomplete. This is a problem, which can not be avoided. If the proportion of the study subjects on whom the information is missing is below 15%, those subjects will be excluded from the analysis. If the proportion is equal or more than 15%, the protocol of the study will be revised and the information obtained through the personal interviews will be used for the analysis.

The maternal hospitals are spread across the city and some of them are difficult to access. It will be necessary to provide transportation to the team members for their visits.

The reliability of the information obtained through the interviews and records may be questionable. There may be a recall bias among mothers of cases and controls. Also, there may be a difference of recalling the history of pregnancy among primiparous and multiparous mothers. Since the parity is associated with the LBW, different recall among mothers of cases and controls may lead to bias.

Ethical Issues

The confidentiality for the subjects will be assured by coding each questionnaire and medical record used in during the study. Unique numbers assigned them during the coding will further identify the subjects.

One of the advantages of case-control studies over other types of studies is that there is no procedure, situation, or material that may be hazardous for the study participants. It is unlikely that questions related to the pregnancy history will sensitize study subjects. However, questions related to the socioeconomic conditions and family income may cause stress to the interviewees.

The methodology of the study does not stipulate excluding women of any age and minority groups. The study does not discriminate against any racial, ethnic al, or religious group.

The study population is expected to be homogenous in terms of race and nationality, and will consist of women who gave birth in 10 maternity hospitals of Yerevan between August 7, 2001 and March 14, 2003.

Analysis

The answers for each question will be coded and entered into the database. Then observations with missing data will be excluded from the analysis. Using all available independent variables and the dependent variable, the initial regression model will be created that will have the following appearance:

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \beta_3(X_3) + \ldots\ldots + \beta_n(X_n)$$

Where Y is the dependent variable (birthweight measured in grams) and the Xs are independent variables.

It is recommended that alternative models be considered, where the dependent variable is nominal (low birthweight, normal birthweight), or ordinal (very low birthweight, moderately low birthweight, normal birthweight). Using alternative models, will allow determining the likelihood of having low birthweight, and the initial model where the BW is a continuous variable, will allow observing the dynamics of the relationship between the independent variables and the LBW.

After this procedure, descriptive statistics (frequency distribution for the categorical variables and means, medians, standard deviations, ranges) on cases and controls will be obtained. The scatterplot of the relationship between the interval ratio variables will be obtained to illustrate and test the line of the relationship. Then the regression model will be run with all independent variables. The model will be checked for multicollinearity and the variables with significant (P>0.05) and severe (r > 0.6) correlation will be isolated. By turn each of the correlating variables will be excluded from the regression and the R-squares will be recorded.

Then, from the correlating variables, one yielding highest R-square of the model will be kept in the model, and the rest will be discarded. After the multicollinearity is dealt with (if one was found) the model will be checked for outliers. These will be the observations that have residuals with values lower or higher of -2σ and 2σ respectively. All outliers will be excluded from the analysis. The third step of the analysis will be to check the model for the normality and homoscedasticiy assumptions. If the assumptions are violated, correcting measures will be introduced. After these steps, the model's significance and r-square will be examined. If the model is significant (P <0.05), the significance of each independent variable will be examined. If the model is not significant, the interactions of different independent variables or their transformations (such as square) will be introduced into the model until it becomes significant. Finally the model will be checked for its predicting ability. If the r-square of the final model is higher than 90% it will be considered appropriate for using in forecasting. All analysis will be conducted either by SPSS software.

Data gathering tools

Data will be obtained through personal interviews and from medical records. There are four medical documents, which are filled during each pregnancy and birth: Pregnant's individual card, Birth history, Exchange card (consists of three sections related to the pregnancy, birth, and newborn), Newborn's development history. The information on 47 variables will be obtained trough interviews (for variables 4, 6-10 and 14-24) and above mentioned medical forms (for variables 1-3, 5, 11-13, and 25-47).

	Variable	Level of Measurement	Options
1.	Birth weight	Numerical	Weight in grams
2.	Gestational age	Numerical	Age in complete weeks
3.	Parity	Numerical	Number of previous live births
4.	Marital status	Ordinal	Currently married / divorced / widowed / single / separated
5.	Residence	Nominal	Urban / Rural
6.	Mother's age (in years)	Ordinal	Below 18 / 18 - 22 / 23 - 27 / 28 - 32 / above 32
7.	Mother's education (in years)	Ordinal	Below 8 / 8-10 / more than 10
8.	Mothers occupation	Ordinal	Housewife / Employed / Self-employed / Unemployed
9.	Number of family members	Numerical	Any discrete number
10.	Monthly household income (in US dollars)	Ordinal	<40 / 41-80 / 81-120 / 121-160 / 161-200/ > 200
11.	Mother's pre-pregnant weight (in kilograms)	Ordinal	Less than 40 / 40-49 / 50-59 / 60-69 / 70-79 / 80-89 / 90 and higher
12.	Mother's height (in centimeters)	Ordinal	Less than 150 / 150-159 / 160-169 / 170-179 / 180 and more
13.	Interpregnancy interval (time between the last birth and the current conception) in months	Ordinal	Less than 6 / 6 - 12 / more than 12
14.	Planned or unplanned pregnancy	Nominal	Planned / Unplanned
15.	Smoking during the pregnancy	Nominal	Smoked / Did not smoke
16.	Average number of cigarettes smoked per day (for smokers)	Ordinal	Less than 10 / 10 – 19 / 20 and more
17.	Number of smokers in family	Numerical	Any discrete number
18.	Number of cigarettes each member smokes at home per day	Ordinal	Less than 10 / 10 - 20 / more than 20

19.	Coffee consumption per day need to specify whether it is black or instant coffee; units: small cups for black coffee and large cups for instant coffee	Ordinal	Less than 1 / 1 - 3 / more than 3
20.	Perceived physical workload during the pregnancy	Ordinal	No work / Light / Moderate / Heavy
21.	Perceived psychological stress during the pregnancy	Ordinal	No stress / light stress / Moderate stress / Heavy stress
22.	Weight gain during the first trimester (kg)	Numerical	Any number
23.	Weight gain during the second trimester (kg)	Numerical	Any number
24.	Weight gain during the third trimester (kg)	Numerical	Any number
25.	Date of the first prenatal visit	Ordinal	Trimester: 1 2 3
26.	Total number of prenatal visits	Numerical	Any discrete number
27.	Number of prenatal visits during the first trimester	Numerical	Any discrete number
28.	Number of prenatal visits during the second trimester	Numerical	Any discrete number
29.	Number of prenatal visits during the third trimester	Numerical	Any discrete number
	Diseases during the first trimester of pregnancy	Nominal	Yes / No for each specified disease
30.	Respiratory infections	Nominal	Yes / No
31.	Eclamspia	Nominal	Yes / No
32.	Anemia	Nominal	Yes / No
33.	Hypertension	Nominal	Yes / No
34.	Chronic kidney disease	Nominal	Yes / No
35.	Urinary tract infections	Nominal	Yes / No

	Diseases during the second trimester of pregnancy	Nominal	Yes / No for each specified disease
36.	Respiratory infections	Nominal	Yes / No
37.	Eclamspia	Nominal	Yes / No
38.	Anemia	Nominal	Yes / No
39.	Hypertension	Nominal	Yes / No
40.	Chronic kidney disease	Nominal	Yes / No
41.	Urinary tract infections	Nominal	Yes / No
	Diseases during the third trimester of pregnancy	Nominal	Yes / No for each specified disease
42.	Respiratory infections	Nominal	Yes / No
43.	Eclamspia	Nominal	Yes / No
44.	Anemia	Nominal	Yes / No
45.	Hypertension	Nominal	Yes / No
46.	Chronic kidney disease	Nominal	Yes / No
47.	Urinary tract infections	Nominal	Yes / No

Discussion

It is possible that the case and the control will be from different regions (Marzes). Residing in a certain region may be a confounder, if the regions are differently associated with risk factors for LBW. However, this not very likely to occur, since the populations in the regions of Armenia are distributed fairly homogeneously.

It is possible that the interviewees will provide inaccurate data on prenatal exposure to LBW risk factors due to recall bias. A study conducted in 1995 compared two sets of information on prenatal exposure received during a case-control study of LBW. The information was abstracted from both interviewing mothers of cases and controls, and from medical records. The odds ratios (ORs) of exposure estimated from the two sets of data did not differ significantly for most of the variables [96].

It is possible and even likely that the LBW cases will not be equally distributed across the ten hospitals. The reason to think so is the fact that high-risk pregnancies may be more often referred to large hospitals, such as Republican Maternity Hospital that is well equipped and staffed. Therefore, it is likely that the large hospitals will have more LBW cases per admission than smaller, district type hospitals. This fact may have implications on logistics of the project, in that more staff may be required for attending larger hospitals.

The study will miss cases of home deliveries. It is hard to predict the exact number of home deliveries occurring during the study, since the data on their incidence in Yerevan are not available. It is reasonable to think that among home deliveries there will be a larger than average proportion of LBW, since home deliveries are associated with LBW risk factors, such as poor socioeconomic status, lack of access to health care facilities, and poor education. Probably, the proportion of VLBW among home deliveries will also be higher than average. The implication of this is that a number of severe LBW will be missed from the study and that fact may be skewing the results of the analysis. Nevertheless, the number of home deliveries can be estimated to be low, since Yerevan's prenatal services and maternal hospitals are scattered across the city, and are easily accessible.

It is almost certain that in the study there will be a number of cases and controls whose mothers do not reside in Yerevan, but come from all over Armenia, mostly from nearby marzes. These cases and controls may differ in some characteristics from the ones in the city. For example, mothers from regions may have higher proportion of high-risk pregnancies than mothers residing in Yerevan. The reason is that, since a number of city's maternal hospitals are considered best equipped and staffed, high-risk pregnancies from nearby regions are routinely referred to these hospitals. Therefore, it is possible that cases from regions will have on average lower birth weight than the cases from Yerevan.

It may also be possible that the mothers of controls from the regions may have higher socioeconomic status than the ones in the city. Since medical fees are higher in Yerevan than in the regions, mothers with higher income from regions are more willing to utilize them, than the ones with low income. This assumption holds true if there are no medical indications for being referred to Yerevan's maternity hospitals.

Project Management

The study will be implemented as a separate project by the Center of Healthcare Services Research (CHSR) at the American University of Armenia. An expatriate faculty member will provide the overall leadership and supervision of the project, as well as communicate with the donor, Ministry of Health officials, and the management of hospitals. S/He will provide guidance during the selection of study subjects, data collection, analysis, and reporting. S/He will be responsible for management of funds and will authorize all project expenditures. A local faculty member will coordinate and supervise the performance of the CHSR staff and Public Health students involved in the study, and provide technical assistance on a needed basis. S/He will be responsible for project logistics. CHSR staff members and graduate students will be responsible for data collection and entry. In addition, CHSR staff will be involved in data analysis and reporting. Two drivers will be hired to provide transportation to the faculty and staff involved in the project. They will work two days per week and use their own cars.

Budget Narrative

The **Expatriate Faculty Member** will be responsible for planning, organizing, and directing the implementation and operations of this project. Specific responsibilities include directing staff, orientation, training, counseling, evaluation, and discipline in accordance with CHSR standards. The expatriate faculty member directly supervises the local faculty member and project staff members. He/She is paid at the net rate of $5,000 per month, and will participate in the project 5% of the time during the whole project.

The **Local Faculty Member** directs the implementation and operations, distributes work, directs and personally handles public relations, oversees and negotiates contracts with subcontractors, monitors and assesses project performance. He/She directly supervises project staff members, graduate students, and drivers. He/She is paid at the net rate of $800 per month, and will participate in the project 20% of the time during the whole project.

The **CHSR Staff Members** make visits to hospitals, collect data, and supervise graduate students. Each of the two staff members will be paid at net rate of $450 per month and will participate in the project 50% of the time during the whole project.

The **Graduate Students** make visits to hospitals, and collect data. Each of the two graduate students will be paid at net rate of $250 per month and will participate in the project 50% of the time during 16 months.

Two Drivers will be hired on the temporary basis and will be paid $15 for a 6-hour working day. They will work a total of 180 days.

Taxes refer to the salaries of local faculty member, CHSR staff members, and graduate students.

Travel costs are calculated based on assumptions that: (1) daily mileage for each car is 70 km during 180 days; (2) average fuel consumption rate is 14 liters per 100 km; (3) total fuel consumption per car is 10 liters per day; (4) average price of gas is $0.6 per liter, or $12 per 20 liters; (5) total daily fuel expense is $12.

All **Equipment** will be purchased during the first 30 days of the project and will be retained by the CHSR at the end of the project.

Overhead costs are 36% of direct costs minus equipment. They cover office space, utilities, services, and fringe benefits.

Office operations include expenditures for Supplies, Telephone, and Duplicating. Office supplies such as tape, stationery, fax paper, pens, pencils, and business cards. Printing costs are calculated on the assumptions that (1) 3200 questionnaires will be needed; (2) each questionnaire will be 5 pages in length; (3) cost of printing per page is 25 Armenian drams (AD); (4) exchange rate is $1=550 (AD).

Budget

Category or Description of Item		2001	2002	2003	Total Amount
Personnel (salaries and wages)					
Expatriate faculty	1 @ $5,000/mo @ 5% @ 24 months	$ 1,500	$ 2,760	$ 1,740	$ 6,000
Local faculty	1 @ $800/mo @ 20% @ 24 months	$ 960	$ 1,766	$ 1,114	$ 3,840
CHSR staff	2 @ $450/mo @ 50% @ 24 months	$ 2,700	$ 4,968	$ 3,132	$ 10,800
Graduate students	2 @ $250/mo @ 50% @ 16 months	$ 1,000	$ 2,400	$ 600	$ 4,000
Drivers	2 @ $15/day @ 180 days	$ 1,350	$ 3,240	$ 810	$ 5,400
Taxes 30%		$ 1,398	$ 2,572	$ 1,622	$ 5,592
Subtotal, Personnel (salaries and wages only)		**$ 8,908**	**$ 17,707**	**$ 9,017**	**$35,632**
Travel					
Fuel		$ 540	$ 994	$ 626	$ 2,160
Subtotal, Travel		**$540**	**$994**	**$626**	**$2,160**
Equipment					
Computer Pentium III		$ 2,000	$ -	$ -	$ 2,000
UPS		$ 250	$ -	$ -	$ 250
Zip Disks 10@$10		$ 100	$ -	$ -	$ 100
Accessories		$ 500	$ -	$ -	$ 500
Printer Desk Jet 895 Cxi		$ 350	$ -	$ -	$ 350
Subtotal, Equipment		**$3,200**	**$0**	**$0**	**$3,200**
Office Operations					
Printing of questionnaires		$ 175	$ 322	$ 203	$ 700
Office supplies	$40/mo @ 24 months	$ 240	$ 442	$ 278	$ 960
Subtotal, Other Expenses		**$415**	**$764**	**$481**	**$1,660**
Direct Costs (excluding equipment)		**$9,863**	**$19,464**	**$10,125**	**$39,452**
Equipment		**$3,200**			**$3,200**
Overhead		**$3,551**	**$7,007**	**$3,645**	**$14,203**
Total Project Costs		**$16,614**	**$26,471**	**$13,770**	**$56,855**

Budget Summary

A total of $56,855 is requested for this project, $16,614 (29%) in year 2001, $26,471 (47%) in year 2002, and $13,770 (24%) in year 2003. In order to more accurately reflect personnel's degree of involvement in the project, salaries of graduate students and drivers are allocated as 25, 60, and 15 percent of their totals among years 2001, 2002, and 2003 respectively. Salaries of other staff are allocated as 25, 46, 29 percent of their totals among years 2001, 2002, and 2003, respectively. Of the total project costs, staff accounts for 62.67, equipment for 5.63, travel expenditures for 3.80, and other items for 2.92

percent. Altogether they comprise 75.02% of the total costs. The remaining 24.98% of the budget is allocated for overhead costs.

Results and Recommendations

The results of this study will be shared with the Ministry of Health in designing programs in the field of maternal and child health that can lower LBW. A special attention will be brought to modifiable risk factors, and activities aimed at reducing these factors among pregnant women will be recommended. Most likely, the recommendations will be related to prevention of anemia in pregnancy, weight gain during the pregnancy, and encouraging prenatal and antenatal clinic attendance. Also, issues of improving psychosocial, nutritional, and health status of pregnants will be covered by the recommendations.

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