Possible Determinants of Birth Defects Responsible for Perinatal Mortality in Yerevan

Master of Public Health Thesis Project Utilizing Research Grant Proposal

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Executive Summary

Background. Birth defects are genetic or developed anomalies of the human organism present at birth. The clinical appearances of them vary from minor undetectable defects with minor clinical symptoms to major defects that require medical interventions. Birth defects are among the leading causes of infant mortality and the first leading cause of perinatal mortality in Armenia.

During the last five years, infant mortality from birth defects has increased in Armenia. To determine the leading type of birth defects a preliminary survey was conducted in Yerevan during June - September 2003. The leading type of birth defects causing perinatal mortality was identified to be central nervous system anomalies, while in the case of infant mortality there were different anomalies. Moreover, it was found that mortality from birth defects in perinatal period was higher than that in infant mortality.

To find possible determinants of birth defects from which newborns die during the perinatal period, it is proposed to conduct a case control research requiring total budget of 3685 USD.

Objectives. The objectives of the proposed research are:

· To determine the prevalence of selected characteristics of mothers of children who died from birth defect during the perinatal period. Those include demographic characteristics: mother's date of birth and/or mother's age, residency area, occupation, number of previous pregnancies, abortions, deliveries, number of alive children, and pregnancy history related to maternal health during pregnancy, diet and substance use during it.

· To identify the association of above mentioned characteristics and their interactions with the occurrence of birth defect causing perinatal mortality.

Methods/Study Instrument. As the initial step, it is planned to review the autopsy reports in Republican Children Pathology Anatomy and Republican Perinatal Centers to determine the hospitals where deaths occurred. From the medical records the necessary data will be obtained and filled into abstract forms. The abstract forms will comprise the questions on above mentioned selected characteristics. After that an interaction of those characteristics with occurrence of birth defect development causing perinatal mortality will be determined through the case-control study.

Sample size. The estimated sample size for detecting the possible association of the selected factors and presence of birth defects causing perinatal death is 150 for cases and 150 for controls; thus, from the total autopsy reports there is a need to extract 300 for the study.

Analyses. In order to identify an association of dependent and independent variables of the study, the Chi-square, t-test, and Logistic Regression will be used.

The results of this study will help to initiate educational programs for women willing to become pregnant in order to increase their knowledge in the prevention of birth defects development.

Specific Aims and Objectives of the Study

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Birth defects are any inborn anomalies present at birth (1). Some may be determined during the pregnancy, delivery and/or immediately after birth or later (2). The consequences of birth defects are various. They may vary from minor deformities (that do not cause harm), to major ones that can result in unavoidable death or require immediate medical intervention (2). Presence of a major inborn anomaly is one of the primary causes of death among infants (3). For instance, birth defects are the leading cause of infant mortality in the United States and contribute significantly to morbidity and long-term disability (4, 5). As the result, birth defects surveillance systems exist in some states of the USA; they provide data on prevalence of birth defects in these states (4).

Existing lack of data on birth defects in Armenia limits the investigation of this problem.

The objectives of the proposed research are:

- To measure the prevalence of demographic characteristics related to mother's date of birth or mother's age, residency area, occupation, number of previous pregnancies, abortions, deliveries, number of alive children, and pregnancy history including maternal health, diet and substance use during the pregnancy.
- To identify possible associations between perinatal mortality due to birth defects and mother age, occupation, residency, infectious and viral diseases, diet and substance use during the pregnancy.

Data will be collected through the review of death reports and medical records of mothers of children who died from birth defects. The necessary data will be extracted into the abstract forms comprising demographic questions and domains related to maternal health, pregnancy history, and diet and substance use during pregnancy.

The findings of this research will provide an opportunity to determine the association of selected behaviors of mothers with mortality from birth defects and develop recommendations for birth defect prevention.

Background Information

Birth Defect Definition

One of the leading causes of infant mortality is a birth defect also known as inborn abnormality (1, 6-8). A definition of birth defects [presented in 9th Revision of "International Classification of Diseases"] is stated as "birth defects are the congenital defects of body structure or function, likely to result in mental or physical handicap or death" (2). Thus, birth defects can be considered as any disorders present at the birth of a child.

Abnormalities may be formed in any part of the body. There are major and minor abnormalities that differ by the magnitude of the caused harm; big physical anomalies lead to deformities of a child appearance and need curative intervention, and the smaller ones do not create critical health or social problems (1). Major abnormalities in most cases are incompatible with the infant life and lead to death in perinatal period (1, 2). As result, birth defects are the first leading cause of death in perinatal mortality in USA (1, 2). Taking into consideration that perinatal mortality due to birth defects increased in Armenia during the past five years, this study will focus on selected specific characteristics leading to the development of major birth defects causing perinatal mortality[1].

Causes of Birth Defects

The factors that lead to development of inborn abnormalities are different, and many of them are unknown (9). At the same time a combination of genetic, environmental factors

[1] Here perinatal mortality is used for children's death occurring during the first 7 days after birth (28).

and multiple exposures present during the pregnancy contribute to the etiology of the birth defect (4). There are known factors associated with pregnancies that increase the risk of birth defect development (9):

· Exposure to teratogens during pregnancy is responsible for about 7% of all congenital defects (9).

· Drug use during pregnancy. Few drugs lead to birth defects, but many of them increase the risk of their development (9). For instance, antibiotics, such as Tetracycline, affect bone growth and cause discoloration of teeth; anti-tuberculosis drugs may cause hearing disorders and harm the nervous system (6, 9). Anticonvulsant can lead to mental retardation and slow growth (6, 9). Antineoplastic agents and hormonal medications may be associated with arm and leg abnormalities, and central nervous system complications among infants (6, 9).

· Alcohol use can lead to development of the fetal alcohol syndrome, which includes mental retardation, heart problems and growth deficiency (6, 9).

· Environmental chemicals such as fungicides, food additives and pollutants are suspected in causing birth defects (6, 9).

· Exposure to ionizing radiation increases the risk of developing embriopathy (9, 10). The duration, timing, and dosage of ionizing radiation exposure the severity of inborn defects are different: high levels of radiation can cause microcephaly, blindness, spina bifida, and a cleft palate (10).

· Viral infections such as Rubella, Cytomegalovirus, and Herpes Simplex or parasites like Toxoplasma gondii and untreated Syphilis increase the possibility of a birth defect formation (6, 9).

· Genetic factors also play a significant role in the development of birth defects (11). According to the World Health Organization (1997) the first referrals due to genetic

disorders is 0.1%, X-linked is 1.0%, irregularly inherited - 9.0%, Chromosomal aberrations is 0.6% (9). Inherited or mutated genes are causes of Downs syndrome, Duchenne muscular dystrophy, hemophilia, achondroplasia, Huntington's disease (a progressive nervous system disorder); Marfan syndrome (disorders of connective tissue); and polydactyl (extra fingers or toes) (11, 12). Genetic disorders are not limited to these syndromes only (3, 11, 12). They can cause abnormalities in all human systems, the clinical appearance of which cannot be identified wholly at the time of childbirth (3, 11, 12).

· Maternal age. The number of birth defects increases with maternal age, and for women less than 20 years (5). Almost 15.0% of mother who have a pregnancy affected by inborn abnormalities are aged 35 years and over (5).

It is still difficult to identify the specific causes of inborn abnormalities because many of them can interactively influence the fetus in any stage of its development (9). For example, cleft lip, clubfoot, ankle or foot deformities, spina bifida, hydrocephalus (water in the brain), and heart defects are likely to be interactions of genetic and environmental factors (6, 9).

Birth Defect Outcomes

Complications of birth defects are various and may be critical for the future life of children. Major birth defects that are not compatible with an infant's life might lead to death soon after birth, while minor abnormalities can cause infant morbidity (3). Some anomalies may be cured surgically in the first days after birth (3). Other inborn anomalies need a lifetime or medical intervention and/or long-term care (3). The treatment as well as care for infants with inborn abnormalities requires significant financial resources. This situation is

especially critical in developing countries with limited access to free medical care, especially advised services.

Thus, birth defects are one of the primary causes of children morbidity and mortality and there are variety of diseases and syndromes that are conditioned by inborn abnormalities (3).

Epidemiology of Birth Defects

From the epidemiological viewpoint the true incidence of birth defects is difficult to determine and birth defects identified at the birth are presenting only the birth prevalence (4). Inborn anomalies are 30.0%-50.0% prevalent in post-neonatal deaths in the USA (15); concurrently, almost 20.0% of the total number of deaths among infants is due to birth defects (9). According to some Russian findings, inborn anomalies are identified in every fourth dead child at autopsy (8). During the first year of life inborn anomalies ranged from 24.0% to 28.0% as one of the leading cause of Infant Mortality in Russia (8).

A few large case-control studies of birth defects have included assessment of drug exposure (periconceptional vitamin, dietary folate, corticosteroids use) during pregnancy (11, 12, 16). Several of these studies were limited by the small number of affected infants, inability to identify the occurrence of birth defects with known etiology from multiple inborn anomalies of unknown ones (11, 12, 16). Evidence from another case-control study, aimed to determine defect prevalence rate, patterns, geographic differences, associated maternal and infant risk factors, and the contribution of the defects to mortality, showed that the most frequently affected systems by birth defects were the cardiac, musculoskeletal and central nervous (17). According to the same study, the diabetes was identified as maternal disease associated with birth defects (17). Older maternal age, grand multiparity and previous abortion have been associated with higher frequency of some birth defects (18).

Taking into consideration the findings of the literature review, for the investigation of the etiology of birth defects the interaction of different factors (e.g., environmental exposure during pregnancy and genetic factors) should be considered.

Situation in Armenia

The difficult socio economic conditions in Armenia since 1990 have significantly affected the medical demographic situation in Armenia (19). As a result, sociodemographic characteristics have changed drastically (19). Per capita income fell from approximately $2,500 in 1991 to $500 in 1998 in Armenia (20). According to the USAID/Armenia, "the official unemployment rate has increased threefold within 1992-1997; and more than half the population now lives below the poverty line, and approximately one quarter lives below the food line" (20). According to a World Bank report, "Armenia's poor typically experience periods of malnutrition, have insufficient heating in winter months, and have less access to educational and health services than before the fall of the Soviet Union" (20).

According to the General Characteristics of Medical Demographic Situation in Armenia, birth rates decreased almost by 50.0% from 1995 to 2000 (19). Moreover, Infant Mortality increased during past five years in Armenia: it was 19.0% in 1998 and became 24.4% in 2001 (19).

Existing socio-economic hardships and limited access to medical services make it especially difficult to handle the problem of infant morbidity and mortality due to birth defects. Birth defects are the leading cause of perinatal death among full term infants (19). Concurrently, the number of birth defects among children of 0-14 years old has increased from 81.9 (in 1997) to 108.4 (in 2000) per 100,000 (21). Furthermore, death from birth defects became the second leading cause of infant mortality from fourth during 1995-2000 (21). According to D.K. Gevorgyan, a primary children pathology anatomist of Armenia, the

current situation of the perinatal and infant mortality and the lack of studies investigating its etiology and prevention in Armenia make it a critical subject (22).

The lack of prenatal care for the prevention and identification of birth defects, as well as delayed medical care, contribute to the increase of infant mortality due to congenital abnormalities. Some birth defects may be preventable, for example anencephaly and spina bifida can be prevented if future mothers take folic acid before and during pregnancy (23, 24). There are also methods for diagnosing birth defects at the first stage of pregnancy through ultrasound observation, amniocentesis, and, in the case of defect, the pregnancy could be terminated (25).

To initiate preventive strategies and address this problem, it is first to investigate the situation of birth defects in Armenia; identify the possible factors that increase the risk of birth defect development, and develop appropriate recommendations. For these reasons a case-control study is proposed to suggest appropriate preventive actions that would lead to lower incidence or early detection of birth defects and decreased infant mortality from them based on the prevailing risk factors.

Preliminary Research

During June - September of 2003 a preliminary investigation was conducted in the Republican Children Pathology Anatomy (RCPA) and Republican Perinatal Centers (RPC) in Yerevan [it has been approved by student project IRB committee within the American University of Armenia (AUA) College of Health Sciences]. This study sought to determine the prevalence of infant death from different birth defects in Yerevan during the last five years (1998-2002) via a review of autopsy reports [unofficial translation of the autopsy report from the Russian version is presented in the Appendix 1]. Taking into consideration that birth defects are rare event, all available 2,726 autopsy reports were reviewed (1940 from

RPC and 786 from RPAC). It was determined that 15.4% cases of perinatal mortality and 30.7% of infant mortality caused by birth defects. Entity, five hundred forty reports indicated birth defects as the main cause of death among stillborn or infants resided in Yerevan.

The data revealed that there was a substantial increase in the number of death from birth defects from 1998 to 2002 (Figure 1).

The findings related to the perinatal mortality during 1998-2000 showed that birth defects were the fourth leading cause of death after other reasons, infectious diseases, and asphyxia. In 2001, it was the third and in 2002, it was the second leading cause of death during perinatal period (see Table 1). In the case of infant mortality birth defects were one of the leading causes of infant mortality: from 1998 to 2000 and in 2002 it was the second leading cause of death after sepsis, and the first in 2001 (see Table 2).

The data revealed that three types of birth defects predominantly causing perinatal mortality over the past five years were central nervous system, gastrointestinal and cardiovascular anomalies (Tables 3). In the case of infant mortality there are no predominated birth defect types (see Table 4).

The research also explored pregnancy complication. In the majority of cases of perinatal and infant mortality caused by birth defects, the pregnancy course among mothers was complicated with infectious and viral diseases (Tables 5, 6). Infectious and viral diseases combined with toxicosis were the next most frequently accompanied complications of the course of pregnancy.

Taking into consideration the lack of surveys directed to investigate the leading causes of perinatal mortality (30), it is necessary to initiate a study to fill the data gap. Special efforts should be directed towards investigation of the factors and preconditions causing perinatal mortality. Moreover, since the birth defects were among the leading causes of perinatal mortality during the last 1998-2002 years, it is proposed to investigate factors

possibly associated with birth defect developments (e.g., selected behaviors among women of reproductive age), and develops recommendations for preventing prenatal mortality from birth defects based on the findings. The results of this study will be helpful for improving clinical care, intense etiologic research, and health education of the community, particularly future mothers.

Methodology

Study Design

This research will have a case-control study design. According to the preliminary research findings, perinatal mortality due to birth defects had increased over the years while the changes in infant mortality due to the same reason stated almost the same. Thus, it is suggested to identify the association of selected factors with the occurrence of birth defects causing perinatal mortality. The cases for the proposed research are children who died because of birth defects during the perinatal period. The controls are children who died from causes other than birth defects during perinatal period and did not have birth defects. This will allow identifying the association of those characteristics with the birth defect development. Appropriate information for case and control groups will be collected from autopsy reports of children and medical cards of mothers.

Sample Size Calculation

To determine sample size for two equal independent samples, the following formula is used:

$$n_1=n_2= [Z_{\alpha/2}x\sqrt{2pq}+Z_{\beta}\sqrt{p_1q_1+p_2q_2}]^{2} /\Delta^{2} \text{ (26)},$$

where $Z_{\alpha/2}$ is equal to 1.96 (α is equal to 0.05 (two-tailed)), Z_{β} is equal to 0.84 (the power of significance test is (1-β) and β is equal to 0.2), p_1 is the proportion of cases whose mothers had infectious diseases during the pregnancy and equal to 0.5; q_1 is equal to (1-p_1) and equal

to 0.5; p_2 is the proportion of controls whose mothers had infectious diseases during the pregnancy, which is presumably equal to 0.3 (27); q_2 is equal to (1- p_2) and equal to 0.7; p is equal to $(n_1p_1+n_2p_2)/(n_1+n_2)$, since n_1 equals to n_2, p is equal to (p1+p2)/2), equal to 0.4; q is equal to (1-p), equal to 0.6; and Δ is the difference of p_1 and p_2, which is equal to 0.2 (27). Thus, the calculated sample is equal to 100 in each group.

This number of cases and control is required to detect a possible association of independent (demographic characteristics, maternal health, pregnancy history, diet and substance use during the pregnancy) and dependent variable (presence of a birth defect causing perinatal death) between these two groups, with a significance level of 0.05 and a power of 0.80. Considering that there is no strong rule of keeping the medical records in particular order and possibility of missing records, it is suggested to increase the sample size by 50% in each group. Thus, it is necessary to review 150 autopsy reports for each group, finally, 300 autopsy reports and medical cards will be reviewed.

Study Population and Study Settings

The proposed study is planned to be conducted in Yerevan, Armenia. The data source is medical reports: autopsy reports registered in RPC and RCPAC and medical cards of mothers registered in maternity and children clinical hospitals.

According to preliminary research there are 1,602 autopsy reports related to perinatal mortality registered in RCP and RCPA. From those 298 were related to perinatal mortality caused by birth defects. All of these reports will be rearranged and randomly numbered. After this, through simple random sampling 150 reports will be chosen. The autopsy reports for the control group will be similarly selected. RPC serves for diagnosing the causes of death of children of perinatal period occurred in all maternity and children hospitals in Yerevan and closest areas. RCPC serves only for children who died at perinatal age in the 2nd maternity

hospital[2]. Based on the information contained in these autopsy reports the number of a maternity or children's clinical hospital where death occurred, ID of mother medical card, mother name, child name and age for cases and controls will be extracted and completed into two separate journal forms. According to these data, the later investigation will be conducted in a maternity or children's clinical hospital where the mother's medical cards will be examined. The necessary information will be extracted and entered into abstract forms.

For the case group inclusion criteria for autopsy reports are the following:

· Stillborn or child dying during 0-7 days after birth caused by birth defects in clinical or maternity hospitals of Yerevan.

· Stillborn or children dying during 0-7 days after birth from birth defects whose parents resided in Yerevan

The exclusion criteria for the case group are:

· Children dying at 8 and over days after birth caused by birth defects as the main cause of death

· Stillborn or children dying from other causes than birth defects

· Stillborn or children dying from any reason whose parents did not reside in Yerevan.

After selection the case groups, autopsy reports for the control group will be randomly selected. For the control group inclusion criteria for autopsy reports are the following:

· Stillborn or children dying during 0-7 days after birth due to other causes than birth defects, death occurred in clinical or maternity hospitals of Yerevan

· Children born stillborn or dying during 0-7 days after birth due to other causes than birth defects whose parents resided in Yerevan

The exclusion criteria for the control group are:

[2] The 2nd Maternity Hospital and RCPAC are the departments of Obstetrician and Gynecology and Children Pathology Anatomy at Yerevan State Medical University.

· Children born stillborn or dying during 0-7 days after birth due to other causes than birth defects having birth defects in the history

· Children dying from any reason whose parents did not reside in Yerevan

Study Instrument

The primary data related to the information of children's clinical and/or maternity hospital will be extracted from the autopsy reports and filled into journal form separately for the case and control groups. Besides this, ID of a mother's medical card, mother name, and child name will also be extracted. Based on these data, the later investigation will be conducted in maternity or children's clinical hospital where mothers' medical cards will be examined, and the obtained data will be filled into abstract forms.

The abstract form will be the study instrument; it will have sections related to possible determinants of birth defects: demographic characteristics of mothers (mother's date of birth/or mother's age, residency area, occupation, number of previous pregnancies, abortions, deliveries, and number of alive children), and pregnancy history including maternal health, diet and substance use during pregnancy (10) (see Attachment 2).

Completion of each abstract form will require from 15 to 20 minutes.

Data collection

A special training program will be provided to the research investigators to make them familiar with autopsy reports and medical cards review. They will be also trained to read various handwritings since the medical cards are handwritten. After that investigators will be assigned to the pathology anatomy centers for review of autopsy reports. In the beginning autopsy records of deaths from birth defects and other causes will be separated and will include all possible reports of children eligible to be cases and controls. From the

autopsy reports hospital number, ID of the appropriate medical card, date of the hospital admission, parents' names, address (particularly mothers) will be obtained and entered into the special journal form. After achievement to the appropriate number of cases and controls, each researcher will be assigned to a particular children's clinical or maternal hospital where the final abstract forms will be completed. In the hospitals after gaining the written permission to the hospital archives from the RCPAC and RCP administration, researchers will randomly select the autopsy reports and complete the journal forms for cases and controls. Based on that data researcher will find the appropriate medical records of mothers and complete the abstract forms. After reaching appropriate sample size for cases and controls the database will be double entered into SPSS statistical software and cleaned for analyses. The clean data set will be transformed into STATA statistical package for further analyses.

Variables and Measures

The dependent variable of the proposed research is the death from birth defect for cases and death from any other reason than birth defects for controls. Independent variables are demographic factors (mother's age, residency, occupation, number of previous pregnancies, abortions, deliveries, and number of alive children) and pregnancy history (maternal health, diet and substance use during pregnancy). Some answers related to demographic characteristics are numerical others are categorical. At the same time, questions related to pregnancy history are dichotomous with " No" and "Yes" answers. Taking into consideration that there could be missed information related to particular questions, there is stated an answer "Not Available". Numeration of the answers is ordered for convenient data entry procedure and its further analyses.

Analyses

In order to identify the descriptive statistics and association of dependent and independent variables, the following methods will be used:

· Chi-square and t-test for categorical and numerical variables with 95% confidence interval (CI) for examining baseline characteristics and outcomes of the obtained data from the medical cards (26, 27).

· Logistic Regression since the response variable is dichotomous, which will allow to determine the association of the independent variables (demographic characteristics and pregnancy history) with dependent one (death from birth defects or other reasons) (26, 27).

Study Limitation

There are several possible limitations that need to be considered:

· Selection bias. The selection of the medical centers is purposeful and convenient, which weaken the external validity.

· Recall bias (specific for case-control study). The information entered into the medical card by the treating physician is mostly based on the recall of mothers.

· Non-adequate control group. Since the controls are children who died from other reasons than birth defects their maternal health status might be similar with maternal health of children from case group.

· It will be difficult to minimize the researcher bias: different researchers might extract different information from the medical records interpreting the information in the cards differently, because the appropriate information may not be written in particular order in the cards.

· Considering that some of the death might be dissected in other pathology anatomy centers (for example Massiv Maternal Hospital is served by the Pathology Anatomy Center of Emergency Hospital) or in the case of households death, the dissection may be rejected, the data cannot be generalized to the whole perinatal mortality in Yerevan.

Timeframe

Duration of the research will last almost four months (Gantt chart, Figure 2). During the first two weeks the following activities will be performed: a renting territory acquirement, appropriate office and supplies preparation, staff recruitment, and abstract forms copy. Two research assistants will be selected on the basis of his/her background (medical background is required, public health is desired) and working experience (minimum a year as a research assistant in a local institution).

During next two weeks of the first month, a training course will be provided to research assistants by program coordinator aimed to make them familiar with the autopsy reports and medical cards. Moreover, they will be trained for reading different handwritings, and extracting and filling the information. During the last week of the first month the study instruments will be pretested on different history of diseases and appropriate modifications will be made.

After the end of each month program coordinator will prepare a monthly report summarizing all activities.

The case and control selection will be conducted within two weeks of the second month in Republican Children Pathology Anatomy Center and Republican Perinatological Center. Finding of history of diseases in hospitals and completion of the abstract forms will be performed during next four weeks. Considering different speed of investigation of the history of diseases, the duration of filling an abstract form will require in average 15-20

minutes; a research assistant daily in a hospital will fill about 18 abstract forms. Taking into consideration that medical cards could be kept in different hospitals, it is anticipated to review daily 10 medical cards in the hospitals of the same region or close area. Thus, two research assistants could conduct 10 medical card reviews in each region, totally 20 medical cards daily or 100 medical cards weekly. An extra week is allocated for unexpected activities. Summing up, there will be required four weeks for completing all medical card review.

During the first two weeks of the third month data entry operators will be hired and trained for data entry procedure. Moreover, for a week a data entry-training course will be provided for research assistants. After these training programs, data entry procedure, data analysis, and preparation of final report will be performed during next 7 weeks.

The average time for entering information from one abstract form is 7-10 minutes. Thus, 36 abstract forms can be entered daily by one data entry operator, and 72 by two of them. Thus, data entry will require 5 days for completion of 300 abstract forms. The double data entry and data cleaning will be performed during next week. During two weeks of the fourth month the data analyses and the final report will be provided.

Logistic Consideration

Budget Allocation and Resources

Implementation of this research will require financial and human resources, the total budget of this program will require 3,680 US $. From the total budget 62.5% is allocated for the personnel salary, which is equal to 2,300 US $. It includes crude salary for program coordinator, research assistants, data entry operators, and financial manager (Table 7).

The operational cost is 30.0% from the total budget, which is equal to 1,105 US $. It will include office and equipment renting, office supplies: cartridge, a copy machine, papers,

stationary, incentive for training programs. Transportation will require 2.5%, which is equal to 100 US $.

From the total budget 5% is allocated for the unexpected expenses, which is equal to 175 US $. Thus the total budget is 3680 US $.

The personnel will consist of a primary investigator who will coordinate the research implementation, staff recruitment and take the responsibility for all program activities (program coordinator). Two research assistants will assist the coordinator and supervise with him logistical flow of the research, data collection, data entry, data analyses and interpretation of final results. Two data entry operators will be needed for a month to perform double data entry. The financial manager will help to prepare financial statements.

Project Feasibility

The proposed project is technically and financially feasible.

Technical consideration. Specialist team, including public health specialist for program coordinator, trained research investigators (health care specialist) with previous work experience will perform the study. The office room, rented equipment and statistical package for data entry and data analysis will increase the technical feasibility.

Financial Consideration. The proposed project is not excessively expensive. However, the implementation of the project depends on donor financial support. Taking into consideration the lack of similar research conducted on mortality due to birth defects in Armenia, it is expected that local and/or international organizations with the mission of maintaining child and mother health will be interested in supporting this program and will provide financial support.

Administrative Consideration. Having a public health specialist, as well as research investigators with similar work experience, accomplishing the proposed research program will be simplified.

Political Consideration. Taking into consideration that birth defects are among the leading causes of perinatal mortality, finding the possible factors causing birth defect development should interest policy makers and the Ministry of Health of Armenia, and they might also assist the study implementation and facilitate its realization.

Ethical Consideration

The data used for the research will be obtained from the medical cards (autopsy reports and history of diseases of mother) in hospital archives. The autopsy reports will be selected by simple random sampling strategy, and medical records of mothers will be chosen based on the data provided in autopsy reports. Considering the sensitivity of the research topic medical cards will be reviewed only after gaining permission from the Ministry of Health of Armenia and provision of informed consent to mother.

The proposed research will be performed in collaboration with the American University of Armenia (AUA), thus the research will be conducted in accordance with AUA IRB human research policy.

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TABLES

Table 1. Main Causes of Perinatal Mortality in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Category	Percent	Percent	Percent	Percent	*Percent*
Infectious Diseases	26.6%	26.6%	26.0%	30.5%	49.6%
Delivery Traumas	4.1%	3.5%	3.8%	1.7%	4.8%
Birth Defects	12.7%	13.4%	14.1%	17.2%	19.6%
Asphyxia	20.7%	15.0%	16.5%	16.9%	12.1%
Hemolytic Diseases	0.3%	0.7%	0.7%	1.7%	1.0%
Pneumopathia	5.9%	5.5%	5.5%	5.0%	1.9%
Iatrogenic Pathology	0.6%	0.7%	0.7.%	0.7%	0.0%
Other	29.0%	34.6%	32.8%	26.5%	10.9%
TOTAL	100.0% (n=338)	100.0% (n=433)	100.0% (n=454)	100.0% (n=302)	100.0% (n=413)

Table 2. Main Causes of Infant Mortality in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Category	Percent	Percent	Percent	Percent	*Percent*
Sepsis	18.0%	29.8%	22.9%	10.6%	13.9%
Different Separate Accidents of Neonatology	25.2%	13.2%	18.8%	35.0%	37.6%
Acute Respiratory Diseases and Pneumonia	3.6%	6.6%	6.3%	3.9%	4.5%
Intestinal Infectious Diseases	18.0%	8.3%	4.9%	4.4%	2.5%
Birth Defects	21.6%	26.4%	33.3%	33.9%	35.1%
Cancer	1.4%	0.0%	0.0%	3.3%	3.5%
Different Diseases	12.2%	15.0%	13.9%	8.9%	3.0%
TOTAL	100.0% (n=139)	100.0% (n=121)	100.0% (n=144)	100.0% (n=180)	100% (n=202)

Table 3. The Distribution of Birth Defect Types Causing Perinatal Mortality in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Types of Birth Defects	Percent	Percent	Percent	Percent	Percent
Central Nervous System Anomaly	34.9%	36.2%	39.1%	38.5%	38.3%
Cardiovascular Anomalies	4.7%	5.2%	1.6%	7.7%	4.9%
Multiple Anomalies	23.3%	27.6%	31.3%	28.8%	28.4%
Gastrointestinal Anomalies	9.3%	10.3%	7.8%	3.8%	0.0%
Down Disease	2.3%	0.0%	1.6%	0.0%	1.2%
Primary Immune Deficiency	4.7%	1.7%	1.6%	1.9%	9.9%
Musculoskeletal Anomalies	4.7%	3.4%	7.8%	3.8%	1.2%
Urinary Tract Anomaly	4.7%	3.4%	1.6%	1.9%	3.7%
Deformities	2.3%	1.7%	1.6%	1.9%	1.2%
Pulmonary System Anomaly	2.3%	3.4%	3.1%	1.9%	1.2%
Chromosomal Anomaly	2.3%	1.7%	3.1%	3.8%	1.2%
Placenta Anomaly	2.3%	3.4%	0.0%	3.8%	6.2%
Endocrine Anomaly	2.3%	1.7%	0.0%	1.9%	2.5%
TOTAL	100.0% (n=43)	100.0% (n=58)	100.0% (n=64)	100.0% (n=52)	100.0% (n=81)

Table 4. The Distribution of Birth Defect Types Causing Infant Mortality in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Birth Defect Types	Percent	Percent	Percent	Percent	Percent
Central Nervous System Anomaly	20.0%	25.0%	25.0%	31.1%	14.1%
Coronary, Heart Anomalies	13.3%	18.8%	12.5%	19.7%	28.2%
Multiple Anomalies	26.7%	21.9%	22.9%	21.3%	8.5%
Gastrointestinal Anomalies	16.7%	18.8%	27.1%	6.6%	29.6%
Down Disease	3.3%	0.0%	10.4%	4.9%	7.0%
Primary Immune Deficiency	10.0%	9.4%	0.0%	6.6%	5.6%
Musculoskeletal Anomalies	6.7%	3.1%	0.0%	9.8%	2.8%
Urinary Tract Anomaly	3.3%	3.1%	2.1%	0.0%	4.2%
Deformities	-	-	-	-	-
Pulmonary System Anomaly	-	-	-	-	-
Chromosomal Anomaly	-	-	-	-	-
Placenta Anomaly	-	-	-	-	-
Endocrine Anomaly	-	-	-	-	-
TOTAL	100.0% (n=30)	100.0% (n=32)	100.0% (n=48)	100.0% (n=61)	100.0% (n=71)

Table 5. Prevalence of Pregnancy Complications among the Mothers of Children Who Died Because of Birth Defects During the Perinatal Period in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Course of pregnancy	Percent	Percent	Percent	Percent	Percent
Normal	11.6%	17.2%	14.1%	19.2%	4.9%
Infectious/ Viral Diseases	23.3%	27.6%	31.3%	28.8%	48.1%
Toxicosis	18.6%	12.1%	21.9%	19.2%	11.1%
Infectious/Viral Diseases and Toxicosis	41.9%	34.5%	20.3%	21.2%	14.8%
Not Available	4.7%	8.6%	12.5%	11.5%	21.0%
TOTAL	100.0% (n=43)	100.0% (n=58)	100.0% (n=64)	100.0% (n=52)	100.0% (n=81)

Table 6. Prevalence of Pregnancy Complications among the Mothers of Infant Who Died Because of Birth Defects in Yerevan, 1998-2002.

	1998	1999	2000	2001	2002
Pregnancy Course	Percent	Percent	Percent	Percent	Percent
Normal Course	3.3%	6.3%	2.1%	18.0%	2.8%
Infectious / Viral Diseases	26.7%	25.0%	31.3%	36.1%	56.3%
Toxicosis	16.7%	12.5%	22.9%	23.0%	8.5%
Infectious / Viral Diseases and Toxicosis	46.7%	50.0%	16.7%	6.6%	11.3%
Not Available	6.7%	6.3%	27.1%	16.4%	21.1%
TOTAL	100.0% (n=30)	100.0% (n=32)	100.0% (n=48)	100.0% (n=61)	100.0% (n=71)

Table 7. Budget Allocation

Personnel	*Duration of the activity*	*Crude Salary (per week in USD)*	*Total Crude Salary (in USD)*
Primary investigator (program coordinator)	15 weeks	50	750
Research assistant 1	8 weeks	40	320
Research assistant 2	8 weeks	40	320
Data entrist 1	2 weeks	40	80
Data entrist 2	2 weeks	40	80
Accounting Consultant	15 weeks	50	750
Subtotal			*2300*
Operational Costs	*Duration of the activity*	*Costs (per week in USD)*	*Total expense (in USD)*
Incentive for training (once)	4 person	15	60
Office rent	15 weeks	25	375
Equipment renting	14 weeks	30	420
Office supplies (Cartridge, Xerox, paper, stationery)	10 weeks	25	250
Subtotal			*1105*
Transportation	4 weeks	25	100
TOTAL			3505
Unexpected expenses	*5.0% from the total*		*175*
GRAND TOTAL			3680

FIGURES

Figure 1. Perinatal and Infant Mortality Caused by Birth Defects in Yerevan, 1998-2002

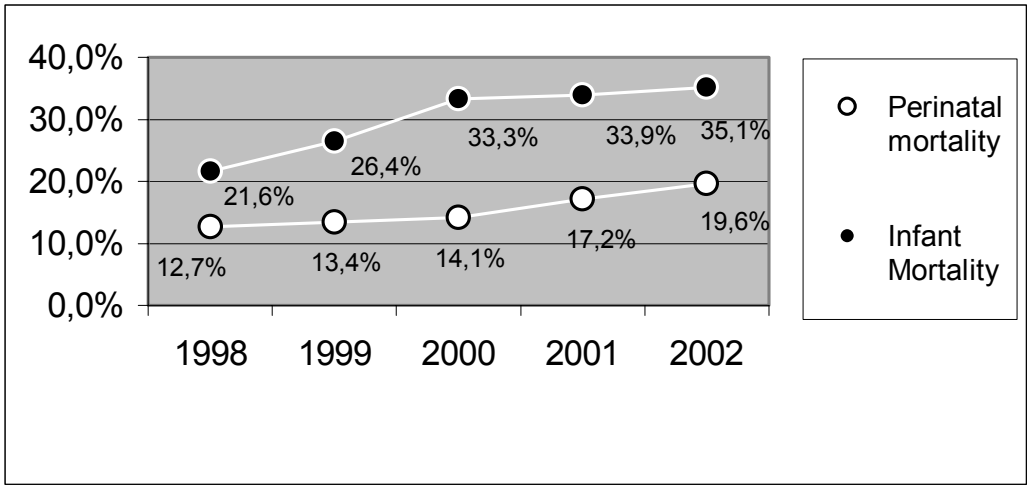

Figure 2.Timeframe

	Month I				Month II				Month III				Month IV			
Activity	**Week I**	**Week II**	**Week III**	**Week IV**	**Week I**	**Week II**	**Week III**	**Week IV**	**Week I**	**Week II**	**Week I**	**Week II**	**Week III**	**Week IV**	**Week I**	**Week II**
Rent space, hire staff, prepare appropriate office and supplies, copy of questionnaires, logistics																
Study researchers trainnig																
Pretest study instrument																
Select cases in RCPA and RPC from autopsy reports																
Select cases and controls in RCPA and RPC from the autopsy reports																
Gain medical cards in hospitals, questionnaire filling																
Monthly Report																
Recruit unfamiliar with the research data entrists, train for data entry																
Train for data entry by researchers																
Entry, data cleanning																
Analyses																
Final Reports																

APPENDIX 1

Autopsy report
[Unofficial translation from Russian]

A. Year of Death _____

B. Birth Defects Caused Death

1 = "Central Nervous System anomaly" 5 = "Down Disease"

2 = “Cardiovascular Anomalies" 6 = "Primary Immune Deficiency"

3 = "Multiple Anomalies" 7 = “Musculoskeletal Anomaly"

4 = "Gastrointestinal Anomaly" 8 = ""Urinary Tract Anomaly"

C. Gender

1. M 2. F

D. Age of child

1. 0 - 30 days 4. 181-270 days

2. 31 - 90 days 5. 271-1 year

3. 31 - 180 days; 00. Stillborn

E. *Gestation period*

0. premature 1. maturated 33. not available

F. Coexistance of other diseases

0. no 1. yes

G. *Mothers age*

1. <=20 years; 2. 21-30 years; 3. 31- 40 years; 4. 41=>years

H. Course of pregnancy

0. normal flow 1. Infect. /Vir. Diseases 2. Toxicosis 3. Infect. /Vir. Diseases and Toxicosis 33. not available

APPENDIX 2

Abstract form

Please, fill the spaces or circle the appropriate number

Date _____ dd/mo/yr

1. Number of History of Diseases _ _ _ _ _

Demographic Questions

2. Date of mother birth _____ dd/mo/yr, or age of mother_____

3. Mother Residency _____

4. Mother Occupation: a. Student b. Employed c. Unemployed

d. Currently Unemployed (previous occupation_____) e. NA

5. Number of previous pregnancy_____, b. number of abortions_____,

number of deliveries_____, d. number of current children_____, e. NA

Pregnancy History

Maternal Health

6. Toxicoses 0. No 1.Yes 33. NA

7. Diabetes 0. No 1.Yes 33. NA

8. Seizures 0. No 1.Yes 33. NA

9. Respiratory illnesses 0. No 1.Yes 33. NA

10. Fever 0. No 1.Yes 33. NA

11. Bladder, Kidney, Urinary Tract Infectious

0. No 1.Yes 33. NA

12. Other Diseases 0. No 1.Yes, specify_____ 33. NA

13. Injuries 0. No 1.Yes 33. NA

14. Surgery 0. No 1.Yes 33. NA

15. X-rays 0. No 1.Yes 33. NA

Diet Substance Use

16. Contraception before pregnancy if 0. No, go to 17,

if 1.Yes: a. oral b. mechanical c.other, specify

33. NA

17. Vitamins consumptions 0. No 1.Yes 33. NA

18. Drug use 0. No 1.Yes 33. NA

19. Alcohol Use 0. No 1.Yes 33. NA

20. Tobacco Use 0. No 1.Yes 33. NA

21. Caffeine Use 0. No 1.Yes 33. NA

22. Prenatal Care 0. No 1.Yes 33. NA