Investigation of Risk Factors for Preeclampsia Development Among Reproductive Age Women Living in Yerevan, Armenia: A Case-Control Study

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by

Arusyak Harutyunyan, MD, MPH Candidate

Advisor: Haroutune Armenian, MD, DrPH

Reader: Varduhi Petrosyan, MS, PhD

College of Health Sciences

American University of Armenia

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LIST OF ABBREVATIONS

AIC	Akaike's Information Criteria
AMD	Armenian Dram
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
cm	centimeter
df	degree of freedom
dL	deciliter
g	gram
IBI	Interbirth Interval
mg	milligram
mm Hg	millimeters of mercury
NHLBI	National Heart Lung and Blood Institute
OR	Odds Ratio
SD	Standard Deviation
TTP	Time to pregnancy
US	United States
VIF	Variance Inflation Factor
WHO	World Health Organization

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ABSTRACT

Introduction: Preeclampsia is a hypertensive disorder of pregnancy of unknown etiology. Worldwide, each year, more than four million women develop preeclampsia and in developing countries, where prenatal care is not adequate, preeclampsia/eclampsia accounts for 40% to 80% of maternal deaths, accounting for about 50,000 deaths yearly.

Objective: To measure the association of parity and interbirth interval (IBI) with preeclampsia status and their interactions with other covariates among reproductive age (18-45) women living in Yerevan.

Methods: The study utilized a case-control study design. Cases (n=89) were reproductive age women living in Yerevan that were diagnosed with preeclampsia in the Institute of Obstetrics (Perinatology), Gynecology and Reproductive Health and the Erebuni Medical Center from 01.01.2008 to 01.04.09. Controls (n=279) were reproductive age women living in Yerevan that gave birth in the same maternity homes with no diagnosis of preeclampsia during pregnancy within the same time period. The study conducted telephone based interviews with both cases and controls through structured questionnaire developed by the research team. Data analysis was performed using STATA software.

Results: The odds of preeclampsia was lower among multiparous women compared to primiparous women (OR=0.27; 95% CI: 0.14, 0.51; p=0.000) after adjusting for age, Body Mass Index (BMI), number of people living in the household and number of employed family members. After adjusting for age, BMI, renal disease the odds of preeclampsia was higher among women with long IBI compared to women with short IBI (OR=2.90; 95% CI: 1.07, 7.86; p=0.036). The interaction term between IBI and the history of previous preeclampsia was 0.11 (95% CI: 0.01, 1.01; p=0.051).

Conclusions: The results showed that parity and IBI were statistically significantly associated with preeclampsia status after controlling for confounders. This study confirmed that the risk of preeclampsia falls sharply after the first birth but it also showed that the risk increased over time and that long IBI was associated with higher risk of preeclampsia development. However, for women without history of previous preeclampsia the risk of preeclampsia increased in subsequent pregnancy with increasing time between births whereas for women with history of previous preeclampsia the risk tended to decrease with increasing interval between births.

1. INTRODUCTION/LITERATURE REVIEW

1.1. Hypertensive Disorders of Pregnancy

Hypertensive disorders during pregnancy are common and form one part of the deadly triad, along with hemorrhage and infection, which results in much of the maternal morbidity and mortality related to pregnancy (1). The hypertensive disorders during pregnancy affect up to 8.0% of all pregnancies and remain a major cause of maternal and neonatal mortality and morbidity in the United States (US) and worldwide (2).

Hypertensive disorders in pregnancy are responsible for 76,000 maternal and 500,000 infant deaths each year worldwide (3). Almost 18.0% of 1,450 maternal deaths in the US from 1987 to 1990 were from complications of pregnancy related to hypertension (4).

A World Health Organization (WHO) analysis of maternal deaths reveals that hypertensive disorders are responsible for 16.1% maternal deaths in developed countries and are the leading cause of maternal death in Latin America and the Caribbean (25.7%), as well as a major contributor to maternal death in Africa (9.1%) and Asia (9.1%) (5).

The US National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy has defined the following categories of hypertensive disorders during pregnancy: chronic hypertension, gestational hypertension, preeclampsia/eclampsia and preeclampsia superimposed on chronic hypertension (Appendix 1) (6). These categories have different epidemiological characteristics, pathophysiology, and risks for the mother and baby (2).

The reported incidence of hypertensive disorders during pregnancy shows great variation, which may be attributable to differences in definition, population composition, demographic and obstetric characteristics, or actual disease incidence (7). Preeclampsia affects 2.0-13.0% of all pregnancies.

1.2 Preeclampsia

Preeclampsia is a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation (1). It is now known to be a multi-system disease and can include placental dysfunction, acute renal failure, cerebral edema, cerebral hemorrhage, seizures (eclampsia), coagulopathy and liver injury.

Preeclampsia is diagnosed in the presence of hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mmHg on at least two occasions, 6 hours to 1 week apart) and proteinuria (≥300 mg in a 24-hour urine collection or 30mg/dL (1+ dipstick) in random urine sample) after 20 weeks' gestation (Appendix1) (6;8;9).

Worldwide, each year, more than four million women develop preeclampsia and in developing countries, where prenatal care is not adequate, preeclampsia/eclampsia accounts for 40% to 80% of maternal deaths, accounting for about 50,000 deaths yearly (10). In some countries it is the main cause of maternal mortality: up to 42.0% of maternal deaths are attributed to this disorder in Colombia (11). It is alarming that the rate of preeclampsia has increased by 40.0% between 1990 and 1999, which is probably the result of a rise in the number of older mothers and multiple births, scenarios that predispose to preeclampsia (2).

In developed countries, where maternal mortality attributable to preeclampsia has been reduced, the condition primarily affects fetal well-being through intrauterine growth retardation, preterm birth, low birth weight, and perinatal death (12). The increased infant morbidity and mortality rates are especially disheartening because at least part of it (20.0%) is attributable to preterm delivery undertaken to prevent further deterioration in the fetus and mother. In fact, 15.0% of all preterm births are indicated early deliveries for preeclampsia (2).

A history of preeclampsia increases the risk of future hypertension, ischemic heart disease, stroke, venous thromboembolism, and death from any cause (13).

Despite extensive research exploring its cause, prevention, and treatment, there has been no improvement in predicting who would be diagnosed with disease and there are no protocols for prevention or cure for the disease other than delivery (even if it is a long time before term). Preeclampsia has been termed the "disease of theories" reflecting the confusion that surrounds its causes and pathophysiology (14). Currently, four hypotheses are favored: placental ischemia, very low-density lipoproteins versus toxicity preventing activity, immune maladaptation, and genetic imprinting. These four hypotheses are not mutually exclusive but probably interactive (15).

A number of risk factors have been identified for preeclampsia development (16). Preeclampsia generally is considered a disease of the first pregnancy because the risk is much lower in pregnant women who have had a previous pregnancy. Preeclampsia occurs mainly in primiparous women[1] who have a 4-5 times higher risk than multiparous women[2] (17-23). Multiparous patients also have milder symptoms, and most of these cases are recurrent cases (17). Women aged ≥ 40 have about twice the risk of developing preeclampsia, whether they were primiparous or multiparous. Nationwide US data suggest that the risk of preeclampsia increases by 30.0% for every additional year of age past 34 (22;23). There were numerous epidemiological studies of previous preeclampsia and they suggested that women who had preeclampsia have approximately seven times the risk of preeclampsia in a subsequent pregnancy (18;19;22-24). Family history of preeclampsia is also shown to be a risk factor for

[1] Women who have carried one pregnancy achieving ≥ 20 weeks' gestation

[2] Women who have carried more that one pregnancy to ≥ 20 weeks' gestation

preeclampsia development. Daughters and sons of women who had preeclampsia during pregnancy have higher risk of preeclampsia in their own (or their partner's) pregnancy. Sisters of these women and men, who themselves were not born after pregnancy complicated by preeclampsia, also have higher risk (22;25).

A long interbirth interval (IBI)[1] increases the risk of preeclampsia. This finding suggests that the protective effect of past pregnancies may decline over time or that another factor correlating with time may also contribute to the increased risk with long intervals between births. Although these studies used different categories of intervals, most of them reported a significant association between long IBI and increased risk of preeclampsia (23;24;26;27). Although the exact length of the interval at which the risk of preeclampsia begins to increase was not clear from the existing evidence, IBIs of 5 years or more appeared to be associated with 60% to 80% increased risk of preeclampsia (26).

A number of epidemiological studies have shown that multiparous women who changed partners had a higher risk of preeclampsia in the following pregnancy than multiparous women with the same partner, and primipaternity rather than primiparity has been suggested to be a major risk factor (19;23;26;28;29). Women who were pregnant by a partner who fathered a preeclamptic pregnancy in another woman had nearly twice the risk in their own pregnancy (23). The effect of previous abortion on the incidence of preeclampsia is still in dispute. Some studies found that previous abortion decreases the risk of preeclampsia (20;30;31). However, there are others that report that previous abortion is not protective (32-34). Some studies linked maternal low birth weight with an increased risk of preeclampsia during their own pregnancies (25;35;36). Less then high level of education (university or PhD degree) is reported to be a risk factor for

[1] Birth date of index child - birth date of preceding birth

preeclampsia. One of the recent studies reported that after adjusting for age, gravidity and multiple pregnancy, women with low educational level were more likely to develop preeclampsia than women with high educational level (37). Although the effect of low education is in part mediated by financial difficulties, the association between educational level and preeclampsia remained largely unexplained. Depression and anxiety in early pregnancy (38;39) and stress, working-related psychological strains (18;40;41) are shown to be associated with the risk of preeclampsia development. Women with pre-existing medical conditions like chronic hypertension (22;24), renal diseases (22;24), chronic autoimmune diseases (22), antiphospholipid syndrome (22;42), diabetes and gestational diabetes (22;24) are more likely to develop preeclampsia compared with those without them. It is well documented that the risk of preeclampsia increases with the increase of Body Mass Index (BMI) (18;21;22;24;30;34). The systematic review of the existing evidence regarding the relationship between cigarette smoking during pregnancy and preeclampsia revealed an inverse association between cigarette smoking during pregnancy and incidence of preeclampsia showing a lower risk of preeclampsia associated with cigarette smoking during pregnancy (21;24;30;34;43). The factors associated with pregnancy like multiple pregnancy (22;44;45), fetal malformations (46), chromosomal abnormalities (47-49), hydatidiform moles[1] (16;17) and hydrops fetalis[2] (16;17) are also reported to increase the risk of preeclampsia. Among primiparas, the proportion with preeclampsia is shown to increase with a longer than 2 months time to pregnancy (TTP) as a

[1] A pregnancy/conceptus in which the placenta contains grapelike vesicles that are usually visible with the naked eye. The vesicles arise by distention of the chorionic villi by fluid

[2] A condition in the fetus characterized by an accumulation of fluid, or edema, in at least two fetal compartments, including the subcutaneous tissue, pleura, pericardium, or in the abdomen

marker of fecundity[1], expressed as the number of cycles required for a couple to conceive from the start of unprotected intercourse. Among multiparous women, only those women waiting more than 12 months appeared to have an increased risk (50). Women using condoms, diaphragms, spermicides and withdrawal are at higher risk of preeclampsia compared to those that use such contraceptive methods that permit exposure of viable sperm with the uterus (28;51).

1.3 Situation in Armenia

In Armenia the maternal mortality ratio from 1990 to 1992 was 38.5 (per 100,000 live births), dropping down to 25.0 between 2002 and 2004 (52). While the maternal mortality rate was reported to be reduced from 1990 to 2004, it is still 1.5 times higher than the maximum of 15.0 per 100,000 live births established by the WHO for Eastern Europe. The maternal mortality structure by gestational age indicates that the majority of registered deaths (64%) occur after 28 weeks of gestation.

In Armenia the main causes of maternal mortality are hemorrhage, hypertension and postpartum complications. In 2003, the structure of maternal mortality by causes was the following: hemorrhage - 28.6%, sepsis - 14.3%, toxicosis - 14.3%, and obstructed labor and other complications - 42.8%. The reduction of maternal mortality by three-quarters from 1990 to 2015 is one of the Millennium Development Goals targeted in Armenia (52).

Women in Armenia are 9 times more likely to die from pregnancy or childbirth complications than women in developed countries. In particular, a woman in Armenia has 1 in 980 lifetime risk of maternal death, compared with a probability of 1 in 8,000 for women in

[1] The ability to reproduce

developed countries and the average of 1 in 1,300 in the region of Central and Eastern Europe and the Commonwealth of Independent States (53).

1.4. Aims and Research Questions of the Study

The aims of the study were:

- To identify risk factors for preeclampsia development among reproductive age (18-45) women living in Yerevan
- To identify interactions between risk factors for preeclampsia development among reproductive age (18-45) women living in Yerevan
- To develop recommendations for guidelines to predict and prevent preeclampsia development before pregnancy or during the early stages of pregnancy

The research questions were:

- Does long IBI, defined as interval between two births more than or equal to 5 years, increase the risk of preeclampsia development among multiparous reproductive age women living in Yerevan after controlling for confounders?
- Is there any interaction between long IBI and other risk factors?
- Does primiparity increase the risk of preeclampsia development among reproductive age women living in Yerevan after controlling for confounders? Is there interaction between parity and other risk factors?

2. METHODS

2.1 Study Design

To address the mentioned research questions the case-control study design was chosen. This method has both operational and conceptual strengths and advantages (54). On an operational level, these advantages include speed, cost, and the need for a limited number of

study subjects with very little risk to the subjects. On a conceptual level, and as a very versatile design, it is the method of choice to study diseases that have a long latency, and to test many hypotheses.

2.2. Study Population

The target population included reproductive age (18-45) women living in Yerevan. The study population included reproductive age (18-45) women living in Yerevan that were admitted to the Institute of Obstetrics (Perinatology), Gynecology and Reproductive Health and the Erebuni Medical Center for delivery from 1 January 2008 to 1 April 2009. Out of all deliveries that took place in the maternity homes in Yerevan between July 1 and December 31, 2008 17.8% and 13.4% of deliveries took place in these maternity homes, respectively (55).

Maternity homes were selected by convenience from the complete list of maternity homes of Yerevan.

2.2.1. Definition of Cases

Cases were reproductive age women living in Yerevan that were diagnosed with preeclampsia in selected maternity homes. The participants were classified as cases if they were diagnosed with preeclampsia using US National Heart Lung and Blood Institute (NHLBI) criteria for diagnosis (6) (Appendix 1).

2.2.2. Definition of Controls

Controls were reproductive age women living in Yerevan that gave birth in the same chosen maternity homes with no diagnosis of preeclampsia during pregnancy.

2.2.3. Exclusion Criteria

Exclusion criteria for both cases and controls were residency outside of Yerevan, absence of contact information, as well as poor knowledge of Armenian. The additional exclusion criteria for cases were the diagnosis of preeclampsia made using other than US NHLBI criteria.

2.3. Sample Size

The student investigator calculated sample size using the formula for proportions difference assuming the ratio of controls to cases as 3:1 with the level of significance 0.05 and power 0.8 using Epi–info statistical software. Considering the proportion of women with long interbirth interval among women with preeclampsia as 27% and proportion of women with short IBI among women without preeclampsia as 18% the sample size was estimated to be 216 cases and 648 controls (multiparous) (31).

2.4. Data Collection

Data collection continued between April 1 and May 31, 2009. First, the study team selected maternity homes by convenience. After getting the permission from the heads of the maternity homes the study used medical records from 1 January 2008 to 1 April 2009 to identify the study population. The student investigator obtained the names and contact information (telephone number) of women from medical records for telephone based interviews. All cases that met the eligibility criteria were chosen. The study selected controls using the following principle: after selecting each case three controls were randomly selected using the table of random numbers from 1-10. Overall, the study selected 102 eligible cases and 306 controls from the registries of two maternity homes.

The student investigator collected the data by telephone interviews. The actual interview lasted approximately 15 minutes.

2.5. Study Instrument

An interviewer-administered structured questionnaire was used during the telephone interviews with both cases and controls (Appendix 3). The student investigator developed the questionnaire. It included questions adopted from questionnaires used in other studies to investigate risk factors for preeclampsia development and questions added by the investigator adopted from other instruments (56-60).

The questionnaire consisted of 39 mainly close-ended questions. It included the following main domains: socio-demographic characteristics, reproductive history, contraceptive history, weight and height, blood group and Rh factor, blood pressure, health status (co-morbidities), smoking and family history of preeclampsia.

Before starting data collection, the developed questionnaire was pre-tested among reproductive age women (n=5, 2 cases and 3 controls) through telephone interviews. Based on the pre-test results some changes were made related to questions about smoking, contraceptives and partner change.

2.6. Study Variables

The dependent (outcome) variable of the study was preeclampsia status during pregnancy clinically confirmed by the doctor at the maternity home.

Independent variables were: age, educational level, parity, marital relationship, general standard of living, average household expenditure, number of people living in the household, number of employed family members, women's birth weight, women's blood group and Rh factor, number of working luxury items in the household, employment status of women during pregnancy, type of used contraceptive one year before pregnancy, TTP, folic acid intake, smoking during pregnancy, exposure to secondhand smoke, total number of stillbirths,

spontaneous abortions, induced abortions, interbirth interval, family history of preeclampsia, history of previous preeclampsia, BMI, chronic hypertension, renal disease, diabetes, gestational diabetes, partner change, and multiple pregnancy. Appendix 4 presents the summary of the study variables.

2.7. Data Management and Analysis

2.7.1. Data Entry

After data collection the student investigator entered the data into SPPS-11 software. After recoding and cleaning procedures through range checking and spot checking the data were transferred into STATA-10 statistical package for statistical analysis.

2.7.2. Statistical Methods

Basic descriptive statistics (means, medians, frequencies and standard deviations) were generated for controls and cases.

The study used independent T-test for comparison of means for continuous data and the Pearson's chi-square test of the null hypothesis of homogeneity for comparison of categorical data to compare differences in proportions/means of independent variables between groups. The study used Fisher's exact test for variables with small frequencies. Continuous variables were converted into ordinal variables to describe their distribution among cases and controls and to explore their relationships with the outcome variable. The study categorized continuous variables using cut-points from previous studies.

To assess the relationships between each independent variable and the dependant variable and to identify confounders for the relationship between IBI and preeclampsia status as well as between parity and preeclampsia status the study performed simple logistic regression. Categorical data were converted into "dummy" variables for the regression analysis.

The study applied multiple logistic regression models to control for potential confounders and explore potential effect modification and, ultimately, to calculate the odds ratio and 95% confidence interval to estimate the strength of associations between independent and dependant variables. Variance Inflation Factor (VIF), which is the method for detecting the severity of multicollinearity, was applied for variables in the final models. The variables that highly correlated to each other were not included in the regression model together.

2.8. Ethical Considerations

The Institutional Review Board/Committee on Human Research (IRB) within the College of Health Sciences at the American University of Armenia approved the study. The ethical issues of privacy, confidentiality, consent and justice have been taken into account while conducting the study. All the women were included in the study after getting oral informed consent (Appendix 2). They could skip any of the questions and stop the interview at any time. Personal information about the participants was available only to the researcher and was not used for other purposes.

3. RESULTS

3.1. Response Rate

The response rate was 95.7% for cases and 95.5% for controls. However, the study team failed to contact 23 subjects due to different reasons: being out of the country, not at home, wrong telephone numbers or the change of the telephone number. Three subjects were not interviewed as they met the exclusion criteria (poor knowledge of Armenian language). The study team stopped the data collection when 368 interviews were completed. The data analysis was based on 89 cases and 279 controls.

The study calculated actual statistical power based on the proportions of the primary variable (IBI) and the sample size and it was 0.98. The actual power based on the proportions of parity was 0.71 (Appendix 5).

3.2. Descriptive Statistics

About 35.87% of women (33 cases and 99 controls) gave birth at the Institute of Obstetrics (Perinatology), Gynecology and Reproductive Health and 64.13% of women (56 cases and 180 controls) gave birth at the Erebuni Medical Center. The mean duration of the pregnancy among cases was 35.54 weeks (SD: 3.41) and 38.44 (SD: 1.05) among controls. Only one woman reported having diabetes and gestational diabetes among cases. Most of the participants (99.46%) were married and only two women among cases reported to be single. Only one woman among cases reported that had pregnancy from another man than the father of the current baby. Two multiple pregnancies were reported among controls. Seven babies only among cases were born dead or died in the maternity home.

Table 1 presents descriptive statistics of the study population by cases and controls. Descriptive statistics showed that the cases were older compared to controls: the mean age of the cases was 28.46 (SD: 6.05) vs. 26.42 (SD: 4.48). The cases had higher BMI than controls: 24.04 kg/m^2 (SD: 6.54) vs. 21.23 (SD: 3.20). The multiparous women among cases were more likely to have IBI more than 5 years compared to controls: 62.16% vs. 26.53%.

Cases and controls were statistically significantly different with respect to the highest level of education, chronic diseases (chronic hypertension and renal diseases), number of people living in the household, number of employed family members, total number of luxury items, TTP, birth weight of the born babies, birth height of the born babies, infertility treatment, parity,

history of previous preeclampsia, total number of stillbirths, family history of preeclampsia, and total number of abortions.

3.3. Simple Logistic Regression

Table 2 presents the results of simple logistic regression analysis for association between preeclampsia status and independent variables without any adjustment for confounding variables with estimated crude odds ratios, CIs, p-values. The estimated crude OR of the association between long IBI and preeclampsia status was 5.26 (95% CI: 2.39-11.57; $p<0.0005$) meaning that the odds of preeclampsia among multiparous women long IBI is 5.26 times higher compared with multiparous women with short IBI. The estimated crude OR of the association between parity and the preeclampsia status was 0.60 (95% CI: 0.37-0.98; $p=0.038$) suggesting that multiparous women are 0.60 times less likely to develop preeclampsia compared to primiparous women. Compared to women who become pregnant right away women with TTP ≥1-2 months were at higher risk of developing preeclampsia. However, the cut-points were different for primiparous and multiparous women (Table 3).

3.3.1. Testing for Confounding

Table 4 presents the results of the simple logistic regression for the association of the IBI and preeclampsia status and other independent variables. TTP with the cut-point of 12 months, abortions between births, induced abortions between births, spontaneous abortions between births, renal disease, age at the delivery, BMI, number of employed family members were statistically significantly associated with IBI with the cut point of 5 years. Number of people living in the household, TTP with the cut-point of 12 months, family history of preeclampsia, age at delivery, renal disease, and BMI (defined as normal vs. overweight or obese) were statistically significantly associated with the preeclampsia status. This analysis concluded that age at the

delivery, BMI, renal disease, TTP with the cut-point of 12 months were confounders of the relationship between preeclampsia status and IBI.

Table 5 presents the results of the simple logistic regression for the association of the parity and preeclampsia status and other independent variables. The results of the simple logistic regression analysis showed that number of people living in the household, number of employed family members, age at the delivery and BMI are the confounders of the relationship between preeclampsia status and parity.

3.4. Linear Spline to Explore Possibility of Non-linear Relationships

Linear spline analysis was conducted between preeclampsia status and age with the cut-point of 30. Linear spline analysis demonstrated a non-linear relationship with a statistically significant spline term with cut-point of 30 (see Figure 1 & Appendix 5).

The spline term was tested for the relationship of preeclampsia status and IBI with the cut-point of 5 years. The spline term with cut-point of 5 years was not statistically significant (Appendix 5) and IBI entered regression model as a categorical variable with cut-point of 5 years.

3.5. Multiple Logistic Regression Analysis

All the identified confounders for the parity entered the multiple logistic regression analysis. After adjusting for the identified confounders (age, BMI, number of people living in the household and number of employed family members) the odds of developing preeclampsia was lower among multiparous women compared to primiparous women (OR=0.27; 95% CI: 0.14-0.51; $p<0.0005$) (Appendix 5). Possible interactions between parity and other independent variables were checked and no statistically significant interaction between parity and other independent variables was identified.

After adjusting for age, BMI, renal disease the odds of having preeclampsia was higher among women with long IBI compared to women with short IBI (OR=2.90; 95% CI: 1.07-7.86; p=0.036) (Table 8). After adjusting for age, BMI and renal disease the odds ratio of having preeclampsia associated with one year increase in IBI was 1.19 (95% CI: 1.04-1.37; p=0.012). Although TTP with cut-point of 12 months was identified as a confounder the IBI was not adjusted for it as only those who planned their pregnancy (111 multiparous women) reported TTP.

Possible interactions between IBI and other independent variables were checked and statistically significant interaction was identified between the history of previous preeclampsia and the IBI (Table 6, Table 7, Table 8 and Appendix 5). The interaction term between IBI with the cut-point of 5 years and the history of previous preeclampsia was 0.11 (95% CI: 0.01-1.01; p=0.051). The interaction term between IBI as a continuous variable and the history of previous preeclampsia was 0.77 (95% CI: 0.58-1.01; p=0.059).

Among women without history of previous preeclampsia the odds of having preeclampsia was 10.1 times higher among women with long IBI compared to those with short IBI (OR=10.1; 95% CI: 3.12-32.73; p=0.000). After adjusting for age, BMI and renal disease the odds ratio of having preeclampsia among women with long IBI compared to those with short IBI was 6.88 (CI: 1.75-27.05; p=0.006) among women without history of previous preeclampsia and 0.60 (CI: 0.07-4.99; p=0.638) among women with history of previous preeclampsia.

After adjusting for age, BMI and smoking the odds of preeclampsia was 4.18 times higher among multiparous women with >12 months of TTP (95% CI: 1.04-16.76; p=0.043) compared to those with <12 wonths of TTP (Table 3).

3.5.1. Predictive Models

Multiple logistic regressions analysis was used to find the predictive final model for multiparous women who planned their pregnancy. Each full model was tested against the nested model using Akaike's Information Criteria (AIC) which is an approximation to the cross-validated prediction error (e.g. criteria for determining the "best "model) (61). The AIC model "penalizes" models with more predictors and thus favors parsimonious models. The best fitting model included the IBI with cut-point of 5 years, time to pregnancy with cut-point of 12 months, BMI, barrier methods of contraception and household monthly income (Table 9, Table 10, and Appendix 5). The model fit was tested with Hosmer-Lemeshow goodness of fit test. The Hosmer-Lemeshow test statistics was 5.0 (df=8, Prob > chi2 = 0.76) indicating good calibration (Appendix 5).

Multiple logistic regression analysis helped to find the model for all women regardless of parity. The best fitting model was chosen by using Akaike's Information Criteria (Table 11). The best fitting model included parity, highest level of education, number of employed family members, infertility treatment, BMI, agespline_30 and pregnancy planning (Table 12 and Appendix 5). The Hosmer-Lemeshow test statistics was 5.5 (df=7, Prob > chi2 = 0.55) indicating good calibration (Appendix 5).

Variance Inflation Factor (VIF) method indicated for both models that none of the variables that entered the final models were highly correlated.

4. DISCUSSION

4.1. Study Limitations

The study had to rely on the hospital records for the diagnosis of preeclampsia. Problems with diagnosis of preeclampsia involve great observer variability in measuring blood pressure

and the commonly used dipstick analysis of random urine sample rather than 24-hour urine analysis (62). The study questionnaire that was developed by the study team and was not validated. The student investigator was aware of the women's case and control status which might lead to a potential interviewer bias as the process of measuring the exposure was not independent from the case-control status. The actual power for parity was 0.71.

4.2. Strengths of the Study

All medical records were reviewed by the student investigator and uncertain diagnoses made based on using other than NHLBI criteria were excluded from the study to reduce the number of false positive diagnoses. Controls were selected by simple random selection. The same data sources were used to identify both cases and controls which increased the confidence that the cases and controls were coming from the same base population and the groups were comparable. The study used incidence density approach for selecting controls meaning that controls were selected from all eligible women that gave birth in the selected maternity homes without diagnosis of preeclampsia in the same month when the cases were diagnosed with preeclampsia in the same maternity homes. "The advantage for such an incidence-density selection strategy of controls is that it establishes comparability between cases and controls as to follow-up time for the detection of disease" (63). The power analysis showed that the actual power was bigger (0.98) than estimated power (0.80) for the main independent variable (IBI). The structure of the sample population regarding IBI was compared to the other studies suggesting consistency in the results (58).

4.3. Main Findings

The presented case-control study investigated associations of IBI and parity and preeclampsia status among reproductive age (18-45) women living in Yerevan. The results

showed that parity and IBI were statistically significantly associated with preeclampsia status after controlling for confounders.

Similar to many other studies this study confirmed the protective effect of multiparity on the risk of preeclampsia development (17-23). The study suggested that the odds of preeclampsia among multiparous women is 0.27 times lower than the odds of preeclampsia among primiparous women after controlling for confounders.

Although our data confirmed that the risk of preeclampsia falls sharply after the first birth but it also showed that the risk increases over time and that long IBI was associated with higher risk of preeclampsia development. The unadjusted ORs of the association of preeclampsia status with long IBI and with each one year increase in IBI were 5.26 and 1.26, respectively. Testing for confounding revealed that age, BMI, renal disease and TTP with cut-point of 12 months were the confounders of the relationship between IBI and preeclampsia status.

This finding about the association of longer than 12 months of TTP and preeclampsia status was consistent with the results of the study conducted by the Danish National Birth Cohort ongoing project among 45,610 women from 1998 to 2001 (50). This study used TTP for the first time as a marker of fecundity for the association with preeclampsia status. The present case-control study identified TTP with cut-point of 12 months being a confounder for the relationship of IBI and preeclampsia status. However, IBI was not adjusted for TTP in this study as only those women that planned their pregnancies reported TTP (111 multiparous women).

The study revealed that after adjusting for age, BMI and renal disease the risk of preeclampsia for each one year increase in IBI since last delivery significantly increased by 19% (OR=1.19). Also, after adjusting for age, BMI and renal disease the odds of preeclampsia development among women with long IBI was 2.90 times higher compared to women with <5

year IBI. The results observed in this study were consistent with other studies showing 10-13% increased ORs for each one year increase in IBI (24;27).

This study demonstrated a statistically significant interaction between long IBI and the history of previous preeclampsia. For women without history of previous preeclampsia the risk of preeclampsia increased in subsequent pregnancy with increasing time between births whereas for women with history of previous preeclampsia the risk tended to decrease with increasing interval between births. Lill Trogstad et al. demonstrated a similar interaction in their study among 547,238 women registered in the Medical Birth Registry of Norway, 1967-1998 (64).

Unfortunately, we did not have sufficient data to address effect modification between the IBI and change of partner reported in the literature with controversial results (27;64) as only one woman in the sample reported that previous birth was from other man than the father of the current baby.

The study developed models for predicting and preventing preeclampsia development before pregnancy or during the early stages of pregnancy. The findings regarding variables included in the final models were consistent with the literature. The identified predictors for preeclampsia development were parity (17-23), education (37), treatment for infertility, pregnancy planning, age>30 years (22;23), BMI (18;21;22;24;30;34), renal disease (22;23) and method of contraception (28;51). The study developed the second predictive model for a subgroup of multiparous women who had planned their pregnancies which included IBI (23;24;26;27), barrier methods of contraception, BMI, and household monthly income (37).

The study failed to investigate the association of preeclampsia status and diabetes, gestational diabetes, smoking, marital status, multiple pregnancy and partner change because of little number of women with indicated characteristics in the sample.

5. RECOMMENDATION

The study recommends designing future studies to replicate the findings of the current study, to assess the extent to which the longer TTP might account for the increased risk associated with IBI, to test and/or improve the predictive power of the developed predictive models.

Health care providers should inform women about the known risk factors of preeclampsia development particularly about modifiable risk factors like high BMI. As each additional year increase in IBI appeared to be a strong risk factor for preeclampsia development among women without history of previous preeclampsia IBI no more than the recommended 3 years might be a recommendation for preventing preeclampsia development (65). Further investigation of the role of the long IBI among women with history of previous preeclampsia may contribute to a new approach in understanding the etiology of preeclampsia and may be useful for developing further recommendations for this particular subgroup of women that are at higher risk for preeclampsia development in subsequent pregnancies.

6. CONCLUSION

The study showed that primiparous women were at higher risk of developing preeclampsia than multiparous women. It also revealed that the risk of preeclampsia changed over time. The effect of IBI on the risk of preeclampsia was different for women with previous preeclampsia compared to women without history of previous preeclampsia.

Women with longer TTP were at higher risk of developing preeclampsia. The study showed that TTP >12 months was a confounder for the association of the IBI and preeclampsia status, suggesting that longer TTP might explain part of the increased risk of preeclampsia associated with long TTP.

The study developed two models for predicting preeclampsia development before pregnancy or during the early stages of pregnancy.

This was the first epidemiologic study in Armenia investigating the risk factors for preeclampsia development which demonstrated consistent results with literature and identified new areas of research.

Reference List

(1) F G Cunningham, N F Gant, et al. Hypertensive disorders of pregnancy. Williams Obstetrics. 2001.

(2) J M Roberts, G Pearson, et al. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 2003; 41:437-445.

(3) Preeclampsia Foundation. Annual Report 2007. Available at: http://www.preeclampsia.org . 2009.

(4) C J Berg, H K Atrash, et al. Pregnancy related mortality in the United States,1987-1990. Obstetrics & Gynecology 1996; 88:161-167.

(5) K S Khan, D Wojdyla. WHO analysis of causes of maternal death: a systematic review. Lancet 2006; 367(9816):1066-1074.

(6) R W Gifford, P A August, et al. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. American Journal of Obstetrics and Gynecology 2000; 183:S1-S22.

(7) World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. American Journal of Obstetrics and Gynecology 1988; 158(1):80-83.

(8) M A Brown, M D Lindheimer, et al. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertension in Pregnancy 2001; 20:9-14.

(9) M A Brown, W M Hague, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. The Australian New Zealand Journal of Obstetrics Gynaecology 2000; 40:139-155.

(10) K Y Lain, J M Roberts. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA 2002; 287:3183-3186.

(11) P Lopez-Jaramillo, Serrano N, et al. Preeclampsia: from epidemiological observations to molecular mechanisms. Brazilian Journal of Medical and Biological Research 2009; 34(10):1227-1235.

(12) R L Goldenberg, D J Rouse, et al. Prevention of premature birth. The New England Journal of Medicine 1998; 339(313):320.

(13) L Bellamy, A D Hingorani, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ 2007; 335:974-986.

(14) B F Pipkin, P C Rubin, et al. Pre-eclampsia--the 'disease of theories'. British Medical Bulletin 1994; 50:381-396.

(15) G A Dekker, B M Sibai. Etiology and pathogenesis of preeclampsia: current concepts. American Journal of Obstetrics and Gynecology 1998; 179:1359-1375.

(16) G A Dekker. Risk Factors for Preeclampsia. Clinical Obstetrics and gynecology 1999; 42(3):422.

(17) J Zhang, J Zeisler, et al. Epidemiology of Pregnancy-induced Hypertension. Epidemiologic Reviews 1997; 19(2):218-232.

(18) B Eskenazi, L Fenster, et al. A multivariate analysis of risk factors for preeclampsia. JAMA 1991; 266:237-241.

(19) L S Trupin, L P Simon, et al. Change in paternity: a risk factor for pre-eclampsia in multiparas. Epidemiology 1996; 7:240-244.

(20) J L Eras, A F Saftlas, t al. Abortion and its effect on risk of preeclampsia and transient hypertension. Epidemiology 2000; 11:36-43.

(21) R Mittendorf, K Y Lain, et al. Preeclampsia. A nested, case-control study of risk factors and their interactions. The Journal of Reproductive Medicine 1996; 41(7):491-496.

(22) K Duckitt, D Harrington. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005; 330:565-567.

(23) R T Lie, S Rasmussen, et al. Fetal and maternal contributions to risk of preeclampsia: population based study. BMJ 1998; 316:1343-1347.

(24) D Mostello, T K Catlin, et al. Preeclampsia in the parous woman: Who is at risk? American Journal of Obstetrics and Gynecology 2002; 187:425-429.

(25) R Skjaerven, L J Vatten, et al. Recurrence of preeclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. BMJ 2005; 331(7521):877-879.

(26) A Conde-Agudelo, A Rosas-Bermudez, et al. Effects of birth spacing on maternal health: a systematic review. American Journal of Obstetrics and Gynecology 2007; 196(4):297-308.

(27) R Skjaerven, A J Wilcox, et al. The interval between pregnancies and the risk of preeclampsia. The New England Journal of Medicine 2002; 346:33-38.

(28) G Dekker. The partner's role in the ethiology of preeclampsia. Journal of Reproductive Immunology 2002; 57:203-215.

(29) P Tubbergen, S M Althuisius, et al. Change in paternity: a risk factor for preeclampsia in multiparous women? Journal of Reproductive Immunology 1999; 45:81-88.

(30) B M Sibai, T Gordon. Risk factors for preeclampsia in healthy nulliparous women: a prospective multicenter study. American Journal of Obstetrics and Gynecology 1995; 172:642-648.

(31) L Trogstad, P Magnus, et al. Previous abortions and risk of pre-eclampsia. International Journal of Epidemiology 2008; 37:1333-1340.

(32) X Xiong, D William, e, et al. History of abortion, preterm, term birth, and risk of preeclampsia: A population-based study. American Journal of Obstetrics and Gynecology 2002; 187:1013-1018.

(33) J L Stone, C J Lockwood, et al. Risk factors for severe preeclampsia. Obstet Gynecol 1994; 83:357-361.

(34) B M Sibai, M Ewell, et al. Risk factors associated with preeclampsia in healthy nulliparous women: The Calcium for Preeclampsia Prevention (CPEP) Study Group. American Journal of Obstetrics and Gynecology 1997; 177:1003-1010.

(35) K E Innes, T E Byers. Association of a woman's own birth weight with her subsequent risk for pregnancy-induced hypertension. American Journal of Epidemiology 2009; 158(9):861-870.

(36) S Rasmussen, L M Irgens. Pregnancy-induced hypertension in women who were born small. Hypertension 2007; 49(4):806-812.

(37) L M Silva, M Coolman, et al. Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. Journal of Hypertension 2008; 26:1200-1208.

(38) C Qiu, S E Sanchez, et al. Associations of depression and depressive symptoms with preeclampsia: results from a Peruvian case-control study. BMC Women's Health 2007; 7:15.

(39) T Kurki, V Hiilesmaa, et al. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstetrics & Gynecology 2000; 95(4):487-490.

(40) H S Klonoff-Cohen, J L Cross, et al. Job stress and preeclampsia. Epidemiology 1996; 7:245-249.

(41) P A Landsbergis, M C Hatch. Psychosocial work stress and pregnancy-induced hypertension. Epidemiology 1996; 7:346-351.

(42) D W Branch, R Andres, et al. The association of antiphospholipid antibodies with severe preeclampsia. Obstetrics & Gynecology 1989; 73:541-545.

(43) A Conde-Agudelo, F Althabe, et al. Cigarette smoking during pregnancy and risk of preeclampsia: a systematic review. American Journal of Obstetrics and Gynecology 1999; 181(4):1026-1035.

(44) D V Coonrod, D E Hickok, et al. Risk factors for preeclampsia in twin pregnancies: A population-based cohort study. Obstetrics & Gynecology 1995; 85:645-650.

(45) J G Santema, I Koppelaar, et al. Hypertensive disorders in twin pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology 1995; 58:9-13.

(46) F Vesce, A Farina, et al. Increased incidence of preeclampsia in pregnancies complicated by fetal malformation. Gynecologic and Obstetric Investigation 1997; 44:107-111.

(47) P J Yong, S Langlois, et al. The association between preeclampsia and placental trisomy 16 mosaicism. Prenatal Diagnosis 2006; 26:956-961.

(48) A Rijhsinghani, J Yankowitz, et al. Risk of preeclampsia in second-trimester triploid pregnancies. Obstetrics & Gynecology 1997; 90:884-888.

(49) J F Tuohy, D K James. Preeclampsia and trisomy 13. British Journal of Obstetrics and Gynaecology 1992; 99:891-894.

(50) O Basso, C R Weinberg, et al. Subfecundity as a Correlate of Preeclampsia: A Study within the Danish National Birth Cohort. American Journal of Epidemiology 2003; 157:195-202.

(51) M Hernandez-Valencia, Q L Saldaca, et al. Barrier family planning methods as risk factor which predisposes to preeclampsia. Ginecología y Obstetricia de México 2000; 68:333-338.

(52) United Nations Development Programme. Millennium Development Goals: Nationalization and Progress. National Report 2005. Armenia. Available at: www.undp.am/docs/mdgs/un_armenia_mdgreport2005eng.pdf . 2009.

(53) United Nations (International) Children's Fund. UNICEF Calls to Improve Services to Prevent Maternal and Infant Deaths. Available at: http://www.unicef.org/armenia/media_10942.html . 2009.

(54) H K Armenian. Problem Investigation and Inferances Using the Case-Control Method. The Case-Control method: Design and Applications. New York: Oxford University Press, 2009: 17-33.

(55) Ministry of Health. Statistics. Available at: http://www.moh.am/Cnndognutyun/Vichak/point.doc . 2009.

(56) Center for Health Services Research and Development.Primary Health Care Reform Project. Household Health Survey: Baseline Evaluation. Available at:http://www.auachsr.com/publications_reports2006.php. 2009.

(57) Centers for Disease Control and Prevention. Pregnancy Risk Assessment Monitoring System (PRAMS). Phase Five Questionnaire. Available at: http://www.cdc.gov/PRAMS/References/Phase5TopicsReferenceindexworks.doc . 2009.

(58) I Khachiyan. An effect of socio-demographic variables on child spacing in Yerevan. American University of Armenia, College of Health Sciences. Available at: http://www.auachsr.com/mph2007.php . 2009.

(59) Norwegian Institute of Public Health. The Norwegian Mother and Child Cohort Study Questionnaire. Available at: http://www.fhi.no/dav/a044bd13cd.pdf . 2009.

(60) S Arakelyan. Investigation of reproductive risk factors for endometrial cancer development among women aged 45-75 years in Yerevan, Armenia. American University of Armenia, College of Health Sciences. Available at: http://www.auachsr.com/mph2007.php . 2009.

(61) Rob Scharpf. Course of Biostatistics.Course Notes. American University of Armenia, Master of Public Health Program 2008.

(62) N L Meyer, B M Mercer, et al. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. American Journal of Obstetrics and Gynecology 1994; 170:137-141.

(63) H K Armenian. Avoiding Bias in Case Control Selection. The Case-Control Method: Design and Applications. New York: Oxford University Press, 2009: 33-63.

(64) L Trogstad, A Eskild. Changing paternity and time since last pregnancy; the impact on preeclampsia risk. A study of 547 238 women with and without pre-eclampsia. International Journal of Epidemiology 2001; 30:1317-1322.

(65) CATALYST consortioum. New Findings on Birth Spacing: Three to Five Years is the Optimal Interval. Available at: http://cat.convio.net/site/PageServer?pagename=Programs_Birth_Spacing_Optimal_Interval . 2009.

TABLES

Table 1. Descriptive Statistics by Cases and Controls

Variable	Values: % (n)		p - value
	Cases 24.18% (n=89)	Controls 75.82% (n=279)	
Maternity home			
Institute of obstetrics (Perinatology), gynecology and reproductive health	37.08% (33)	35.48% (99)	0.785
Erebuni Medical Center	62.92% (56)	64.52% (180)	
Level of education (years)			
≤13 years	61.80% (55)	45.52% (127)	0.007
>13 years	38.20% (34)	54.48% (152)	
Age at the delivery (years)			
Mean	28.46	26.42	
Median	26.88	25.78	0.001
SD	6.05	4.42	
Min & Max	19.32-44.27	18.12-40.53	
BMI(kg/m^2)			
Mean	24.04	21.23	p<0.0005
Median	22.86	20.55	
SD	5.64	3.20	
Min & Max	15.88-59.18	14.82-34.89	
BMI kg/m^2			
Normal(≤24.9)	61.80% (55)	89.25% (249)	p<0.0005
Overweight(25.0-29.9)	25.84% (23)	7.17% (20)	
Obese(≥30.0)	12.36% (11)	3.58% (10)	
Renal disease			
No	87.64% (78)	97.49% (272)	Fisher's Exact
Yes	12.36% (11)	2.51% (7)	p=0.001
Chronic hypertension			
No	83.53% (71)	99.64% (278)	Fisher's Exact
Yes	15.73% (14)	0.36% (1)	p<0.0005
Women's weight at birth			
≤2000	3.37% (3)	2.15% (6)	
2000-2499	3.37% (3)	1.43% (4)	Fisher's Exact
2500-2999	19.10% (17)	12.90% (36)	p=0.385
3000-3499	35.96% (32)	37.63% (105)	
3500-3999	15.73% (14)	23.30% (65)	
≥4000	5.62% (5)	7.53% (21)	
Don't know	16.85% (15)	15.05% (42)	
Women's blood group			
I (O)	23.53% (20)	28.00% (77)	
II (OA)	53.47% (48)	54.55% (150)	Fisher's Exact
III (OB)	10.59% (9)	9.09% (25)	p=0.839
IV (AB)	8.61% (8)	8.36% (23)	

Variable	Values: % (n)		p - value
	Cases 24.18% (n=89)	Controls 75.82% (n=279)	
Women's Rh factor			
Positive	87.21% (75)	90.29% (251)	0.415
Negative	12.79% (11)	9.71% (27)	
Number of people living in the household			
Mean	4.24	4.77	0.016
Median	4.00	5.00	
SD	1.66	1.85	
Min & Max	2.00-9.00	1.00-13.00	
Number of employed family members			
Mean	1.87	2.16	0.025
Median	2.00	2.00	
SD	1.07	1.11	
Min & Max	0.00-5.00	0.00-6.00	
Perceived general standard of living			
Below average	7.87% (7)	4.66% (13)	Fisher's Exact
Average	48.31% (43)	49.82% (139)	p=0.486
Above average	43.82% (39)	45.52% (127)	
Household monthly expenditure (AMD)			
≤100.000	50.00% (40)	40.26% (93)	0.129
>100.000	50.00% (40)	59.74% (138)	
Total number of luxury items			
Mean			
Median	4.24	4.71	0.038
SD	4.00	5.00	
Min & Max	1.94	1.82	
	0.00-8.00	0.00-8.00	
Employment status of the women during pregnancy			
Yes	35.96% (32)	37.28% (104)	Fisher's Exact
No	58.45% (52)	55.20% (154)	p=0.809
Student	5.62% (5)	7.53% (21)	
The birth weight of the born baby (g)			
Mean	2557.73	3262.23	0.000
Median	2785.00	3200.00	
SD	899.68	417.29	
Min & Max	420.00-4650.00	1800.00-4800.00	

Variable	Values: % (n)		p - value
	Cases 24.18% (n=89)	Controls 75.82% (n=279)	
The birth height of the born baby (cm)			
Mean	47.48	50.64	<0.0005
Median	49.00	51.00	
SD	4.72	2.02	
Min & Max	31.00-57.00	41.00-58.00	
Gender of the born baby			
Boy	39.33% (35)	45.88% (128)	0.315
Girl	59.55% (53)	54.12% (151)	
Method of contraception			
Non barrier method	71.91% (64)	75.63% (211)	0.482
Barrier method	28.09% (25)	24.37% (68)	
Pregnancy planning			
Not planned	25.84% (23)	21.15% (59)	0.354
Planned or partly planned	74.16% (66)	78.85% (220)	
Infertility treatment			
No	87.64% (78)	94.98% (265)	0.017
Yes	12.36% (11)	5.02% (14)	
Time to pregnancy(TTP)			
Become pregnant right away	20.00% (13)	43.46% (93)	
1-2 month	27.69% (18)	22.43% (48)	Fisher's Exact
3-5 month	23.08% (15)	16.82% (36)	p=0.006
6-12 month	9.23% (6)	7.48% (16)	
>12 month	20.00% (13)	9.81% (21)	
The highest systolic BP during pregnancy(mm Hg)			
Mean	167.19		
Median	160.00		
SD	25.16		
Min & Max	140-260		
The highest diastolic BP during pregnancy(mm Hg)			
Mean	103.44		
Median	100.00		
SD	11.72		
Min & Max	90-140		
Time of preeclampsia onset (weeks)			
Mean	30.28		
Median	32.00		
SD	7.05		
Min & Max	11-39		
Smoking			
Never	89.89% (80)	93.55% (261)	Fisher's Exact
Ever	10.11% (9)	6.45% (18)	p=0.177

Variable	Values: % (n)		p - value
	Cases 24.18% (n=89)	Controls 75.82% (n=279)	
Smoking during pregnancy**			
Yes	22.22% (2)	-[1]	
Stopped during pregnancy	33.33% (9)	44.44% (8)	Fisher's Exact
No	44.44% (9)	55.56% (10)	p=0.165
Exposure to secondhand smoke			
Never	59.55% (53)	48.39% (135)	0.067
Ever	40.45% (36)	51.61% (144)	
Family history of preeclampsia			
No	82.56% (71)	93.02% (240)	0.004
Yes	17.44% (15)	6.98% (18)	
Parity			
Primipara	61.54% (54)	46.40% (129)	0.038
Multipara	38.46% (35)	53.60% (150)	
IBI (years)***			
Mean	7.27	4.21	
Median	6.17	3.51	p<0.0005
SD	4.50	2.78	
Min & Max	1.42-18.33	0.77-15.59	
IBI (years)***			
<5	34.29% (12)	73.29% (107)	p<0.0005
≥5	6.71% (23)	26.71% (39)	
Number of stillbirths***			
0	93.26% (83)	97.85% (273)	Fisher's Exact
1	6.74% (6)	2.15% (6)	p=0.044
Number of abortions			
0	69.66% (62)	72.76% (203)	
1	14.61% (13)	19.00% (53)	Fisher's Exact
2	8.99% (8)	6.81% (19)	p=0.051
≥3	6.74% (6)	1.43% (4)	
Number of spontaneous abortions			
0	84.27% (75)	87.46% (244)	Fisher's Exact
1	11.24% (10)	10.75% (30)	p=0.375
2	3.37% (3)	1.43% (4)	
≥3	1.12% (1)	0.36% (1)	
Number of induced abortions			
0	82.02% (73)	83.51% (233)	
1	7.87% (7)	11.83% (33)	Fisher's Exact
2	4.49% (4)	3.58% (10)	p=0.065
≥3	5.62% (5)	1.08% (3)	
Abortions between births***			
Never	61.11% (22)	64.86% (96)	
Ever	38.89% (14)	35.14% (52)	0.674

Variable	Values: % (n)		p - value
	Cases 24.18% (n=89)	Controls 75.82% (n=279)	
Spontaneous abortions between births***			
Never	91.67% (33)	89.86% (133)	0.744
Ever	8.33% (3)	10.14% (15)	
Induced abortions between births***			
Never	66.67% (24)	71.62% (106)	0.588
Ever	33.33% (12)	28.38% (42)	
History of previous preeclampsia***			
No	52.78% (19)	95.83% (138)	Fisher's Exact
Yes	47.22% (17)	4.17 % (6)	p<0.0005

*Among those who planned or partly planned the pregnancy

**Among ever smokers

***Among multiparous women

[1]For those variables, the data were insufficient to obtain interpretable results

Table 2.Odds Ratios (OR) of Preeclampsia Associated With Risk Factors

Variable	OR (95% CI)	p-value
Level of education (years)		
≤13 years	1.00	
>13 years	0.52 (0.32 - 0.84)	0.008
Age at the delivery (years)	1.08 (1.03-1.14)	0.001
BMI**(**kg/m2**)**	1.19 (1.11-1.28)	<0.0005
BMI**(**kg/m2**)**		
Normal(≤24.9)	1.00	
Overweight(25.0-29.9)	5.20 (2.67-10.14)	<0.0005
Obese(≥30.0)	4.98 (2.01-12.3)	0.001
Renal disease		
No	1.00	0.001
Yes	5.48 (2.06-14.60)	
Chronic hypertension		
No	1.00	<0.0005
Yes	54.00 (7.09-423,87)	
Women's weight at birth		
≤2000	2.32 (0.52-10.42)	0.272
2000-2499	3.48 (0.70-17.32)	0.127
2500-2999	2.19 (0.97-4.96)	0.059
3000-3499	1.41 (0.70-2.85)	0.331
3500-3999	1.00	
≥4000	1.47 (0.69-3.17)	0.321
Women's blood group		
I (O)	1.00	
II (OA)	1.23 (0.68-2.22)	0.488
III (OB)	1.39 (0.56-3.43)	0.481
IV (AB)	1.34 (0.52-3.44)	0.544
Women's Rh factor		
Positive	1.00	0.416
Negative	1.36 (0.65-2.88)	
Number of people living in the household	0.84 (0.72-0.97)	0.021
Number of employed family members	0.77 (0.61-0.97)	0.027
Household monthly expenditure (AMD)		
≤100,000	1.00	
>100,000	0.67 (0.40-1.12)	0.130

Variable	OR (95% CI)	p-value
Perceived general standard of living		
Below average	1.74 (0.65-4.64)	0.268
Average	1.00	
Above average	0.99 (0.60-1.63)	0.977
Total number of luxury items	0.87 (0.77-0.99)	0.039
Employment status of the women during pregnancy		
Yes	0.91 (0.55-1.51)	0.719
No	1.00	
Student	0.71 (0.25-1.96)	0.504
Gender of the born baby		
Boy	1.00	
Girl	1.28 (0.79-2.09)	0.315
Method of contraception		
Non barrier method	1.00	0.483
Barrier method	1.21 (0.71-2.07)	
Pregnancy planning		
Planned or partly planned	1.00	
Not planned	1.30 (0.75-2.26)	0.355
Time to pregnancy (TTP)		
Become pregnant right away	1.00	
1-2 month	2.68 (1.21-5.93)	0.015
3-5 month	2.98 (1.29-6.88)	0.010
6-12 month	2.68 (0.89-8.09)	0.080
>12 month	4.42 (1.80-10.92)	0.001
Folic acid intake		
No	1.00	
Yes	0.68 (0.41-1.14)	0.144
Infertility treatment		
No	1.00	
Yes	2.67 (1.17-6.12)	0.020
Exposure to secondhand smoke		
Never		
Ever	1.00	0.068
	0.64 (0.39-1.03)	
Smoking		
Never	1.00	
Ever	0.61 (0.27-1.42)	0.253
Family history of preeclampsia		
No		
Yes	1.00	0.006
	2.81 (1.35-5.87)	
Parity		
Primipara	1.00	
Multipara	0.60 (0.37-0.98)	0.039
IBI (years)	1.26 (1.13-1.40)	<0.0005

Variable		OR (95% CI)	p-value
IBI* (years)			
	<5	1.00	
	≥5	5.26 (2.39-11.57)	<0.0005
Number of stillbirths*			
	0	1.00	
	1	3.29 (1.03-10.47)	0.044
Number of abortions			
	0	1.00	
	1	0.80 (0.41-1.57)	0.521
	2	1.38 (0.57-3.30)	0.471
	≥3	3.25 (1.34-17.96)	0.016
Number of spontaneous abortions			
	0	1.00	
	1	1.08 (0.51-2.32)	0.835
	2	2.44 (0.53-11.15)	0.250
	≥3	3.25 (0.20-52.64)	0.406
Number of induced abortions			
	0	1.00	
	1	0.68 (0.29-1.60)	0.372
	2	1.27 (0.39-4.19)	0.687
	≥3	5.31 (1.24-22.80)	0.024
Abortions between births*			
	Never	1.00	
	Ever	1.17 (0.55-2.49)	0.674
Spontaneous abortions between births*			
	Never	1.00	
	Ever	0.81 (0.22-2.95)	0.745
Induced abortions between births*			
	Never	1.00	0.559
	Ever	1.26 (0.58-2.75)	
History of previous preeclampsia*			
	No	1.00	
	Yes	20.57 (7.22-58.63)	<0.0005

*Among multiparous women

Table 3. Association Between TTP and Preeclampsia Status

Variable	Primiparous		Multiparous	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Time to pregnancy (TTP)				
Become pregnant right away	1.00		1.00	
1-2 months	2.27 (0.88-5.81)	0.089	5.32 (0.99-28.63)	0.052
3-5 months	2.77 (1.08-7.10)	0.033	3.00 (0.38-23.49)	0.295
6-12 months	2.18 (0.57-8.37)	0.255	5.57 (0.67-46.35)	0.112
>12 months	2.23 (0.65-7.71)	0.205	15.6 (2.86-85.23)	0.002
Time to pregnancy (TTP)				
Become pregnant right away	1.00			
1-2 months	2.27 (0.88-5.81)	0.089		
>3 months	2.51 (1.10-5.74)	0.029		
Time to pregnancy (TTP)*				
Become pregnant right away	1.00			
1-2 months	2.12 (0.78-5.76)	0.140		
>3months	2.29 (0.96-5.48)	0.063		
Time to pregnancy (TTP)				
Become pregnant right away			1.00	
1-12 months			4.64 (0.96-22.53)	0.057
>12 months			15.60 (2.86-85.23)	0.002
Time to pregnancy (TTP)*				
Become pregnant right away			1.00	
1-12 months			4.20 (0.80-21.87)	0.089
>12 months			11.44 (1.84-71.28)	0.009
Time to pregnancy (TTP)				
<12 months			1.00	
>12 months			5.40 (1.78-16.38)	0.003
Time to pregnancy (TTP)*				
<12 months			1.00	
>12 months			4.11 (1.17-14.45)	0.027

*Adjusted for age, BMI and smoking

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Table 4. Simple Logistic Regression: Testing for Confounding

Factor	Association between IBI and covariates OR, (95% CI), p-value	Association between preeclampsia status and covariates OR, (95% CI), p-value
Level of education (years)		
≤13 years	1.00	1.00
>13 years	1.09 (0.59-2.01) p=0.752	0.71 (0.34 - 1.49) p=0.371
BMI(kg/m2)		
Normal(≤24.9)	1.00	1.00
Overweight(25.0-29.9)	5.46 (2.25-13.22) p<0.0005	8.97 (3.56-22.65) p<0.0005
Obese(≥30.0)	2.12 (0.74-6.11) p=0.163	5.83 (1.93-17.60) p=0.002
BMI(kg/m2)	1.16 (1.07-1.27) p=0.000	1.26 (1.14-1.40) p<0.0005
Renal disease		
No	1.00	1.00
Yes	6.27 (1.23-32.04) p=0.027	5.81 (1.47-22.87) p=0.012
Number of people living in the household	0.87 (0.72-1.05) p=0.154	0.74 (0.57-0.96) p=0.024
Number of employed family members	0.67 (0.49-0.93) p=0.017	0.69 (0.47-1.03) p=0.068
Perceived general standard of living		
Below average	0.57 (1.14-2.30) p=0.433	0.35 (0.04-2.87) p=0.327
Average	1.00	1.00
Above average	0.63 (0.33-1.19) p=0.155	0.75 (0.35-1.59) p=0.452
Household monthly expenditure (AMD)		
≤100.000	1.00	1.00
>100.000	1.09 (0.56-2.11) p=0.800	0.84 (0.39-1.80) p=0.652
Total number of items	1.09 (0.92-1.29) p=0.297	0.91 (0.75-1.10) p=0.329
Method of contraception		
Non barrier method	1.00	1.00
Barrier method	1.19(0.64-2.24) p=0.581	1.70(0.81-3.56) p=0.157
Pregnancy planning		
Planned or partly planned	1.00	1.00
Not planned	0.35 (0.18-0.70) p=0.003	1.48 (0.71-3.09) p=0.301
Infertility treatment		
No	1.00	1.00
Yes	3.39 (0.78-14.69) p=0.103	2.60 (0.59-11.43) p=0.206
Exposure to secondhand smoke		
Never	1.00	1.00
Ever	1.01 (0.55-1.87) p=0.971	0.85 (0.41-1.76) p=0.662
Family history of preeclampsia		
No	1.00	1.00
Yes	1.44 (0.48-4.38) p=0.517	4.85 (1.57-14.97) p=0.006
Abortion between births		
Never	1.00	1.00
Ever	4.10 (2.14-7.89) p<0.0005	1.17 (0.55-2.49) p=0.674
Induced abortion between births		

Factor		Association between IBI and covariates OR, (95% CI), p-value	Association between preeclampsia status and covariates OR, (95% CI), p-value
	Never	1.00	1.00
	Ever	3.71 (1.90-7.25) p<0.0005	1.26 (0.58-2.75) p=0.559
Spontaneous abortion between births			
	Never	1.00	1.00
	Ever	3.45 (1.26-9.42) p=0.016	0.81 (0.22-2.95) p=0.745

Table 5. Simple Logistic Regression: Testing for Confounding

Factor	Association between parity and covariates OR, (95% CI), p-value	Association between preeclampsia status and covariates OR, (95% CI), p-value
Level of education (years)		
≤13 years	1.00	1.00
>13 years	0.84 (0.56-1.26) p=0.404	0.52 (0.32-0.84) p=0.008
BMI**(**kg/m2**)**		
Normal (≤24.9)	1.00	1.00
Overweight or Obese (≥25.0)	2.58 (1.45-4.58)p=0.001	5.13 (2.89-9.08) p<0.0005
Renal disease		
No	1.00	1.00
Yes	1.00 (0.39-2.58) p=1.000	5.48 (2.06-14.60) p=0.001
Number of people living in the household	1.19 (1.06-1.36) p=0.005	0.84 (0.72-0.97) p=0.021
Number of employed family members	0.75 (0.62-0.91) p=0.004	0.77 (0.61-0.97) p=0.027
Perceived general standard of living		
Below average	1.14 (0.45-2.89) p=0.776	1.74 (0.65-4.64) p=0.268
Average	1.00	1.00
Above average	0.85 (0.56-1.30) p=0.450	0.99 (0.60-1.63) p=0.997
Household monthly expenditure (AMD)		
≤100.000	1.00	1.00
>100.000	1.19 (0.76-1.86) p=0.452	0.67 (0.40-1.12) p=0.130
Total number of luxury items	0.94 (0.84-1.05) p=0.291	0.87 (0.77-0.99) p=0.039
Method of contraception		
Non barrier method	1.00	1.00
Barrier method	3.73 (2.22-6.25) p<0.0005	1.21 (0.71-2.07) p=0.483
Pregnancy planning		
Planned or partly planned	1.00	1.00
Not planned	7.12 (3.82-13.26) p<0.0005	1.30 (0.75-2.26) p=0.355
Infertility treatment		
No	1.00	1.00
Yes	0.45 (0.19-1.06) p=0.068	2.67 (1.17-6.12) p=0.020
Exposure to secondhand smoke		
Never	1.00	1.00
Ever	1.42 (0.94-2.14) p=0.096	0.64 (0.39-1.03) p=0.068
Family history of preeclampsia		
No	1.00	1.00
Yes	0.71 (0.35-1.47) p=0.362	2.81 (1.35-5.87) p=0.006
Time to pregnancy (TTP)		
Become pregnant right away	1.00	1.00
1-2 month	1.17 (0.63-2.18) p=0.626	2.68 (1.21-5.93) p=0.015
3-5 month	0.66 (0.32-1.35) p=0.258	2.98 (1.29-6.88) p=0.010
6-12 month	1.10 (0.43-2.80) p=0.845	2.68 (0.89-8.09) p=0.080
>12 month	1.78 (0.82-3.89) p=0.145	4.42 (1.80-10.92) p=0.001

Table 6. Interaction Between IBI and the History of Previous Preeclampsia (1)

History of previous preeclampsia	IBI	Unadjusted OR (95% CI) p-value	Interaction term (Ratio of Odds Ratios) (95% CI) p-value	Adjusted OR* (95% CI) p-value	Interaction term*(Ratio of Odds Ratios) (95% CI) p-value
Yes	Short(<5year)	1.00		1.00	
	Long(≥5year)	1.13 (0.17-7.24) p=0.901	0.11 (0.01-1.01) p=0.051	0.60 (0.07-4.99) p=0.638	0.09 (0.01-0.96) p=0.046
No	Short(<5year)	1.00		1.00	
	Long(≥5year)	10.1 (3.12-32.73) p=0.000		6.88 (1.75-27.05) p=0.006	

*Adjusted for age, BMI renal disease

Table 7. Interaction Between IBI and History of Previous Preeclampsia (2)

History of previous preeclampsia	IBI	Unadjusted OR (95% CI) p-value	Adjusted OR* (95% CI) p-value
Yes	Short(<5year)	67.33(12.79-354.50) p<0.0005	59.41(10.14-348.13) p<0.0005
	Long(≥5year)	75.75 (14.62-392.40) p<0.0005	35.73(5.41-235.99) p<0.0005
No	Short(<5year)**	1.00	1.00
	Long(≥5year)	10.1 (3.12-32.73) p<0.0005	6.88 (1.75-27.05) p=0.006

*Adjusted for age, BMI renal disease
** Reference group

Table 8. Multiple Logistic Regression Models for IBI, Confounders and Interaction

Model	IBI	Age	BMI	Renal disease	History of previous preeclampsia	History of previous preeclampsia*IBI
IBI	5.25 (2.39-11.57)					
IBI+Age+BMI +Renal disease	2.90 (1.07-7.86)	1.03 (0.93-1.14)	1.23 (1.11-1.37)	0.97 (0.16-5.96)		
IBI+Age+BMI +Renal disease+History of previous preeclampsia	3.80 (1.19-12.09)	1.02 (0.91-1.14)	1.22 (1.08-1.38)	0.87 (0.09-8.19)	19.11 (5.55-65.83)	
IBI+ History of previous preeclampsia	5.89 (2.27-15.32)				23.79 (7.43-76.11)	
IBI+ History of previous preeclampsia+ History of previous preeclampsia*IBI	10.1 (3.12-32.73)				67.33 (12.79-354.50)	0.11 (0.01-1.01)
IBI(cont.)+ History of previous preeclampsia+ History of previous preeclampsia*IBI(cont.)	1.34 (1.17-1.59)				99.12 (13.26-740.77)	0.77 (0.58-1.01)
IBI+Age+BMI +Renal disease+History of previous preeclampsia+ History of previous preeclampsia*IBI	6.88 (1.75-27.05)	1.02 (0.91-1.14)	1.23 (1.08-1.39)	0.94 (0.11-7.66)	59.41 (10.14-384.13)	0.087 (0.01-0.96)
IBI (cont.)+Age+BMI +Renal disease+History of previous preeclampsia+ History of previous preeclampsia*IBI(cont.)	1.32 (1.09-1.59)	0.97 (0.85-1.11)	1.22 (1.08-1.38)	0.87 (0.09-8.06)	77.04 (9.29-638.95)	0.77 (0.58-1.03)

Table 9. Results of AIC for Alternative Multiple Logistic Models for Multiparous Women

Model	Covariates	AIC= -2(log likelihood)+2(model df)
Model 1	IBI+TTP12	2*42.69+2*2=89.38
Model 2	IBI+TTP12+barrier methods of contraception	2*41.51+2*3=89.02
Model 3	IBI+TTP12+BMI	2*38.28+2*4=84.56
Model 4	IBI+TTP12+BMI+ barrier methods of contraception	2*36.56+2*5=83.18
Model 5	IBI+TTP12+BMI(cont)+ barrier methods of contraception	2*36.27+2*4=80.54
Model 6 (Final)	IBI+TTP12+BMI(cont)+ barrier methods of contraception+ household monthly expenditure	2*31.68+2*5=73.36
Model 7	IBI+TTP12+BMI(cont)+ barrier methods of contraception+ household monthly expenditure +age	2*31.47+2*6=74.94

Table 10. Predictive Model for Multiparous Women Who Have Planned Their Pregnancies

Variable	Unadjusted OR (95%CI) p-value	Adjusted OR (95%CI) p-value
IBI		
Short (<5 years)	1.00	1.00
Long (≥5 years)	5.26 (2.39-11.57) p<0.0005	4.49 (1.12-17.99) p=0.034
BMI(kg/m2)	1.19 (1.11-1.28) p<0.0005	1.20 (1.04-1.38) p=0.014
TTP12		
<12 months	1.00	1.00
>12 months	5.40 (1.78-16.38) p=0.003	5.99 (1.39-25.83) p=0.016
Method of contraception		
Non barrier method	1.00	1.00
Barrier method	1.70 (0.81-3.56) p=0.157	3.63 (0.90-14.67) p=0.070
Household monthly expenditure (AMD)		
≤100,000	1.00	1.00
>100,000	0.84 (0.39-1.80) p=0.652	0.28 (0.08-1.04) p=0.058

Table 11. Results of AIC for Alternative Multiple Logistic Regression Models for All Women

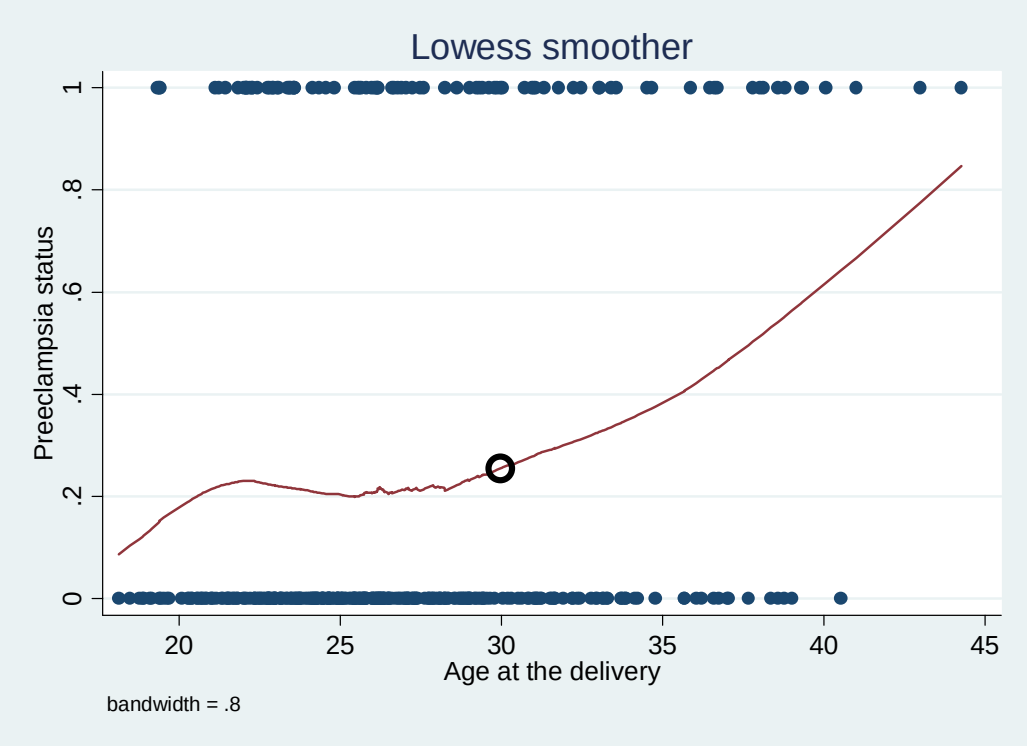
Model	Covariates	AIC= -2(log likelihood)+2(model df)
Model 1	Parity+education+ renal disease+ barrier methods of contraception+BMI	2*175.86+2*5=361.72
Model 2	Parity+education+ renal disease+ barrier methods of contraception+ BMI +infertility treatment	2*173.27+2*6=358.54
Model 3	Parity+education+ renal disease+ barrier methods of contraception+ BMI +infertility treatment+pregnancy planning	2*171.44+2*7=356.88
Model 4 (Final)	Parity+education+ renal disease+ barrier methods of contraception+ BMI +infertility treatment+pregnancy planning+agespline_30	2*164.06+2*8=344.12
Model 5	Parity+education+ renal disease+ barrier methods of contraception+ BMI +infertility treatment+pregnancy planning+age+agespline_30	2*163.51+2*9=345.02

Table 12. Predictive Model for All Women

Variable		Unadjusted OR (95%CI) p-value	Adjusted OR (95%CI) p-value
Parity			
	Primipara	1.00	1.00
	Multipara	0.60 (0.37-0.98) p=0.039	0.21 (0.10-0.43) p<0.0005
Level of education (years)			
	≤13 years	1.00	1.00
	>13 years	0.52 (0.32 - 0.84) p=0.008	0.42 (0.23-0.75) p=0.003
Renal disease			
	No	1.00	1.00
	Yes	5.48 (2.06-14.60) p=0.001	2.78 (0.92-8.35) p=0.069
BMI**(**kg/m2**)**			
	Normal (≤24.9)	1.00	1.00
	Overweight (25.0-29.9)	5.20 (2.67-10.14) p<0.0005	5.29 (2.51-11.17) p<0.0005
	Obese (≥30.0)	4.98 (2.01-12.3) p=0.001	6.02 (2.04-18.79) p=0.001
Method of contraception			
	Non barrier method	1.00	1.00
	Barrier method	1.21 (0.71-2.07) p=0.483	1.59 (0.83-3.08) p=0.161
Infertility treatment			
	No	1.00	1.00
	Yes	2.67 (1.17-6.12) p=0.020	3.60 (1.38-9.42) p=0.009
Pregnancy planning			
	Planned or partly planned	1.00	1.00
	Not planned	1.30 (0.75-2.26) p=0.355	2.03 (0.99-4.15) p=0.054
Age at the delivery (agespline_30, years)		1.20 (1.09-1.31) p<0.0005	1.25 (1.12-1.41) p<0.0005

FIGURES

Figure 1. Linear Spine to Explore Possibility of Non-linear Relationship Between Age and Preeclampsia Status



APPENDICES

Appendix 1

Diagnosis of Hypertensive Disorders Complicating Pregnancy

Gestational Hypertension

BP≥140/90 mm Hg for first time during pregnancy

No proteinuria

BP return to normal <12 weeks' postpartum

Final diagnosis made only postpartum

Preeclampsia

BP≥140/90 mm Hg after 20 weeks' gestation

Proteinuria ≥ 300mg/24 hours or ≥30mg/dL (1+ dipstick) in random urine sample

Eclampsia

Seizures that cannot be attributed to other causes in a woman with preeclampsia

Superimposed Preeclampsia (on chronic hypertension)

New-onset proteinuria ≥ 300mg/24 hours in hypertensive women but no proteinuria before 20 weeks' gestation

A sudden increase in proteinuria or blood pressure or platelet count <100,000 /mm^3 in women with hypertension and proteinuria before 20 weeks' gestation

Chronic hypertension

BP≥140/90 mm Hg before pregnancy or diagnosed before 20 weeks' gestation or

Hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' gestation

Source: National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy, 2000

Proteinuria is described as 300 mg or more of urinary protein per 24 hours or persistent 30 mg/dL (1+dipstick) in random urine samples

Appendix 2

Oral Consent Form for Cases (English)
American University of Armenia
Institutional Review Board # 1/Committee on Human Research
College Of Health Sciences Subcommittee for Student Theses

Title of Research Project: Investigation of risk factors for preeclampsia development among reproductive (18-45) age women living in Yerevan.

Hello, my name is Arusyak Harutyunyan. I am a gynecologist and a second year student of Master of Public Health Program at the American University of Armenia. I am conducting a study to investigate the risk factors for preeclampsia development among reproductive age women living in Yerevan.

You have been selected to participate in this study as you had elevated blood pressure (preeclampsia) diagnosed with preeclampsia by the physician in the maternity home. Your contact information has been obtained from your medical record. Permission to collect your contact information has been received from the head of maternity home.

If you are willing to participate I will ask you some questions concerning you socio-demographic status, health status, and reproductive history. The interview will take place once at any time that is convenient for you and last no more than 15 minutes.

Your participation in the study is voluntary. You may ask any questions during the interview, or skip any question you think is inappropriate and stop it at any moment you want with no further negative consequences. I really appreciate your participation in the current study.

Your participation in the study poses no risk for you. The information provided by you is of great value for investigation of risk factors for preeclampsia development, which will be very helpful for science and/or for other women with similar disease. There will be no monetary benefits for you if you participate in this project.

The information you provided is fully confidential and will be used only for the study. Contact information will be destroyed upon completion of the research.

If you want to talk to anyone about this research study you can contact Varduhi Petrosyan vpetrosi@aua.am or call Arusyak Harutyunyan (094)630077

If you want to talk to anyone about the research study because you feel you have not been treated fairly or think you have been hurt by joining the study you should contact Yelena Amirkhanyan at (010) 51 25 68.

Thank you very much for your participation.

Oral Consent Form for Controls (English)

American University of Armenia

Institutional Review Board # 1/Committee on Human Research
College Of Health Sciences Subcommittee for Student Theses

Title of Research Project: Investigation of risk factors for preeclampsia development among reproductive (18-45) age women living in Yerevan.

Helle, my name is Arusyak Harutyunyan. I am a gynecologist and a second year student of Master of Public Health Program at the American University of Armenia. I am conducting a study to investigate the risk factors for preeclampsia development among reproductive age women living in Yerevan.

You have been selected to participate in this study as you gave birth in one of the maternity homes of Yerevan and were not diagnosed with preeclampsia during pregnancy (elevated blood pressure during pregnancy). Your contact information has been obtained from your medical record. Permission to collect your contact information has been received from the head of maternity home.

If you are willing to participate I will ask you some questions concerning you socio-demographic status, health status, and reproductive history. The interview will take place once at any time that is convenient for you and last no more than 15 minutes.

Your participation in the study is voluntary. You may ask any questions during the interview, or skip any question you think is inappropriate and stop it at any moment you want with no further negative consequences. I really appreciate your participation in the current study.

Your participation in the study poses no risk for you. There will be no monetary benefits for you if you participate in this project. The information provided by you is of great value for investigation of risk factors for preeclampsia development, which will be very helpful for science and/or for other women with similar disease.

The information you provided is fully confidential and will be used only for the study. Contact information will be destroyed upon completion of the research.

If you want to talk to anyone about this research study you can contact Varduhi Petrosyan vpetrosi@aua.am or call Arusyak Harutyunyan (094)630077

If you want to talk to anyone about the research study because you feel you have not been treated fairly or think you have been hurt by joining the study you should contact Yelena Amirkhanyan at (010) 51 25 68.

Thank you very much for your participation.

Հայաստանի ամերիկյան համալսարան

Գիտահետազոտական էթիկայի հանձնաժողով
Հանրային առողջապահության ֆակուլտետ
Բանավոր համաձայնագիր (դեպքերի համար)

Հետազոտության անվանումը. պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնների ուսումնասիրությունը Երևան քաղաքի վերարտադրողական տարիքի կանանց շրջանում:

Բարև Ձեզ, իմ անունը Արուսյակ Հարությունյան է: Ես մանկաբարձ-գինեկոլոգ եմ և Հայաստանի ամերիկյան համալսարանի «Հանրային առողջապահության» ֆակուլտետի երկրորդ կուրսի ուսանողուհի: Ես անցկացնում եմ հետազոտություն, որի նպատակն է բացահայտել պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնները Երևան քաղաքի վերարտադրողական տարիքի կանանց շրջանում:
Դուք ընտրվել եք մասնակցելու այս հետազոտությանը, քանի որ հղիության ընթացքում Ձեզ մոտ ախտորոշվել է զարկերակային ճնշման բարձրացում (պրեէկլամպսիա) Երևան քաղաքի ծննդատան բժշկի կողմից: Ձեր տվյալները վերցվել են ծննդատնից՝ տնօրենի համաձայնությամբ:
Եթե Դուք համաձայն եք մասնակցել այս հետազոտությանը, ապա ես Ձեզ կտամ հարցեր սոցիալ-ժողովրդագրական հատկանիշների, առողջական վիճակի և վերարտադրողական անցյալի վերաբերյալ: Հարցազրույցը տեղի կունենա մեկ անգամ, Ձեզ համար առավել հարմար ժամանակ, և կտևի ոչ ավելի, քան 15 րոպե:
Ձեր մասնակցությունը այս հետազոտությանը կամավոր է: Դուք կարող եք տալ հարցեր հարցազրույցի ընթացքում ցանկացած պահի, ինչպես նաև իրավունք ունեք չպատասխանել այն հարցերին, որոնք կարող են Ձեզ տհաճություն պատճառել կամ դադարեցնել հարցազրույցը, երբ ցանկանաք՝ առանց որևէ հետագա բացասական հետևանքների: Ես գնահատում եմ Ձեր պատրաստակամությունը մասնակցելու այս հետազոտությանը:
Ձեր մասնակցությունը այս հետազոտությանը որևէ ռիսկ չի ներկայացնում Ձեզ համար: Այս հետազոտությանը Ձեր մասնակցության դեպքում որևէ դրամական խրախուսանք նախատեսված չէ: Ձեր կողմից տրամադրված տվյալները կլինեն շատ օգտակար բացահայտելու պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնները, կլինեն շատ կարևոր գիտական տեսանկյունից, ինչպես նաև այն կանանց համար, ովքեր ունեն նման խնդիր:
Ձեր կողմից տրամադրված ողջ տեղեկությունները կպահվեն գաղտնի և կօգտագործվեն միայն հետազոտության նպատակներով: Ձեր հաղորդակցության տվյալները կոչնչացվեն հետազոտության ավարտից անմիջապես հետո:
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ այս հետազոտության մասին, կարող եք դիմել Վ. Պետրոսյանին հետևյալ էլէկտրոնային հասցեով՝ vpetrosi@aua.am:
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ այս հետազոտության մասին, քանի որ գտնում եք, որ ձեզ հետ անարդարացի են վարվել կամ մտածում եք, որ մասնակցությունը վնասել է Ձեզ, ապա զանգահարեք Ելենա Ամիրխանյանին (37410) 51 25 68 հեռախոսահամարով:
Շնորհակալություն մասնակցության համար:

Հայաստանի ամերիկյան համալսարան
Գիտահետազոտական էթիկայի հանձնաժողով
Հանրային առողջապահության ֆակուլտետ
Բանավոր համաձայնագիր (ստուգիչ խմբի համար)

Հետազոտության անվանումը. պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնների ուսումնասիրությունը Երևան քաղաքի վերարտադրողական տարիքի կանանց շրջանում:

Բարև Ձեզ, իմ անունը Արուսյակ Հարությունյան է: Ես մանկաբարձ-գինեկոլոգ եմ և Հայաստանի ամերիկյան համալսարանի «Հանրային առողջապահության» ֆակուլտետի երկրորդ կուրսի ուսանողուհի: Ես անցկացնում եմ հետազոտություն, որի նպատակն է բացահայտել պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնները Երևան քաղաքի վերարտադրողական տարիքի կանանց շրջանում:
Դուք ընտրվել եք մասնակցելու այս հետազոտությանը քանի որ հղիության ընթացքում Ձեզ մոտ չի դիտվել զարկերակային ճնշման բարձրացում: Ձեր տվյալները վերցվել են ծննդատնից՝ տնօրենի համաձայնությամբ:
Եթե Դուք համաձայն եք մասնակցել այս հետազոտությանը, ապա ես Ձեզ կտամ հարցեր սոցիալ-ժողովրդագրական հատկանիշների, առողջական վիճակի և վերարտադրողական անցյալի վերաբերյալ: Հարցազրույցը տեղի կունենա մեկ անգամ, Ձեզ համար առավել հարմար ժամանակ, և կտևի ոչ ավելի, քան 15 րոպե:
Ձեր մասնակցությունը այս հետազոտությանը կամավոր է: Դուք կարող եք տալ հարցեր հարցազրույցի ընթացքում ցանկացած պահի, ինչպես նաև իրավունք ունեք չպատասխանել այն հարցերին, որոնք կարող են Ձեզ տհաճություն պատճառել կամ դադարեցնել հարցազրույցը, երբ ցանկանաք՝ առանց որևէ հետագա բացասական հետևանքների: Ես գնահատում եմ Ձ եր պատրաստակամությունը մասնակցելու այս հետազոտությանը:
Ձեր մասնակցությունը այս հետազոտությանը որևէ ռիսկ չի ներկայացնում Ձեզ համար: Այս հետազոտությանը Ձեր մասնակցության դեպքում որևէ դրամական խրախուսանք նախատեսված չէ:Ձեր կողմից տրամադրված տվյալները կլինեն շատ օգտակար բացահայտելու պրեէկլամպսիայի զարգացմանը նպաստող ռիսկի գործոնները, կլինեն շատ կարևոր գիտական տեսանկյունից, ինչպես նաև այն կանանց համար, ովքեր ունեն նման խնդիր:
Ձեր կողմից տրամադրված ողջ տեղեկությունները կպահվեն գաղտնի և կօգտագործվեն միայն հետազոտության նպատակներով: Ձեր հաղորդակցության տվյալները կոչնչացվեն հետազոտության ավարտից անմիջապես հետո:
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ այս հետազոտության մասին, կարող եք դիմել Վ. Պետրոսյանին հետևյալ էլէկտրոնային հասցեով՝ vpetrosi@aua.am:
Եթե Դուք ցանկանում եք խոսել որևէ մեկի հետ այս հետազոտության մասին, քանի որ գտնում եք, որ ձեզ հետ անարդարացի են վարվել կամ մտածում եք, որ մասնակցությունը վնասել է Ձեզ, ապա զանգահարեք Ելենա Ամիրխանյանին (37410) 51 25 68 հեռախոսահամարով:
Շնորհակալություն մասնակցության համար:

Appendix 3

QUESTIONNAIRE

Date of the interview: _ _ _ _ /_ _ _ _ /_ _ _ _ **Status:** 1. Case
(Day) (Month) (Year) 0. Control

1. **Maternity Home**_____
2. **ID**_____
3. **3.Date of birth** _ _ _ _/_ _ _ _/_ _ _ _
(Day) (Month)(Year)

4. Indicate the highest level of education that you have completed.

1. School (less than 10 years)
2. School (10 years)
3. Professional technical education (10-13 years)
4. Institute/University
5. Postgraduate

5. Have you been told by a physician that you had or have each condition below? *(Check **all** that apply)*

Disease	Yes	No
a. Diabetes		
b. Gestational Diabetes		
c. Renal (kidney) disease		

6. What was your birth weight? _____g 88. Don't know

7. What is your blood group, _____ 88. Don't know
And RH _____ 88. Don't know

Now I am going to ask questions about the pregnancy that ended ……_ _ __/ _ __/_ _ _
(Day) (Month)(Year)

8. What was your marital status during that pregnancy?

1. single
2. married
3. widowed
4. divorced
5. Refused to respond

9. How much did you weight before that pregnancy? _____kg 88. Don't know

10. How tall are you? _____cm 88. Don't know

11. What was the total number of people (including yourself and children under 18) living in your household during that pregnancy?_____

12. How many members of your household (including yourself) were employed during that pregnancy? _____

13. **How would you rate your family's general standard of living during that pregnancy?**

1. Substantially below average
2. Little below average
3. Average
4. Little above average
5. Substantially above average

88. Not sure/difficult to answer

14. During that pregnancy, the approximate amount of household income spent by all of your household members per month was

1. Less than 25,000 drams
2. From 25,000 – 50,000 drams
3. From 51,000 – 100,000 drams
4. From 101,000 – 250,000 drams
5. Above 250,000drams

99. Don't know

15. Please tell me whether your household or any member of it had the following working items during that pregnancy

Item	Yes	No
a. Individual heating system (Baxi)		
b. DVD player		
c. Automobile		
d. Automatic washing machine		
e. Personal computer		
f. Satellite		
g. Cell phone		
h. Vacation home/villa		

17. Were you employed during that pregnancy?

1. Yes
2. No ***(Go to the Q.21)***

3.I was a student

18. What were your working hours?
1. <4 hours
2. 4-8 hours
3. >8 hours
4. Other a. *specify* _____

19. How had your work (studying) situation changed during pregnancy?
1. It did not change ***(Go to the Q.21)***
2. I had stopped working (studying)
3. I had reduced my working (studying) hours
4. Other _____a. *specify*

20. In which week of your pregnancy had your work (studying) situation changed?
_____weeks of pregnancy

21. How many babies were born during that birth? _____

22. **What was that baby's gender, weight, height at birth?**
a.___ kg 88. Don't know b. ___ cm 88. Don't know c. gender 1.boy 2. girl 88. Don't know

a.___ kg 88. Don't know b. ___ cm 88. Don't know c. gender 1.boy 2. girl 88. Don't know

23. Have you/your partner at any time during one year before that pregnancy used the following methods to avoid becoming pregnant?
1. Condom
2. Diaphragm
3. IUD
4. Hormone injection
5. Oral contraceptives
6. Spermicides (foam, suppositories, cream)
7. Safe period
8. Withdrawal
9. Abstinence
10. Lactation Amenorrhea Method (breast feeding)
11. No such methods
12. Other (specify)_____

23. Was this pregnancy planned?
1. Planned
2. Partly planned
3. Not planned (***(Go to the Q.25)***
4. Don't know
5. Do not wish to answer

24. How long did you try to become pregnant before you succeeded?
1. became pregnant right away
2.1–2 months
3.3–5 months
4.6–12 months
5. More than 12 months
88. Don't know
99. Do not wish to answer

25. Did you take folic acid (vitamin B6) before/during that pregnancy?
1. Yes ___weeks before to _____ weeks of that pregnancy
2. Yes from____ weeks to ____weeks of that pregnancy
3. No
88. Don't know

26. Did you receive treatment from a doctor, nurse, or other health care worker to help you get pregnant with your new baby? (This may include infertility treatments such as fertility-enhancing drugs or assisted reproductive technology.)
1. Yes
2. No ***(Go to the Q.28)***

27. Did you use any of the following treatments *during the month you got pregnant* with your new baby? Check <u>all</u> that apply

1. Fertility-enhancing drugs prescribed by a doctor
2. Artificial insemination or intrauterine insemination
3. Other medical treatment a. specify_____

28. Had the midwife or doctor told you that you have or have had high blood pressure during that pregnancy?
1. Yes a. specify the highest reading during that pregnancy_____/_____99.Don't know
b. specify the time of onset ____weeks or ____month 99.Don't know
2. No
99. Don't know

29. Have you had high blood pressure without being pregnant?
1. Yes a. specify the highest reading before this pregnancy _____/_____99.Don'tknow
2. No
99. Don't know

30. Have you ever smoked cigarettes? 1. Yes
2. No (***Go to Q.33)***

31. Did you smoke during that pregnancy? (*Go to Q.33*)
1. Sometimes _____ cigarettes per week ***(Go to Q.33)***
2. Daily_____ cigarettes per day ***(Go to Q.33)***
3. I stopped smoking at ___ weeks of that pregnancy ***(Go to Q.33)***
4. No

32. **When did you stop smoking?**
1. _____months before that pregnancy
2. I did not smoke before that pregnancy

33. How many cigarette smokers, not including yourself, were living in your home during that pregnancy? ____

34. During that pregnancy, about how many hours a day, on average, were you in the same room with another person who was smoking? _____hours

35. Had anybody from your relatives (mother, sister, aunt etc.) have preeclampsia (high blood pressure) during pregnancy?
1. Yes a. specify_____
2. No
88. Don't know

36. Have you been pregnant before that pregnancy? (Include all pregnancies that ended in life births, spontaneous or induced abortions, ectopic pregnancy and stillbirth as well)
1. Yes
2. No (finish)

37. Indicate all earlier pregnancies started from the first one, including all pregnancies that ended in life births, spontaneous or induced abortions, ectopic pregnancies and stillbirths as well. State the date/year the pregnancy ended and the gestational weeks of their termination. State whether or not you had preeclampsia (high BP) during that pregnancy.

N	Date/year of outcome	Life birth	Spontaneous abor-tion (<22 weeks)	Induced abortion (<22 weeks)	Ectopic pregnancy	Stillbirths (>22 weeks)	Gestational weeks at termi-nation	Preeclampsia (High BP during pregnancy)
1								
2								
3								
4								
5								
6								
7								

38. Were all your mentioned pregnancies from the same man?

1. Yes (Finish)
2. No
3. Refuse to respond

39. Have you had other pregnancy from the father of the baby born in _ __/ _ __/_ _ ___ .
(Day) (Month)(Year)

1. Yes
2. No
3. Refuse to respond

Հարցաթերթիկ

Հարցազրույցի ամսաթիվը _ _ _ _ /_ _ _ _ /_ _ _ _ **Կարգավիճակը:** 1. դեպք
(օր) (ամիս) (տարի) 0. ստուգիչ

1.Ծննդատունը_____
2. ID_____ **3.Ծննդյան ամսաթիվ** _ _ _ _/_ _ _ _/_ _ _ _
(օր) (ամիս)(տարի)

4. Նշեք ամենաբարձր կրթությունը, որ Դուք ստացել եք:

1. Թերի միջնակարգ (դպրոց, 10 տարուց պակաս)
2. Միջնակարգ (դպրոց, 10 տարի)
3. Միջին մասնագիտական (ուսումնարան, 10-13 տարի)
4. Բարձրագույն (ինստիտուտ կամ համալսարան)
5. Հետդիպլոմային (մագիստրատուրա, ասպիրանտուրա, դոկտորանտուրա)

6. **Ձեզ երբևէ բժիշկը ասե՞լ է, որ ունեք ներքոնշյալ վիճակներից որևէ մեկը՝**

(Նշեք բոլոր համապատասխանող տարբերակները)

Հիվանդություն	Այո	Ոչ
a. Դիաբետ/շաքարախտ		
b. Հղիության դիաբետ		
c. Երիկամի հիվանդություն		

6. Որքա՞ն է եղել Ձեր քաշը ծնվելիս _____գ 88. Չգիտեմ

7. **Ո՞րն է Ձեր արյան խումբը** _____88. Չգիտեմ և

Rh պատկանելիությունը _____ 88. Չգիտեմ

Այժմ ես Ձեզ կտամ հարցեր այն հղիության վերաբերյան, որն ավարտվել է _ _ _ /_ _ _ /_ _ _
(օր) (ամիս)(տարի)

8. Ձեր ամուսնական կարգավիճակը այդ հղիության ընթացքում:

1. Ամուսնացած
2. Միայնակ
3. Ամուսնալուծված
4. Այրի

88. Հրաժարվում եմ պատասխանել_____

9. Որքա՞ն էր Ձեր քաշը մինչ այդ հղիությունից _____**կգ** 88. Չգիտեմ

10. Որքա՞ն է Ձեր հասակը _____**սմ** 88. Չգիտեմ

11. Քանի՞ հոգի էր ապրում Ձեր ընտանիքում (ներառյալ Դուք և 18 տարեկանից ցածր երեխաները) այդ հղիության ընթացքում : _____

12. Ձեր ընտանիքի բոլոր անդամներից (ներառյալ Դուք) քանի՞սն էին աշխատում այդ հղիության ընթացքում: _____

13. Ընդհանուր առմամբ, ինչպե՞ս կբնութագրեիք Ձեր ընտանիքի կենսամակարդակը այդ հղիության ընթացքում: ***(Կարդացեք պատասխանները)***

1.Միջինից բավականին ցածր
2.Միջինից մի փոքր ցածր
3.Միջին
4. Միջինից մի փոքր բարձր
5.Միջինից բավականին բարձր
6. Համոզված չեմ/դժվարանում եմ պատասխանել

14. Միջինում ամսեկան որքա՞ն գումար է ծախսել Ձեր ընտանիքն այդ հղիության ընթացքում: ***(Կարդացեք պատասխանները)***

1. 25 000 դրամից քիչ
2. 25 000 – 50 000 դրամ
3. 51 000 – 100 000 դրամ
4. 101 000 – 250 000 դրամ
5. 250 000 դրամից շատ

88. Չգիտեմ

15. Ձեր ընտանիքն ունե՞ր հետևյալ հարմարությունները սարքին վիճակում այդ հղիության ընթացքում:

	Այո	Ոչ
a. Անհատական ջեռուցման համակարգ (Baxi)		
b. DVD նվագարկիչ		
c. Ավտոմեքենա		
d. Ավտոմատ լվացքի մեքենա		
e. Համակարգիչ		
f. Արբանյակային ալեհավաք		
g. Բջջային հեռախոս		
h. Ամառանոց		

16. Դուք աշխատու՞մ էիք այդ հղիության ընթացքում

1. Այո
2. Ոչ (Անցեք Հարց 21)
3. Ես ուսանող էի

17.Միջինում օրեկան քանի ժամ էիք աշխատում (սովորում):

1.<4 ժամ
2.4-8 ժամ
3. >8 ժամ
6. Այլ (նշել) _____

18. Ինչպե՞ս փոխվեց Ձեր աշխատանային (ուսումնական) իրավիճակը այդ հղիության ժամանակ:

1. Այն չփոխվեց (***(Անցեք հարց 20***)
2. Ես դադարեցրի աշխատանքս (ուսումս)
3. Ես քչացրի աշխատանքային (ուսման) ժամերս
4. Այլ (նշել) _____

19.Այդ հղիության ո՞ր ժամկետում փոխվեց Ձեր աշխատանային (ուսումնական) իրավիճակը:
_____շաբաթ

20. Այդ հղիության արդյունքում քանի՞ երեխա ծնվեց _____

21. Նշեք այդ երեխայի (ների) սեռը, քաշը և հասակը ծնվելիս:

a._____ գ 88. Չգիտեմ b. _____ սմ 88. Չգիտեմ c.սեռը 1. տղա 2. աղջիկ 88. Չգիտեմ
a._____ գ 88. Չգիտեմ b. _____ սմ 88. Չգիտեմ c.սեռը 1. տղա 2. աղջիկ 88. Չգիտեմ

22. Դուք կամ Ձեր երեխայի հայրը այդ հղիությունը նախորդող մեկ տարվա ընթացքում ի՞նչ մեթոդ եք օգտագործել հղիությունից խուսափելու համար: (Նշեք բոլոր համապատասխանող տարբերակները)
1.Պահպանակ
2. Դիաֆրագմա
3. Ներարգանդային պարույր (սպիրալ)
4. Հորմոնային ներարկումներ
5. Հակաբեղմնավորիչ հաբեր
6. Սպերմիցիդներ (կրեմ, մոմիկ, դոնդող)
7. Ֆիզիոլոգիական գրաֆիկի մեթոդ
8. Ընդհատված սեռական հարաբերություն
9. Սեռական հարաբերությունից խուսափում
10. Կրծքով կերակրման մեթոդ
11. Ոչ մի մեթոդ
12. Այլ (նշել) _____

23. Այդ հղիությունը պլանավորվա՞ծ էր:
1. Այո
2. Որոշ չափով էր պլանավորված
3. Ոչ **(անցեք հարց 25)**
88. Չգիտեմ
99. Հրաժավուրմ եմ պատասսխանել

24. Սկսած այն պահից, երբ դուք ցանկանում էիք հղիանալ, որքան ժամանակ հետո հղիացաք :
1. Անմիջապես հղիացել եմ
2. 1-2 ամիս
3. 3–5 ամիս
4. 6-12 ամիս
5. Ավելի քան 12 ամիս
88. Չգիտեմ
99. Հրաժարվում եմ պատասխանել

25. Դուք օգտագործել ե՞ք ֆոլաթթու (վիտամին B9) այդ հղիությունից առաջ կամ այդ հղիության ընթացքում:
1. Այո _____ շաբաթ մինչ այդ հղիություն մինչև այդ հղիության_____ շաբաթ
2. Այո այդ հղիութան _____ շաբաթից մինչև _____ շաբաթ
3. Ոչ
4. Չգիտեմ

26. Դուք ստացել եք բժշկից, մանկաբարձուհուց կամ այլ բուժաշխատողից որևէ բուժում, որը կօգներ Ձեզ հղիանալ: (Անպտղության բուժում օրինակ դեղերայք, արհեստական բեղմնավորում)

1. Այո
2. Ոչ *(Անցեք հարց 28)*

27. Այդ հղիությամբ հղիանալու ամսվա ընթացքում դուք ստացել եք նշված բուժումներից որևէ մեկը (Նշեք բոլոր համապատասխանող տարբերակները):

1. Բժշկի կողմից նշանակված բեղմնավորումը խթանող դեղորայք
2. Արհեստական սերմնավորում
3. Այլ բուժում (նշել) _____

28. Բժիշկը կամ մանկաբարձուհին ասել են, որ դուք ունեք արյան բարձր ճնշում այդ հղիության ընթացքում:

1. Այո a. նշեք ամենաբարձր արժեքը այդ հղիության ընթացքում _____/___99.Չգիտեմ

b. Նշեք արյան բարձր ճնշման ախտորոշման ժամկետը __շաբաթ կամ __ամիս 99.Չգիտեմ
2. Ոչ
99. Չգիտե

29. Մինչև այդ հղիությունը երբևե դուք ունեցել եք արյան բարձր ճնշում:

1. Այո a. նշեք ամենաբարձր արժեքը մինչ այդ հղիությունը _____/___99.Չգիտեմ
2. Ոչ
99. Չգիտեմ

30. Դուք երբևէ ծխել ե՞ք:

1. Այո
2. Ոչ *(Անցեք հարց 34)*

31. Դուք ծխու՞մ էիք այդ հղիության ընթացքում:

1.Երբեմն_____ գլանակ շաբաթական *(Անցեք հարց. 34)*
2.Ամեն օր _____ գլանակ օրական *(Անցեք հարց .34)*
3.Դադարեցրել եմ այդ հղիության _____ շաբաթում *(Անցեք հարց .34)*
4.Ոչ

32. Ե՞րբ եք դադարեցրել ծխելը:

1. Այդ հղիությունից _____ ամիս առաջ
2. Մինչ այդ հղիությունը ես չէի ծխում

33. Այդ հղիության ընթացքում ,չհաշված Ձեզ, քանի՞ ծխող էր ապրում Ձեր տանը: _____

34. Այդ հղիության ընթացքում, օրեկան միջինում քանի ժամ էիք գտնվում միևնույն սենյակում, որտեղ տվյալ պահին կար ծխող անձնավորություն: _____ժամ

35. Ձեր հարազատերից որևէ մեկը ունեցել է պրեէկլամպսիա (արյան բարձր ճնշում) հղիության ընթացքում:

1. Այո a.նշեք_____
2. Ոչ

88. Չգիտեմ

36. Մինչ այդ հղիությունը երբևէ հղի եղել ե՞ք: (Ներառյալ բոլոր հղիությունները, որոնք ավարտվել են ինքնաբեր վիժմամբ, աբորտով, արտարգանդային հղիությամբ, կենդանածնությանբ, մեռելածնությամբ)
1. Այո
2. Ոչ **(Ավարտել)**

37. Նշեք բոլեր հղիությունները սկսած առաջինից ներառելով բոլոր հղիությունները, որոնք ավարտվել են ինքնաբեր վիժմամբ, աբորտով, արտարգանդային հղիությամբ, կենդանածնությանբ, մեռելածնությամբ: Նշեք յուրաքանչյուր հղիության ելքի տարեթիվը, ժամկետը և արդյոք ունեցել եք պրեէկլամպսիա (արյան բարձր ճնշում):

N	Ելքի ամսաթիվը/ տարեթիվը	Կենդանի պտղով ծննդ.(քաշը)	Ինքնաբեր վիժում (<22 շաբ.)	Արհեստական վիժում (<22 շաբ.)	Արտարգանդային հղիություն	Մահացած պտղեվ ծննդ. (>22 շաբ.)	Ելքի ժամկետը շաբաթներով	Պրեէկլամսիա
1								
2								
3								
4								
5								
6								
7								

38. Ձեր նշած բոլոր հղիությունները միևնույն տղամարդու՞ց են եղել:
1. Այո **(Ավարտել)**
2. Ոչ
3.Հրաժարվում եմ պատասխանել

39. Խնդրում եմ նշեք ունեցե՞լ եք արդյոք այլ հղիություն _ _ _ _/_ _ _ _/_ _ _ _ ծնված երեխայի հորից:
(օր) (ամիս)(տարի)

1.Այո
2. Ոչ
3.Հրաժարվում եմ պատասխանել

Appendix 4

Description of study variables

Variable name	Level of measurement	Measure
Presence of preeclampsia	Binary	1 case 0 control
Maternity home	Binary	1 Institute of Obstetrics (Perinatology). Gynecology and Reproductive health 2 Erebuni Medical Center
Age at the delivery (years)	Continuous	Numbers
Highest level of education	Ordinal	1 School (less than 10 years) 2 School (10 years) 3 Professional technical education (10-13 years) 4 Institute/University 5 Postgraduate
Highest level of education (years)	Binary	1 ≥13 years 0 <13 years
Diabetes	Binary	1 yes 0 no
Gestational diabetes	Binary	1 yes 0 no
Renal disease	Binary	1 yes 0 no
Chronic hypertension	Binary	1 yes 0 no
Women's weight at birth (g)	Ordinal	2 ≤2000 3 2000-2499 4 2500-2999 5 3000-3499 1 3500-3999 6 ≥4000
Women's blood group	Ordinal	1 I (O) 2 II (OA) 3 III (OB) 4 IV (AB)
Women's Rh factor	Binary	1 negative 0 positive
Marital status	Nominal	1 single 2 married 3 widowed 4 divorced
Body mass index (BMI) kg/m^2	Ordinal	1 Normal(≤24.9)

Variable name	Level of measurement	Measure
		2 Overweight(25.0-29.9) 3 Obese(≥30.0)
Body mass index (BMI) kg/m^2	Binary	1 Normal(≤24.9) 2 Overweight or Obese(≥25.0)
Body mass index (BMI) kg/m^2	Continuous	Numbers
Number of people living in the household (including the woman and the children under 18)	Continuous	Numbers
Number of employed family members (including the woman)	Continuous	Numbers
Perceived general standard of living	Ordinal	1 Substantially below average 2 Little below average 3 Average 4 Little above average 5 Substantially above average
Perceived general standard of living	Ordinal	2 Below average 1 Average 3 Above average
Household monthly expenditure (AMD)	Ordinal	1 <25.000 2 25.000 – 50.000 3 51.000 – 100.000 4 101.000 – 250.000 5 >250.000
Household monthly expenditure (AMD)	Binary	0 ≤100.000 1 >100.000
Total number of luxury items	Continuous	
Employment status of the women during pregnancy	Nominal	1 No 2 Yes 3 Student
Multiple pregnancy	Binary	1 No 0 Yes
Gender of the born baby	Binary	1 Girl 0 Boy
Method of contraception	Binary	1 Barrier method 0 Non barrier method
Pregnancy planning	Binary	0 Planned or partly planned 1 Not planned
Time to pregnancy (TTP)	Ordinal	1 Become pregnant right away 2 1-2 month 3 3-5 month 4 6-12 month

Variable name	Level of measurement	Measure
		5 >12 month
Time to pregnancy (TTP 12)	Binary	1 >12 months 0 <12 months
Infertility treatment	Binary	1 yes 0 no
Folic acid intake	Binary	1 yes 0 no
Smoking	Binary	1 Ever 0 Never
Smoking during pregnancy****	Nominal	0 No 1 Yes 2 Yes, but stopped during pregnancy
Exposure to secondhand smoke	Binary	1 Ever 0 Never
Family history of preeclampsia	Binary	1yes 0 no
Parity	Binary	0 Primipara 1 Multipara
Delivery time (weeks)	Continuous	Numbers
History of previous preeclampsia	Binary	1 yes 0 no
Number of stillbirths	Binary	0 1
IBI (years)	Continuous	Numbers
IBI (years)	Binary	1 Long (≥5 years) 0 Short (<5 years)
Total number of abortions	Ordinal	0 1 2 >=3
Total number of spontaneous abortions	Ordinal	0 1 2 >=3
Total number of induced abortions	Ordinal	0 1 2 >=3
Total number of abortions between births	Binary	1 Ever 0 Never
Total number of spontaneous	Binary	1 Ever

Variable name	Level of measurement	Measure
abortions between births		0 Never
Total number of induced abortions between births*	Binary	1 Ever 0 Never

Appendix 5

STATA Output Analysis

1. Power calculation based on the proportions of long IBI

```
Estimated power for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1
                  and p2 is the proportion in population 2
Assumptions:

         alpha =   0.0500  (two-sided)
            p1 =   0.2700
            p2 =   0.6600
sample size n1 =      146
            n2 =       35
         n2/n1 =     0.24

Estimated power:

         power =   0.9873
```

2. Power calculation based on the proportions of primiparity

```
. sampsi 0.46 0.62, n1(279) n2(89)

Estimated power for two-sample comparison of proportions

Test Ho: p1 = p2, where p1 is the proportion in population 1
                  and p2 is the proportion in population 2
Assumptions:

         alpha =   0.0500  (two-sided)
            p1 =   0.4600
            p2 =   0.6200
sample size n1 =      279
            n2 =       89
         n2/n1 =     0.32

Estimated power:

         power =   0.7122
```

3. Spline for age with cut-point of 30 years

```
. gen agespline_30=0

. replace agespline_30=age-30 if age>=30 & age!=.
(83 real changes made)

. logistic status age agespline_30

Logistic regression                               Number of obs   =        368
                                                  LR chi2(2)      =      15.20
                                                  Prob > chi2     =     0.0005
Log likelihood = -195.97948                       Pseudo R2       =     0.0373

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.002243   .0446048     0.05   0.960      .918524    1.093594
agespline_30 |   1.193787   .1049988     2.01   0.044     1.004755    1.418384
------------------------------------------------------------------------------

. lincom age+agespline_30

 ( 1)  age + agespline_30 = 0

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.196466   .0664717     3.23   0.001     1.073026    1.334105
------------------------------------------------------------------------------
```

4. Spline for IBI with cut-point of 5 years

```
. gen interbirspline_5=0
. replace interbirspline_5=interbir-60 if interbir>=60 & interbir!=.
(63 real changes made)

. logistic status interbir interbirspline_5

Logistic regression                               Number of obs   =        181
                                                  LR chi2(2)      =      20.10
                                                  Prob > chi2     =     0.0000
Log likelihood = -78.835998                       Pseudo R2       =     0.1130

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    interbir |   1.020616   .0163394     1.27   0.202     .9890884    1.053148
interbirs~_5 |   .9985876     .02025    -0.07   0.944     .9596767    1.039076
------------------------------------------------------------------------------

. lincom interbir+interbirspline_5

 ( 1)  interbir + interbirspline_5 = 0

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   1.019174   .0068348     2.83   0.005     1.005866    1.032659
```

5. Model with parity and the confounders

```
. logistic status nullipar age bmi2 newfam empmemb

Logistic regression                               Number of obs   =        368
                                                  LR chi2(5)      =      57.87
                                                  Prob > chi2     =     0.0000
Log likelihood = -174.64157                       Pseudo R2       =     0.1421
------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    nullipar |   .2695975   .0888956    -3.98   0.000     .1412684    .5145013
         age |   1.094929   .0327553     3.03   0.002     1.032575    1.161047
        bmi2 |   5.647947    1.86103     5.25   0.000      2.96084    10.77374
      newfam |   .9506509   .0829493    -0.58   0.562     .8012154    1.127958
     empmemb |   .8073861   .1115887    -1.55   0.122     .6157959    1.058585
------------------------------------------------------------------------------
```

6. Model with IBI with cut-point of 5 years and the confounders

```
. logistic status interbir5 age bmi renal

Logistic regression                               Number of obs   =        176
                                                  LR chi2(4)      =      33.13
                                                  Prob > chi2     =     0.0000
Log likelihood = -68.368373                       Pseudo R2       =     0.1950

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   interbir5 |   2.901716    1.47531     2.10   0.036     1.071226    7.860106
         age |   1.031666   .0533386     0.60   0.547     .9322469    1.141688
         bmi |   1.233304   .0671079     3.85   0.000     1.108546    1.372103
       renal |    .977625   .9014901    -0.02   0.980     .1604206     5.95778
```

7. Interaction between IBI with cut-point of 5 years (60 months) and the history of previous preeclampsia

```
. gen interbir5_preeclam=interbir5*preeclam
(191 missing values generated)

. logistic status interbir5 preeclam  interbir5_preeclam

Logistic regression                               Number of obs   =        177
                                                  LR chi2(3)      =      57.02
                                                  Prob > chi2     =     0.0000
Log likelihood = -59.502197                       Pseudo R2       =     0.3239
------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   interbir5 |       10.1   6.059167     3.85   0.000     3.116526    32.73196
    preeclam |   67.33333   57.06413     4.97   0.000     12.78933    354.4969
i~5_preeclam |   .1113861   .1251635    -1.95   0.051     .0123125    1.007668
------------------------------------------------------------------------------
. lincom interbir5+interbir5_preeclam

 ( 1)  interbir5 + interbir5_preeclam = 0
------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |      1.125   1.068914     0.12   0.901     .1747377    7.242999
```

8. Interaction between IBI with cut-point of 5 years (60 months) and the history of previous preeclampsia adjusted for age, BMI, renal disease

```
. logistic status interbir5 age bmi renal preeclam interbir5_preeclam

Logistic regression                                     Number of obs   =        172
                                                        LR chi2(6)      =      64.24
                                                        Prob > chi2     =     0.0000
Log likelihood = -51.971605                             Pseudo R2       =     0.3820

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   interbir5 |   6.883856   4.806112     2.76   0.006     1.752052    27.04683
         age |   1.017323   .0600289     0.29   0.771     .9062168     1.14205
         bmi |   1.228996   .0789595     3.21   0.001     1.083586     1.39392
       renal |   .9386561   1.005574    -0.06   0.953     .1149799    7.662864
    preeclam |   59.41127   53.59542     4.53   0.000     10.13894    348.1329
i~5_preeclam |    .087368   .1068903    -1.99   0.046     .0079424    .9610681
------------------------------------------------------------------------------

. lincom interbir5+interbir5_preeclam

 ( 1)  interbir5 + interbir5_preeclam = 0

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   .6014288    .649821    -0.47   0.638     .0723591    4.998908
------------------------------------------------------------------------------
```

9. Model for multiparous women who planned their pregnancies with the IBI as the main variable.

```
. logistic status interbir5 ttp12 bmi barmeth newincome

Logistic regression                                     Number of obs   =         95
                                                        LR chi2(5)      =      28.88
                                                        Prob > chi2     =     0.0000
Log likelihood = -31.676589                             Pseudo R2       =     0.3131

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   interbir5 |   4.489681   3.179196     2.12   0.034     1.120649    17.98711
       ttp12 |   5.992662   4.467602     2.40   0.016     1.390077    25.83454
         bmi |   1.198652   .0882344     2.46   0.014     1.037612    1.384686
     barmeth |   3.634211   2.587921     1.81   0.070      .900056    14.67407
   newincome |    .283576   .1882427    -1.90   0.058     .0772017    1.041626
------------------------------------------------------------------------------

. lfit,group(10)

Logistic model for status, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)

       number of observations =        95
             number of groups =        10
     Hosmer-Lemeshow chi2(8) =         5.00
                 Prob > chi2 =         0.7577
```

```
. vif

    Variable |       VIF       1/VIF
-------------+----------------------
         bmi |      1.13    0.887197
   interbir5 |      1.13    0.887279
       ttp12 |      1.12    0.888959
     barmeth |      1.08    0.921897
   newincome |      1.00    0.995991
-------------+----------------------
    Mean VIF |      1.09
```

10. **Model for all women regardless of parity.**

```
. logistic status nullipar edu13 renal barmeth bmi2 trtcat plannedcat agespline_30

Logistic regression                                     Number of obs   =        368
                                                        LR chi2(8)      =      79.03
                                                        Prob > chi2     =     0.0000
Log likelihood = -164.06191                             Pseudo R2       =     0.1941

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    nullipar |   .2159365   .0771673    -4.29   0.000     .1071865     .435023
       edu13 |   .4183221   .1244298    -2.93   0.003     .2335184    .7493772
       renal |    2.77847   1.559953     1.82   0.069      .924495    8.350395
     barmeth |   1.593296   .5324543     1.39   0.163      .827634    3.067288
        bmi2 |   5.485985   1.877513     4.97   0.000     2.805053    10.72922
      trtcat |   3.612371   1.768767     2.62   0.009     1.383594    9.431396
  plannedcat |    2.02056   .7388902     1.92   0.054     .9867325    4.137558
agespline_30 |   1.252286   .0738941     3.81   0.000     1.115518    1.405823
------------------------------------------------------------------------------.
. lfit,group(10)

Logistic model for status, goodness-of-fit test

  (Table collapsed on quantiles of estimated probabilities)
  (There are only 9 distinct quantiles because of ties)

       number of observations =       368
             number of groups =         9
     Hosmer-Lemeshow chi2(7) =         5.95
                 Prob > chi2 =         0.5460


. vif

    Variable |       VIF       1/VIF
-------------+----------------------
    nullipar |      1.29    0.775831
  plannedcat |      1.16    0.859171
agespline_30 |      1.15    0.868921
        bmi2 |      1.11    0.903758
     barmeth |      1.10    0.909477
       renal |      1.08    0.924313
       edu13 |      1.07    0.933937
      trtcat |      1.03    0.970165
-------------+----------------------
    Mean VIF |      1.12
```