DIABETES MELLITUS AMONG ARSENICOSIS AFFECTED MOTHER AND THEIR REPRODUCTIVE OUTCOME

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Diabetes Mellitus among Arsenicosis affected Mother and their Reproductive Outcome

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Dedicated
To
Loving memory of my Parents

Declaration

I do hereby declare that this thesis entitled **"Diabetes Mellitus among Arsenicosis affected Mother and their Reproductive Outcome"** is based on the research work carried out by me. No part of it had been presented previously for any higher degree. The research was carried out under the Faculty of Post Graduate Medical Science and Research, University of Dhaka, Dhaka, Bangladesh with the supervision of Dr. Shah Md. Keramat Ali, Professor of Clinical Nutrition, Institute of Nutrition and Food Science (INFS), University of Dhaka, Dhaka, Bangladesh and Dr. A. Wadud Khan, Ex Professor and Head, Department of Community Medicine, National Institute of Preventive and Social Medicine (NIPSOM), Dhaka, Bangladesh.

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Certificate

"Diabetes mellitus among arsenicosis affected mother and their reproductive outcome" submitted by Dr. Md. Nazrul Islam for the award of Doctor of Philosophy (Ph.D) in Maternal and Child Health is an independent research work done under the Faculty of Post Graduate Medical Science and Research, University of Dhaka, Bangladesh and this thesis has not been used as the basis for the award of any degree or fellowship.

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25/10/2007

Dr. Md. Nazrul Islam

Abstract

Title:

Diabetes Mellitus among Arsenicosis affected Mother and their Reproductive Outcome.

Background:

The World Health Organization (WHO) calls the arsenic poisoning in Bangladesh the largest mass poisoning of a population in history at a scale beyond that of the accidents at Bhopal and Chernobyl. The number of arsenicosis mother is increasing rapidly and morbidity and mortality also increasing day by day. Arsenic crosses the placental barrier and there is extensive documentation of adverse reproductive outcome in both animal and man. As suggested in few earlier studies, there is possible association between arsenicosis and diabetes mellitus. On the basis of epidemiological studies, arsenic exposure has been associated with a number of adverse health outcomes, and relatively less attention has been directed toward the potential impact of arsenic on human reproductive system. Conclusion on the causality of the relationship between arsenicosis, diabetes mellitus and reproductive outcomes are suggestive and less clear. Several studies have examined a number of reproductive end points in relation to arsenic exposure, and the result suggests elevations of adverse reproductive outcome. However, there is no consistent evidence for any one particular end point of reproductive outcome. There is an urgent need to conduct research addressing arsenic poisoning in Bangladesh since the situation can be described as a public health threat due to devastating effects of arsenic on human health and reproductive lives.

Objective:

The aim of this study is to investigate diabetes mellitus (type-2) among arsenicosis affected mothers of child bearing ages (15-49 years) and their reproductive outcome in two rural areas which has a well documented history of arsenic exposed and non-exposed from naturally contaminated ground water.

Methods and Materials:

The cross sectional, comparative study was carried out in (Laksham and Muradnagar Upazillas of Comilla District), arsenic hyper-endemic areas where arsenic level more than 0.05mg/l and Dhunat Upazilla of Bogra District and Trisal Upazilla of Mymensingh District where arsenic concentration less than 0.02mg/l. The study population was mother of reproductive age (15-49 years) who previously had at least one outcome of pregnancy and who had lived in the study places and used the same tube-well water for more than 2 years. Eligible mother divided into two groups-arsenic exposed and arsenic nonexposed. The exposed group was further categorized into arsenicosis (had clinical manifestations) and nonarsenicosis (had no clinical manifestation) sub groups. So we took 400 mother of arsenicosis and 400 mother of non-arsenicosis from exposed group and 400 mother from nonexosed group. Thus, the total sample size 1200 mother were investigated.

Pre-tested structured interview questionnaire were used to collect relevant information regarding demographic, socio-economic, glycaemic status, reproductive events and drinking water sources. Every mother underwent a thorough physical examination by two trained physician and clinical data were collected including the presence of melanosis, keratosis, rain drop pigmentation. Consensus diagnosis were made through decision between study physician and compared with diagnosis confirmed by WHO, UNICEF, Community Hospital, DPHE, British Geological Survey (BGS) and used by other previous study. Water sample collected directly from tube-wells and measured by UNICEF provided arsenic test kit. All mothers were also examined for hyperglycemia after overnight fasting and 2 hours after 75gm glucose by glucose peroxidase enzymatic method (BM-Test Glucose, Boehringer Mannheim GmbH, Mannheim, Germany). Standing height and body weight were measured and individual body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Data analysis was done by SPSS, Excel and Epi-Info soft ware package. The presence of differences in the mean and median values was assessed using a one way analysis of variance (ANOVA) for continuous variables, general association (Chi-square) statistic for categorical variables. Bivariate analysis were performed to determine when reproductive outcomes and selected covariates varied across arsenic exposure categories. Prevalence

ratio with 95% confidence interval was calculated to evaluate the associations between independent variables and reproductive outcome (dependent variables). Pearson's correlation and Z-test and Logistic Regression models were used for assessing whether any associations existed between arsenic exposure and selected outcome of interest reproductive outcome and diabetes mellitus. Significance level (p-value), odd ratio (OR) and relative risk (RR) was calculated to know the strength of association between predictors and outcome variable and to make inferences (chance we reject the null hypothesis/accept the research hypothesis.

Results and Findings:

The mean age of mother with arsenicosis was 33.58 (SD±7.63), nonarsenicosis was 30.08 (SD±6.82) in the exposed group while 29.45 (SD±6.17) in the mother in nonexposed group. The educational status of the mother in the exposed group, 59.3 percent mother with arsenicosis, 59.7 percent mother with nonarsenicosis while 54.0 percent mother in nonexposed group were literate. It was also found that 94.5 percent mother with arsenicosis, 89.8 percent mother with nonarsenicosis in exposed group and 98.0 percent mother in nonexposed group were housewives. The mean income was Tk.3592.75 (SD±1935), 3566.75 (SD±1887) and 3636.06 (SD±4555) in different groups respectively. In the exposed group, 50.3 percent mother with arsenicosis, 41.0 percent mother with nonarsenicosis while 62.3 percent mother in nonexposed group had no exposure to any media.

The mean duration of drinking water were 12.98 (SD±5.91) years, 9.93 (SD±2.85) years and 9.92 (SD±2.85) years respectively in different groups. It has been observed that, 87.0 percent mother with arsenicosis, 69.7 percent mother with nonarsenicosis and 66.5 percent mother in nonexposed group had a long duration (more than 2 years) of drinking arsenic contaminated water. We also found that 23.3 percent mother had raindrop pigmentation, 21.58 percent had melanosis and 20 percent had keratosis in arsenicosis mother. Normal blood glucose level 2 hours after 75gm glucose was 81.3 percent in arsenicosis, 85.4 percent in nonarsenicosis in exposed group and 86.3 percent in nonexposed group. The diabetes mellitus were 7.0 percent, 4.3 percent and 4 percent

were in arsenicosis, nonarsenicosis and nonexposed group respectively. IFG and DM were 18.7 percent mother with arsenicosis, 14.6 percent mother with nonarsenicosis in exposed group while 13.7 percent in nonexposed group. Blood glucose level 2 hours after 75gm glucose was significantly associated with arsenicosis and nonexposed group. Odds ratio (OR) and relative risk (RR) showed that IFG and DM was positively associated with arsenic exposure ($p<0.05$; OR=1.45; RR=1.19). Mean body mass index (BMI) was 20.18 (Sd±2.85), in arsenicosis, 20.40 (Sd±2.47) in nonarsenicosis in exposed group while 19.52 (SD±2.94) in nonexposed group.

The pregnancy outcome not alive was significantly higher in the mean age 31.7 (SD±7.17) of the respondent ($p<0.05$) than the mean age 29.6 (SD±6.55). The mean age of marriage was 16.7 (SD±1.86), 17.2 (SD±1.61) and 16.0 (SD±2.30 years in different groups respectively, was significantly associated with exposed and nonexposd group ($p<0.005$), and arsenicosis and non-arsenicosis group ($p<0.005$). Birth order more than two 73.3 percent of arsenicosis were significantly higher than that of 62.8 percent of nonarsenicosis and 58.0 percent of nonexposed group respectively ($p<0.001$). Odds Ratio (OR=1.66) means that birth order >2 was positively associated with arsenicosis and Relative Risk (RR=1.30) means that 1.30 times higher risk in arsenicosis than nonarsenicosis. It was also found that birth order was significantly associated with arsenicosis and nonexposed group ($p<0.000$). In all three groups, mean birth order whose pregnancy outcome was not alive was significantly higher than whose pregnancy outcome was alive respectively ($p<0.05$). The age, income, age of marriage, education and occupation were significantly correlated with arsenic level of water ($p<0.05$).

The reproductive outcome of the mother was significantly associated with arsenic exposure, 70.8 percent with arsenicosis and 77.8 percent with nonarsenicosis in the exposed group, while 90.3 percent mother in nonexposed group delivered alive child ($p<0.05$). The adverse reproductive outcome, Neonatal death 4.0 percent, 3.5 percent and 2.1 percent; Stillbirth 4.3 percent 3.8 percent and 2.3 percent; Premature 6.5 percent, 4.8 percent and 1.8 percent; Handicapped 1.3 percent 0.8 percent 0.3 percent; Miscarriage 7.8 percent. 5.3 percent and 2.0 percent; Abortion 5.5 percent, 4.3 percent and 1.5 percent in different groups respectively.

The adverse reproductive outcome were significantly higher in exposed than nonexposed group group ($Z=16.05$; $p<0.001$; $\lambda^2=41.04$; $p<0.001$; OR=3.21; RR=1.35) and in arsenicosis and nonarsenicosis group ($Z=2.27$; $p<0.05$; $\lambda^2=4.77$; $p<0.05$; OR=1.44; RR=1.19). The adverse reproductive outcome were also significantly higher in arsenic osis group than nonexposed group ($Z=2.71$; $p<0.005$; $\lambda^2=47.2$; $p<0.001$; OR=3.83; RR=1.71) and in nonarsenicosis than nonexposed group ($Z=4.90$; $p<0.001$; $\lambda^2=22.33$; $p<0.001$; OR=2.65; RR=1.50). It was also found that strength of positive association and degree of risk of exposure higher in exposed group than nonexposed group. The adverse reproductive outcome increases when number of pregnancy increases. Degree of relationship of exposed group was higher than that of nonexposed group ($p<0.001$). From the results of Odds ratio (OR) and relative risk (RR), it was found that adverse reproductive outcome were positively associated with arsenicosis and nonarsenicosis and arsenic exposed and nonexposed group.

Study Implications:

This study will help to identify the association of arsenicosis, diabetes mellitus and women' reproductive outcome. However, limited research has been directed at the association of arsenic exposure, diabetes and women's reproductive outcome. Results of this study may be helpful to assess the prevalence of diabetes mellitus and adverse reproductive outcomes due to arsenic toxicity which is not yet established. The findings suggest a causal relationship between development of arsenical skin lesions (arsenicosis) and diabetes mellitus. The results may also help to develop the need based intervention program and to increase awareness of the mother about hazardous effects of arsenic on reproductive health.

Conclusion:

The toxic effects of arsenic in pregnancy is a potential threat to pregnancies are likely to be adversely affected and thus may have serious implications on reproductive health. There is a suggestive evidence that the prevalence of diabetes mellitus and adverse reproductive outcomes is higher among exposed mother than those who were not exposed. Therefore, new prospective research which is very much relevant to the national health priorities is needed to assess the prevalence rate of diabetes mellitus and to

establish the causal relationship between arsenicosis and diabetes mellitus, and to overcome adverse reproductive outcome and arsenic related reproductive health problems.

Key words:

Diabetes Mellitus, Arsenicosis, Reproductive Outcome.

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Acronyms

As	*Arsenic*
AE	*Arsenic Exposed*
DART	*Development And Reproductive Toxicant*
In-As	*Inorganic Arsenic*
MMA	*Monomethyl Arsenate*
DMA	*Dimethyl Arsenate*
HDG	*Hydroxy Deoxy Guanosine*
DNA	*Deoxy Ribo Nucleic Acid*
RNA	*Ribo Nucleic Acid*
EPA	*Environmental Protection Agency*
iAs	*Inorganic Arsenic*
Se	*Selinium*
PPM	*Parts Per Million*
NAE	*Non Arsenic Exposed*
WHO	*World Health Organization*
CVD	*Cardio Vascular Diseases*
NCDs	*Non Communicable Diseases*
IDDM	*Insulin Dependent Diabetes Mellitus*
NIDDM	*Non Insulin Dependent Diabetes Mellitus*
IFG	*Impaired Fasting Glucose*
IGT	*Impaired Glucose Tolerance*
IGTT	*Impaired Glucose Tolerance Test*
DM	*Diabetes Mellitus*
CI	*Confidential Interval*

OR	*Odd Ratio*
RR	*Relative Risk*
BG	*Blood Glucose*
GDM	*Gestational Diabetes Mellitus*
BMI	*Body Mass Index*
WHR	*Waist-to-Hip Ratio*
AGT	*Abnormal Glucose Tolerance*
MS	*Metabolic Syndrome*
LGA	*Large for Gestational Age*
UK	*United Kingdom*
USA	*United State of America*
SD	*Standard Deviation*
CPM	*Combined Perinatal Mortality*
HDL	*High Density Lipo-protein*
LDL	*Low Density Lipo-protein*
LBW	*Low Birth Weight*
ADA	*American Diabetic Association*
MAC	*Mid Arm Circumferance*
MSAFP	*Maternal Serum Alpha-Foeto-Protein*
HP	*High Protein*
MAFA	*Maternal Arm Fat Area*
CED	*Chronic Energy Defiency*
CRSP	*Collaboration Research Support Programme*
RCH	*Reproductive and Child Health*
MCH	*Maternal and Child Health*
As III	*Arsenic Trivalent*
As V	*Arsenic Pentavalent*
AS_2O_3	*Arsenolite*
FeAsS	*Arsenopyrite*
SEAR	*South East Asian Region*
TAs	*Total Arsenic*
IRS	*Insulin Resistance Syndrome*

CHAPTER-1

INTRODUCTION

Chapter-1

Background and Rationale

1.1 Introduction:

The World Health Organization (WHO) calls the arsenic poisoning in Bangladesh the largest mass poisoning of a population in history (Smith et al. 2000; Rahman et al. 2001), at a scale beyond that of the accidents at Bhopal, India, in 1984, and Chernobyl, Ukraine, in 1986. The evidence that has accumulated since 1997 has only confirmed that this is a public health threat of great magnitude.[1] [2] The presence of arsenic above the Bangladeshi limit of safe drinking water (50µg/l, WHO 2001) was first detected in groundwater of the Bengal Delta Plain (BDP) aquifers in Bangladesh on 1993 (Bhattacharya et al. 2002, 2004, Nickson et al. 2000, Smedley & Kinniburgh 2002, Ahmed et al. 2004). This has resulted in a severe environmental disaster affecting several million people in the region, as groundwater is the main source of potable water for nearly 98 percent of the population in Bangladesh WHO (2003) [3]

What was a success story is now poised to threaten the lives of millions of people living in 61 out of the 64 districts in Bangladesh. Given the present scenario of safe water status, it would not be possible for Bangladesh as well as other arsenic affected parts of the globe to ensure the target of the Millennium Development Goals (MDGs) of ensuring safe drinking water supply to its inhabitants by the year 2015, if necessary measures are to be taken on an urgent basis to alleviate the crisis. The Government of Bangladesh, non-governmental organizations (NGOs) and donors are working together to address this critical issue.[4] Arsenic contamination affects millions of people in Bangladesh. Experts called the greatest mass poisoning in history: high concentrations of naturally occurring arsenic, found in well water in Bangladesh, are affecting enormous numbers of people in one of the poorest and most densely populated countries in the world. Half of Bangladesh population are at risk of arsenic poisoning. [5]

A dose-response relation between cumulative arsenic exposure and the prevalence of diabetes mellitus was also demonstrated after adjustment for multiple risk factors. Rahman and Axelson carried out a case-control study and observed an increased risk of dying from diabetes mellitus with increasing arsenic exposure. In a similar study carried out among glass workers, indications of a relationship between arsenic exposure and diabetes mellitus have also been reported. In a community-based survey of diabetes mellitus in Bangladesh, Rahman et al. observed a dose-response trend between the prevalence of diabetes mellitus and the arsenic level in drinking water.[6]

Overall study indicates that presently, in 2,000 villages in 50 of the total 64 districts of Bangladesh, groundwater contains arsenic concentrations ≥50µg/l, and the British Geological Survey (BGS) has estimated that more than 35 million people are drinking water containing concentrations of arsenic ≥50 µg/l (BGS 2001). Over half the country, 269 out of 460 administrative units, is affected. Similar problems exist in many other parts of the world.[7] In India, more than 6 million people from 9 affected districts (population 50 million) are drinking water containing ≥50µg/l arsenic,[8] and more than 300,000 people may have visible arsenical skin lesions (Chakraborti et al. 2002). The arsenic content of the biologic samples indicates that many more may be subclinically affected. In the combined areas of West Bengal and Bangladesh, around 150 million people are at risk from arsenic-contaminated groundwater (Rahman et al. 2001). [9]

Chronic arsenic poisoning has become a worldwide public health issue. Most human arsenic exposure occurs from consumption of drinking water containing high amounts of inorganic arsenic. Chronic effects of arsenic exposure via drinking water include skin lesions, neurological effects, hypertension, peripheral vascular disease, cardiovascular disease, respiratory disease, diabetes mellitus, adverse reproductive effects and malignancies including skin cancer. The skin is quite sensitive to arsenic, and skin lesions are some of the most common and earliest nonmalignant effects related to chronic arsenic exposure. Skin, lung, bladder, kidney, liver, and uterus are considered as sites arsenic-induced malignancies. [10]

On the basis of epidemiological studies, arsenic exposure has been associated with a number of adverse health outcomes, relatively less attention has been directed toward the potential impact of arsenic on human reproductive system, despite studies in both

humans and experimental animals demonstrating that arsenic and its methylated metabolites cross the placenta. Evidence from human studies suggests the potential for adverse reproductive impacts among the offspring in different countries. [11]

The association between arsenic exposure and diabetes mellitus is a relatively new finding. Up to now, there are some epidemiological reports linking diabetes mellitus with arsenic exposure from environmental and occupational sources. In Bangladesh, prevalence of diabetes mellitus among arsenic-exposed subjects with keratosis was about five times higher than nonexposed subjects. Increasing trends of diabetes mellitus with indices of arsenic exposure in drinking water seems to be independent of the presence of skin lesions associated with arsenic exposure. Although these studies consistently show an association between arsenic exposure and diabetes mellitus, the weak study designs of cross-sectional or case-control, the use of glucosuria or diabetes death as diagnostic criteria and the lack of adjustment for possible confounders in some studies, are major limitations that may reduce the strength of the evidence.[12]

1.2 Background to the research

The World Health organization predicts that by 2030, the number of type 2 diabetes cases world-wide will be double to 350 million. Such predictions indicate that over the next several decades, more and more women of reproductive age will have type 2 diabetes (Thomas Moore) "This is going to be really a major health crisis when dealing with pregnant women," he warned. Infants have an increased risk for birth defects when they are borne by women with diabetes. In addition, type 2 diabetes appears to carry an especially high risk, with miscarriage and congenital malformations almost twice that seen in type 1 diabetes.[13]

Chronic exposure to arsenic through drinking water has the potential to cause adverse pregnancy outcomes, although the association has not been demonstrated conclusively. The cross-sectional study assessed the association between arsenic in drinking water and spontaneous abortion, stillbirth, and neonatal death. Excess risks for spontaneous abortion and stillbirth were observed among the participants chronically exposed to higher concentrations of arsenic in drinking water after adjusting for participant's height, history of hypertension and diabetes, and (for

neonatal death only) age at first pregnancy. These study findings suggest that chronic arsenic exposure may increase the risk of fetal and infant death. [14]

Arsenicosis is a serious environmental chemical disease in China mainly caused by drinking water from pump wells contaminated by high levels of arsenic. Chronic exposure of humans to high concentrations of arsenic in drinking water is associated with skin lesions, peripheral vascular disease, hypertension, blackfoot disease, and high risk of cancers. [15] Surface soil and groundwater in Australia have been found to contain high concentrations of arsenic. [16]

Only after a decade from 1993, arsenic contamination of groundwater in Bangladesh has been reported as the biggest arsenic catastrophe in the world. It is a burning public health issue in this country. More than 50 percent of the total population is estimated at risk of contamination. Already thousands of people have been affected by the disease arsenicosis. Many more may be on the way to manifest lesions in future. The water is unfortunately now a great threat for the human being due to high level of arsenic. Continuous arsenic exposure can lead people to develop arsenicosis, which in turn elevates the risk of cancer. Skin lesions are the most common manifestations in arsenicosis patients. [17]

A group of women of reproductive age (15-49 years) who were chronically exposed to arsenic through drinking water to identify the pregnancy outcomes in terms of live birth, stillbirth, spontaneous abortion, and preterm birth. They compared pregnancy outcomes of exposed respondents with pregnancy outcomes of women of reproductive age who were not exposed to arsenic-contaminated water. Adverse pregnancy outcomes in terms of spontaneous abortion, stillbirth, and preterm birth rates were significantly higher in the exposed group than those in the nonexposed group. [18]

1.3 Problem statement and scope:

Chronic arsenic exposure has been suggested to contribute to diabetes development. A systematic review of the experimental and epidemiologic evidence on the association of arsenic and type 2 diabetes provide limited insight on potential mechanisms. The evidence from occupational studies and from general populations was inconsistent. The current available evidence is inadequate to establish a causal role of arsenic in

diabetes. Because arsenic exposure is widespread and diabetes prevalence is reaching epidemic proportions, experimental studies using arsenic concentrations relevant to human exposure and prospective epidemiologic studies measuring arsenic biomarkers and appropriately assessing diabetes should be a research priority.[19]

1.4 Research Hypothesis:

Prevalence of diabetes mellitus (type-2) among arsenicosisis mother not higher than non-arsenicosis mothers in both arsenic exposed and non exposed group and it is not a risk factor for development of arsenicosis. The mother with arsenicosis have the same reproductive outcomes as those of their counterparts the mother with non-arsenicosis.

1.5 Research objective(s):

1.5.1 General Research Objective:

The aim of this study is to investigate diabetes mellitus (type-2) among arsenicosis affected mothers of child bearing ages (15-49 years) and their reproductive outcome in two rural areas which has a well documented history of arsenic exposed and non-exposed from naturally contaminated ground water.

1.5.2 Specific Research Objective(s):

1.52.1 To find out socio-demographic characteristics and reproductive events of arsenic exposed and nonexpsed mother

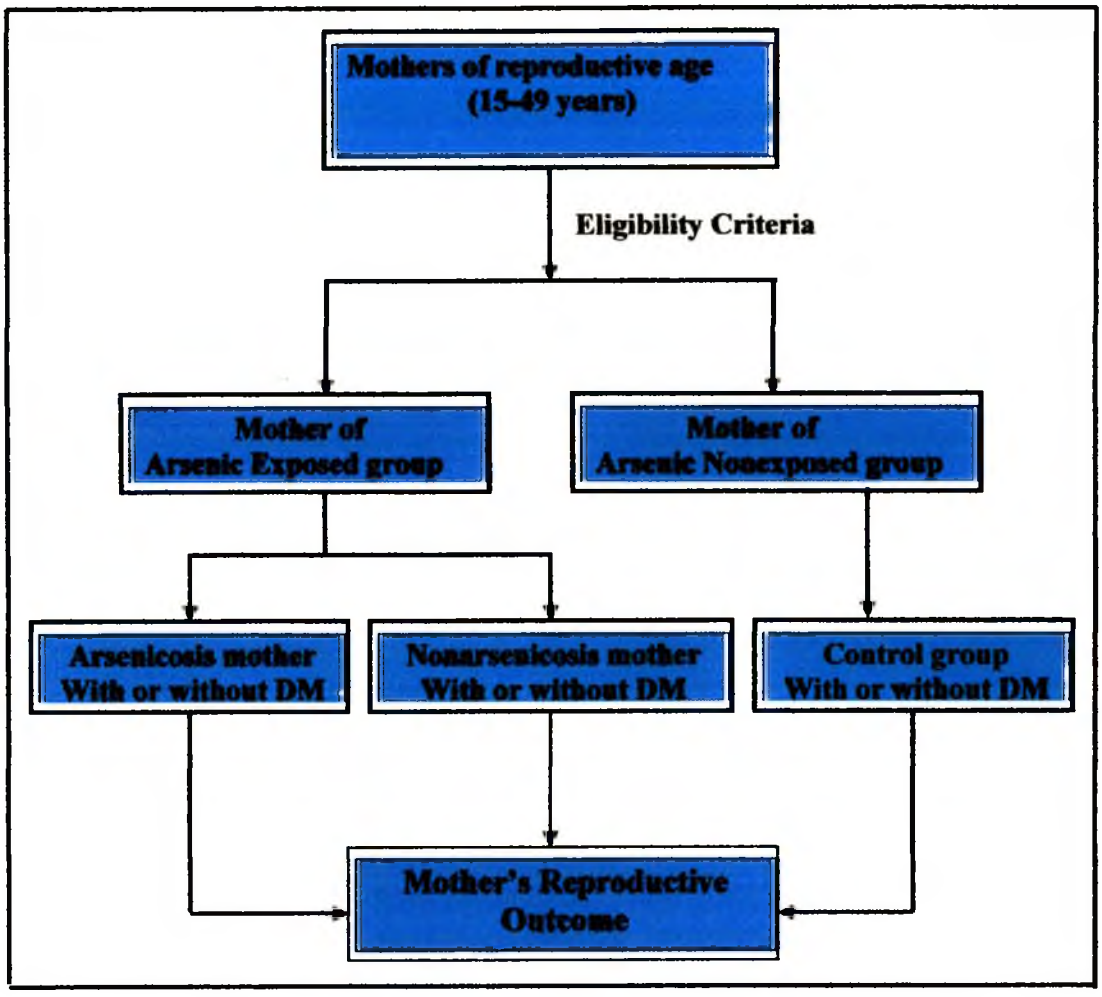
1.5.2.2 To screen diabetes mellitus (type 2) among arsenicosis and non-arsenicosis mothers in arsenic exposed and non-exposed group.

1.5.2.3 To identify reproductive outcomes among arsenicosis and nonarsenicosis mothers in arsenic exposed and nonexposed group.

1.5.2.4 To compare reproductive outcomes among arsenicosis and non-arsenicosis mothers in arsenic exposed and nonexposed group.

1.5.2.5 To relate the socio-demographic characteristics and reproductive events with reproductive outcomes of arsenicosis and nonarsenicosis mother in arsenic exposed and non exposed group.

1.6 Conceptual Framework:



Conceptual Framework

1.7 Diabetes Mellitus (DM):

Diabetes mellitus is a group of metabolic diseases characterizes by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the B-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one

or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. [20] [21] [22] [23]

1.7.1 Classification of Diabetes Mellitus:

NDDG The World Health Organization (WHO) Expert Committee on diabetes in 1980 and, later, the WHO Study group on Diabetes Mellitus endorsed the substantive recommendations of the NDDG. These groups recognized two major forms of diabetes, which they termed insulin-dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin-dependent diabetes mellitus (NIDDM, type 2 diabetes), but their classification system went on to include evidence that diabetes mellitus was an etiologically and clinically heterogeneous group of disorders that share hyperglycemia in common. These and other lines of evidence were used to divide diabetes mellitus into five distinct types (IDDM, NIDDM, gestational diabetes mellitus [GDM], malnutrition-related diabetes, and other types). The different clinical presentations and genetic and environmental etiologic factors of the five types permitted discrimination among them. All five types were characterized by either fasting hyperglycemia or elevated levels of plasma glucose during an oral glucose tolerance test (OGTT). In addition, the 1979 classification included the category of impaired glucose tolerance (IGT), in which plasma glucose levels during an OGTT were above normal but below those defined as diabetes. [20] [21] [22] [23]

Type 1 diabetes:

Immune-mediated diabetes. This form of diabetes, previously encompassed by the terms insulin-dependent diabetes, type 1 diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. In this form of diabetes, the rate of β-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults. Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual β-cell function sufficient to prevent ketoacidosis for many years. Many such individuals

with this form if type1diabetes eventually become dependent on insulin for survival and are at risk for ketoacidosis. At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma c-peptide. Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. [23] [24]

Type 2 diabetes:

This form of diabetes, previously referred to as non-insulin-dependent diabetes, type 2 diabetes, or adult-onset diabetes, is a term used for individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes, and it is likely that the proportion of patients in this category will decrease in the future as identification of specific pathogenic processes and genetic defects permits better differentiation among them and a more definitive sub classification. Although the specific etiologies of this form of diabetes are not known, autoimmune destruction of β-cell does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Ketoacidosis seldom occurs spontaneity usually arises in association with the. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes are at increased risk of developing macro vascular and micro vascular complications. The risk of developing this form of diabetes increases activity. It occurs more frequently in women with prior GDM and in individuals with hypertension or dyslipidemia, and its frequency varies in different racial/ethnic subgroups. It is often associated with a strong genetic predisposition, more so the autoimmune form of type 1diabetes. However the genetics of this form of diabetes are complex and not clearly defined. [24] [25]

Gestational diabetes mellitus (GDM):

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that begins or first detected during pregnancy. GDM affects~7% of all pregnancies, resulting in > 200,000 cases per year. Depending on the population sample and diagnostic criteria, the prevalence may range from 1 to 14%. Of all pregnancies complicated by diabetes,

GDM accounts for~90%. The oral glucose tolerance test (OGTT) most commonly used to diagnose GDM in the United States is the 3-hour, 100-g OGTT. According to diagnostic criteria recommended by the American Diabetes Association (ADA). GDM is diagnosed if two or more plasma glucose levels meet or exceed the following thresholds: fasting glucose concentration of 95 mg/dl, 1-hour glucose concentration of 180 mg/dl. 2hour glucose concentration of 155mg/dl, or 3-hour glucose concentration of 140 mg/dl. These values are lower than the thresholds recommended by the National Diabetes Data Group and are based on the Carpenter and Coustan modification. The ADA recommendations also include the use of a 2-hour 75-g OGTT with the same glucose thresholds listed for fasting, 1-hour, and 2-hour values. The World Health Organization (WHO) diagnostic criteria, which are used in many countries outside of North America, are based on a 2-hour 75-g OGTT. GDM is diagnosed by WHO criteria if either the fasting glucose is>126 mg/dl or the 2-hour glucose is >140 mg/dl. Table 1 summarizes ADA and WHO criteria for the diagnosis of GDM. [23] [24] [25] [26]

ADA and WHO Criteria for the Diagnosis of GDM

	ADA 100-g OGTT	ADA 75-g OGTT	WHO 75-g
OGTT			
Fasting (mg/dl)	95	95	126
1-hour (mg.dl)	180	180	___
2-hour (mg/dl)	155	155	140
3-hour (mg/dl)	140	___	___

[27]

To determine if gestational diabetes is present in pregnant women, a standard OGTT should be performed after overnight fasting (8–14 hours) by giving 75gm anhydrous glucose in 250–300 ml water. Plasma glucose is measured fasting and after 2 hours. Pregnant women who meet WHO criteria for diabetes mellitus or IGT are classified as having Gestational Diabetes Mellitus (GDM). After the pregnancy ends, the woman should be re–classified as having either diabetes mellitus, or IGT, or normal glucose tolerance based on the results of a 75gm OGTT six weeks or more after delivery. It should be emphasized that such women, regardless of the 6–week post–pregnancy result, are at increased risk of subsequently developing diabetes. The

significance of IFG in pregnancy remains to be established. Any woman with IFG, however, should have a 75gm OGTT. [23] [24] [28]

Malnutrition related diabetes (MRDM):

Diabetes mellitus seen in undernourished populations. Whilst it appears that malnutrition may influence the expression of several types of diabetes, the evidence that diabetes can be caused by malnutrition or protein deficiency. The former subtype of MRDM, Protein– Deficient Pancreatic Diabetes (PDPD or PDDM), may be considered as a malnutrition modulated or modified form of diabetes mellitus for which more studies are needed. The other former subtype of MRDM, Fibrocalculous Pancreatic Diabetes (FCPD), is now classified as a disease of the exocrine pancreas, fibrocalculous pancreatopathy, which may lead to diabetes mellitus. [23] [24] [29]

Impaired glucose regulation:

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG). Impaired glucose regulation (IGT and IFG) refers to a metabolic state intermediate between normal glucose homeostasis and diabetes. It should be stated unequivocally, however, that IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation, one in the fasting state and one post-prandial. IGT, rather than being a class as in the previous classification, is categorized as a stage in the natural history of disordered carbohydrate metabolism. A stage of IFG is also recognized because such subjects, like those with IGT, have increased risks of progressing to diabetes. This stage includes individuals who have IGT and individuals with fasting glucose levels ≥ 110 mg/dl (6.1 mmol/l) but <126 mg/dl (7.0 mmol/l) (IFG). The term IFG was coined by Charles et al. (115) to refer to a fasting plasma glucose (FPG) level ≥ 110 mg/dl (6.1 mmol.l) but <140mg/dl (7.8mmol/l). We are using a similar definition, but with the upper end lowered to correspond to the new diagnostic criteria for diabetes. A fasting glucose concentration of 109 mg/dl (6.1mmol/l) has been chosen as the upper limit of "normal" [23] [24] [25]

Idiopathic diabetes:

Some forms of type1 diabetes have no known etiologies. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have on evidence of autoimmunity. Although only a minority of patients with type 1 diabetes fall into this

category, of those who do, most are of African or Asian origin. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying episodes. This form of diabetes is strongly inherited, lacks immunological evidence for β-cell autoimmunity, and is not HLA associated, and absolute requirement for insulin replacement therapy in affected patients. [23] [24] [25]

Other specific types of diabetes:

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern. Abnormalities at three genetic loci on different chromosomes have been identified to date. Genetic abnormalities that result in the inability to convert pro-insulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant. The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism. [23] [24] [25]

Genetic defects in insulin action:

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes. [23] [24] [25]

1.7.2 Criteria for diagnosis of Diabetes:

If a diagnosis of diabetes is made, the clinician must feel confident that the diagnosis is fully established since the consequences for the individual are considerable and lifelong. The requirements for diagnostic confirmation for a person presenting with severe symptoms and gross hyperglycaemia differ from those for the asymptomatic

person with blood glucose values found to be just above the diagnostic cut–off value. Severe hyperglycaemia detected under conditions of acute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. The diagnosis of diabetes in an asymptomatic subject should never be made on the basis of a single abnormal blood glucose value. For the asymptomatic person, at least one additional plasma/blood glucose test result with a value in the diabetic range is essential, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT). If such samples fail to confirm the diagnosis of diabetes mellitus, it will usually be advisable to maintain surveillance with periodic re-testing until the diagnostic situation becomes clear. In these circumstances, the clinician should take into consideration such additional factors as ethnicity, family history, age, adiposity, and concomitant disorders, before deciding on a diagnostic or therapeutic course of action. An alternative to blood glucose estimation or the OGTT has long been sought to simplify the diagnosis of diabetes. [21] [22] [23] [24] [25]

For epidemiological or population screening purposes, the fasting or 2-h value after 75gm oral glucose may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms. Classification Terminology- It is recommended that the terms "insulin–dependent diabetes mellitus" and "non–insulin–dependent diabetes mellitus" and their acronyms "IDDM" and "NIDDM" no longer be used. These terms have been confusing and frequently resulted in patients being classified on the basis of treatment rather than pathogenesis. [21] [23] [24] [25]

1.8 Arsenicosis:

Arsenicosis is a chronic pathological condition clinically manifested by melanosis and keratosis occurring alone or in combination, with or without the involvement of internal organs likely to develop malignancy, due to chronic ingestion of arsenic contaminated water (ground) having arsenic level exceeding maximum permissible limit (0.05mg/l) in Bangladesh (WHO).[30] [31]

1.8.1 Some common arsenic compounds and their toxicity: [32]

Name	Synonyms	Toxicity
A. Inorganic arsenic	Arsenite	More toxic than organic
a) Trivalent Arsenic:	Arsenic Trioxide	form. More toxic than
Arsenic (iii) oxide	White arsenic	Pentavalent.
	Arsenous oxide	
Arseneous acid	Arsenious acid.	
b) Pentavalent Arsenic:	Arsenate Arsenic	
Arsenic (v) oxide Arsenic	pentaoxide	Less toxic than trivalent
acid Arsenenic acid	Orthoarsenic acid Meta-	
	arsenic acid	
B. Organic Arsenic:		
Monomethyl arsenic acid	-	
Dimethyl arsenic acid	Methane arsenic acid	Less toxic than inorganic
Arsenobetaine	Cacodylic acid	form.
Arseno choline	-	
	-	

1.8.2 Signs and symptoms of arsenic toxicity:

Acute Poisoning:

If swallowed Within 30 minutes, or after several hours if taken food: sudden abdominal pain and vomiting, severe diarrhea, sore throat, dry mouth and thirst, the breath may smell of garlic, signs of shock: weak fast pulse, cold damp skin, low blood pressure and blue skin, delirium and sudden unconsciousness, fits. The patient may die within 24 hours. If not, after 24 hours there may be: jaundice and signs of liver damage, signs of kidney damage, If breathed in : same effects as when swallowed, but without abdominal pain, vomiting or diarrhea. On the skin: same effects as when breathed in redness, blisters. In the eyes: severe irritation with pain and redness.[31] [32]

Chronic Poisoning:

Long term exposure to small doses over many weeks or years, by swallowing or breathing in may result in: weakness, loss of appetite, nausea, vomiting, diarrhea or constipation, skin rash, thick skin on the palms of hands or the soles of the feet,

hoarse voice and sore throat, sometimes the patient can taste metal, and the breath and sweat smell of garlic, jaundice as a result of liver damage, blood in the urine as a result of kidney damage, numbness or pain in the soles or the feet because the nerves have been damaged, hair loss, white lines on the nails, cancer of the skin or liver, The clinical manifestations due to chronic arsenic toxicity develop very insidiously after six months to two years or more depending upon the amount of arsenic intake. Chronic toxicity of arsenic is best discussed in terms of the organ/systems affected: skin, nervous system, liver, cardiovascular system, and respiratory tract. [31] [32]

Clinical features indicating arsenic sis:

Signs and symptoms of chronic arsenicosis differ in manifestation in different countries. In Bangladesh skin manifestations are prime and most common. Arsenicosis may be divided into 4 stages: (I) preclinical, (II) clinical, (III) internal complications, and (IV) malignancy. [31] [32]

(I) Preclinical Stage Preclinical or asymptomatic arsenicosis may be sub-grouped into (a) labile chemical or blood phase after the intake of arsenic-contaminated water, blood and urine analyses indicate elevated levels of arsenic that clear within a few days of withdrawal of the arsenic source and (b) stable subclinical or tissue phase- in this phase, assays of the nails, hair, and skin scales or other body tissues show elevated concentrations of arsenic, but the clinical features of arsenic toxicity are absent. Unaffected members of a family drinking the same arsenic-contaminated water are often in this stage. [31] [32] [33]

(II) Clinical Stage (Symptomatic or Overt Stage):

(a) Onset Our field survey experience for the last 7 years in Bangladesh and 14 years in West Bengal indicates that 6 months to 10 years, or even more, may be required for the development of clinical features. The appearance of arsenical skin lesions depends on the concentration of arsenic in contaminated water, quantity of water consumed per day, and nutritional status.

(b) Major Dermatological Signs: (i) Melanokeratosis: Melanosis, i.e., dark pigmentation, diffuse or spotted with keratosis, e.g., dry, rough, spotted nodules of the plams and soles, are the chief symptoms of arsenical dermatosis (ASD). Various genetic and acquired before making the diagnosis of ASD and verification by an

experienced dermatologist is essential. (ii) Diffuse melanosis: Diffuse darkening of skin starts on the palms and gradually spreads to the entire body. Comparison with a normal palm or a sibling's palm can reveal mild melanosis as the earliest feature. (iii) Spotted melanosis (raindrop pigmentation): Arsenic patients normally show spotted melanosis on the chest and back, and sometimes on the limbs. (iv) Leucomelanosis: arsenic patients with spotted melanosis may develop pigmented and depigmented spots on the legs or trunk. Stimulation of the melanocytes produces pigmentation; damage in a later stage is responsible for depigmented spots. Leucomelanosis typically develops after cessation of exposure. (v) Keratosis: After 5-10 years of continuous exposure, palmoplantar skin may show spotted keratosis, although this may appear earlier with intense exposure and malnutrition. The skin becomes dry and thickened due to diffuse keratosis. There is gradual thickening of the soles producing hyperkeratotic cracks and fissures. If the disease is of long duration (more than 10-15 years), keratosis also develops in the dorsal skin of hands, feet, legs (dorsal keratosis), or in multiple areas. (c) Minor Dermatological features (i) Buccal mucous membrane pigmentation: Pigmentation on the tongue, inner sides of lips, gums, or mucous membrane of mouth. (ii) Nonpitting edema: Edema of feet that does not pit on pressure with exclusion of other causes. (iii) Conjunctional congestion: Arsenicosis patients may have red eyes resembling conjunctional congestion but without inflammatory signs of a grating sensation, pain, or discharge. [31] [32] [33]

(III) Internal stage:

In this stage, nondermatological toxic features appear in addition to dermatological signs. **Common Complications** (i) Lungs: Asthmatic bronchitis (cough, expectoration, breathlessness, restrictive asthma). The association of restrictive or obstructive pulmonary disease with arsenic is often noted but causality is not defined. (ii) Liver: Hepatomegaly with a hard liver, but rarely with jaundice and ascites, due to noncirrhotic portal fibrosis (NCPF) with maintenance of lobular architecture. (iii) Spleen: Splenomegaly. (b) Rare Complications and Signs Requiring careful evaluation for exclusion of other causes. (i) Anemia and general weakness; (ii) Myalgia (muscle pain) and myopathy (electromyographic change); (iii) Chronic laryngitis (hoarseness of voice); and (iv) Suprarenal hypofunction (low plasma cortisol). [31] [32] [33]

.(IV) Malignant stage:

Gangrene and Bowen's Disease In this state, there is persistent enlargement of a nodule or skin ulcer, peripheral atherosclerosis, gangrene, or malignancy. Arteriosclerosis obliterans and cancer leading to amputation (Fig.5) are not rate in the affected villages. Bowen's disease (carcinoma in situ) develops after long-term exposure with severe keratosis and melanosis. Cancers may develop 15-20 or more years after the first symptoms, Squamous cell carcinoma is common and can be monocentric and multicentric. It is usually of slow progression, but rapid growth and death have occurred. Lung, bladder, liver, and uterine cancers are found in association with intense melanosis and keratosis in the older arsenic-exposed population, but the epidemiologic studies are incomplete. [31] [32] [33]

1.9 Operationalisation of Main Variables:

1.9.1 Type 2 Diabetes:

Diabetes mellitus (Type 2) is a chronic, complex disorder which adversely affect both longevity and quality of life due to multiple, potential serious complications. It is common in middle ages and elderly individuals. Type 2 diabetes mellitus (which replaces the terms non insulin dependant diabetes NIDD) is the commonest form of the disease accounting for 85-95 percent of all cases worldwide. [24] [34]

1.9.2 Arsenicosis Case Definition:

For this study, mother of reproductive age (15-49 years) showing as the 'presence of characteristic arsenical skin lesions e.g melanosis (hyper-pigmentation) and/or keratosis with or without other manifestations of chronic arsenic toxicity with a history of drinking arsenic contaminated water for more than 2 years were diagnosed as a case of arsenicosis. This definition was also validated by other reports (Kaufmann et al. 2001; Rahman 2003). The diagnosis of arsenical skin lesions were reported in earlier publications (Milton et al. 2001; Milton and Rahman 2002).[34]

1.9.3 Reproductive Outcome:

1.9.3.1 Maternal Outcome:

Menstrual History:

- Age at menarche
- Excessive, scanty and irregular bleeding

- Painful menstruation
- Lower abdominal pain and backache

History of Antenatal (ANC), Intra-natal (INC) and Post-natal care (PNC)

Reproductive Events:

- Age at first marriage
- Age at first birth
- Number of pregnancy
- Outcome of pregnancy (Live birth, Stillbirth, Neonatal death, Pre-term birth, Abortion, Miscarriage and Congenital anomalies)

Reproductive Behavior:

- Use of contraceptives
- Sexual responsiveness
- Reproductive health seeking behavior (according to symptom)

Maternal Status:

- Glycaemic Status
- Hypertension
- Toxaemia of pregnancy and unconsciousness
- Excessive PV bleeding

Mode of delivery:

- Place of delivery
- Mode of delivery
- Person conducted delivery

Fertility Pattern:

- Number of living child
- Sex of child
- Birth spacing
- Menstrual Regulation (MR)

1.9.3.2 Fetal Outcome:

Gestational age:

- Pre-term baby (<37 weeks)
- Full-term (37 - <42 weeks)
- Post-term (42 weeks or more)

Status of Child:

- Alive and healthy
- Stillbirth (Stillbirth was defined as death in utero after 20-28 weeks or with birth weight >500gm but no signs of life)
- Neonatal death (death within first week of life) and
- Congenital abnormality [35] [36]

1.10 Scientific and Public Health Relevance of the study:

Arsenic contamination of ground water is a recently added public health threat in Bangladesh. A large number of people including women have been suffering and many of them are dying from arsenicosis and related complications. Millions of women in the rural areas still drinking highly contaminated arsenic water because they have no alternative sources of safe drifting water. Most of the women do not know whether their drinking water from tube wells is arsenic free or not. People of Bangladesh facing an environmental disaster of drinking water. Analysis of present state of affaires on managing this disaster, give rise to serious question that are we sincere and serious in dealing with the problem of this magnitude? Arsenic toxicity can produce many damages, but the women's are not aware of its exact problems on health particularly its toxic effects on mothers reproductive health. This study will help to identify the association of arsenicosis, diabetes mellitus and women' reproductive outcome. Much priority and special emphasis should be given to promote maternal reproductive outcome in order to reduce both maternal and child morbidity and mortality. However, limited research has been directed at the association of arsenic exposure, diabetes and women's reproductive outcome.[32] [33] [36]

Conclusion on the causality of the relationship between arsenicosis, diabetes mellitus and reproductive outcomes are suggestive and less clear. Several studies have examined a number of reproductive end points in relation to arsenic exposure, and the result suggest elevations in fetal, neonatal, and postnatal mortality, lowered birth weight and spontaneous abortions. However, there is no consistent evidence for any one particular end point. Better exposure-response studies are required to characterize the potential health effects at low level of exposure notably, epidemiological studies on reproductive end points for which associations have already been suggested. In the case of developing countries, attention must be paid to the nutritional status of the

mother, which may modify the toxicity of certain environmental chemicals. In fact, the study conducted in West Bengal suggested that malnourished individuals, having less than 80 percent of the standard body weight, were more susceptible to chronic arsenic toxicity, judging from the body mass index (BMI). [32 33]

Further research is urgently needed in order to reduce the uncertainties in reproductive risk assessment of arsenic in drinking water. There may also be under estimation of the effect due to the relatively short period of exposure. Even negative skin signs are no assurance of low risk for cancer development (Tsuda et. al. 1995). Arsenic causes a number of other cancer and non cancer health effects are noted as well, such as spontaneous abortions and still births but thus far epidemiological evidence has not been consistent. However, quantitative information about the scale of the arsenic contamination has been author limited until recently. [11 18] There is an urgent need for a project to address arsenic poisoning in Bangladesh since the situation can be described as a "crisis" due to devastating effects of arsenic on human health and reproductive lives.

1.11 Organization of this thesis:

The thesis has been organized into 5 chapters:

Chapter 1: Chapter one has briefly outlined the introduction and background to the research, problem statement and scope, research hypothesis and research objectives, operationalisation of main variables: diabetes mellitus, arsenicosis and reproductive outcomes, scientific and public health relevance of the study, organization of this thesis and conclusions of this chapter.

Chapter 2 Following this first introductory chapter, chapter 2 review the literature from a number of different areas and the associated fields women's reproductive outcomes are also discussed. The chapter also reviews the literature on a descriptive and explanatory framework of reproductive outcome of mother. We particularly focus on the prevalence of diabetes mellitus (type 2) among arsenicosis and non-arsenicosis mother. Moreover, we address the comparison of reproductive outcomes of diabetes mellitus and arsenicosis mother. This chapter sets the subsequent comparative analysis of arsenic and its impact on reproductive health.

Chapter 3 describes the research design, population, study locations required data and methods of data collection. We elaborates the research methods and discuss the conceptual models for quantitative and qualitative approach to ensure research objectives. It begins with the discussion of why we used both quantitative and qualitative methods. Comparative statistical analysis was used for the quantitative analysis. The chapter outlines how and when qualitative data was done from respondents response through semi-structured questionnaire. Finally, issues of validity, reliability, limitations, ethical considerations of the study are considered, reinforcing the rigor of the research process and acknowledging the researcher's biases.

Chapter 4 Presents results and findings comparing prevalence of diabetes mellitus (type 2) among arsenicosis and non-arsenicosis mother. We calculated stillbirth, live birth, pre-term birth, neonatal death, abortion, miscarriage and congenital anomalies using the total number of live births as the denominator. Subsequently, we compared these reproductive events in the exposed (both arsenicosis and non-arsenicosis) and non-exposed groups.

Chapter 5 We discuss conclusions of this research with detailed discussion of important findings and compared with other relevant national and internal findings. This chapter also introduces the policy implications and needs of further research in this regard. Besides summarizing the main results, we also look at important theoretical considerations that should be taken into account when quantitative and qualitative analysis was undertaken to compare prevalence of diabetes mellitus and difference in pregnancy outcome of arsenicosis and non-arsenicosis mother.

1.12 Conclusions of this chapter:

This introductory chapter has laid the foundations for the report. It briefly overviewed the research problem, justify the research problem, formulate research hypothesis and research objectives. We designed a cross sectional comparative study as the main methodology reflected the use of both quantitative and qualitative approaches. The methodology were briefly described and operationalized the key variables The report was outlined and organized in five chapters. On these foundations, the report can proceed with a detailed description of this research.

CHAPTER-2

LITERATURE REVIEW

Chapter-2

Literature Review

2.1 Introduction:

This chapter provides a comprehensive review of theories, explanations, experiences and findings on the following sections: Diabetes mellitus, effects of pregnancy on diabetes, effects of diabetes in pregnancy, diabetes mellitus and reproductive outcomes, placental transfer of arsenic, reproductive toxicity of arsenic, association between arsenicosis and diabetes mellitus (type 2), arsenicosis and reproductive outcomes and social aspect of arsenic crisis. This chapter analyses the theoretical framework on which the analysis are based on the research has been undertaken to review of prevalence of diabetes mellitus in arsenicosis and reproductive outcomes. This identifies the need to investigate whether the research achieves its stated course objectives. It also points out that adverse reproductive outcomes is based on the individual writers own experiences, but there is a lack of empirical research into the key elements of reproductive outcomes. The review points out that the use of more qualitative methods has been advocated to investigate why the variation of prevalence of diabetes mellitus and reproductive outcomes occurs in arsenic exposed and nonexposed group.

2.2.1 Epidemiology of diabetes mellitus:

The recent WHO report on diabetes prevalence alarmed that diabetes has posed a serious threat to entire population of the world irrespective of stages of industrialization and development. The prevalence of diabetes of all ages worldwide was estimated to be 2.8 percent in 2000 and 4.4 percent in 2030. The number of diabetic population was estimated to rise from 171 million in 2000 to 366 million in 2030. According to the recent report, the highest relative increase will occur in the Middle East, Sub-Saharan

Africa, India and Bangladesh. In 2000, Bangladesh had 2.3 million people with diabetes which will occupy the 7th position with 11.1 million in 2030. As estimated on the basis of present prevalence rates of diabetes (NIDDM~5.2 percent and IGT~12.5 percent. In the protected population, more than 10 million population of Bangladeshies will suffer from different diseases in the year 2010.[22] [24]

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. Type 2 diabetes is more common in individuals with a family history of the disease and in members of certain racial/ethnic groups. It occurs more frequently in women with prior GDM or polycystic ovary syndrome and in individuals with hypertension, dyslipidemia, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG). There is every reason to expect that over the next decade, the epidemic of NIDDM will continue to escalate (McCarty and Zimmet 1994) so that diabetes and its complications will emerge as one of major threats to future public health resources throughout the world at a huge economic and social cost, particularly in developing countries (Vaughan et al. 1989).[24] [25]

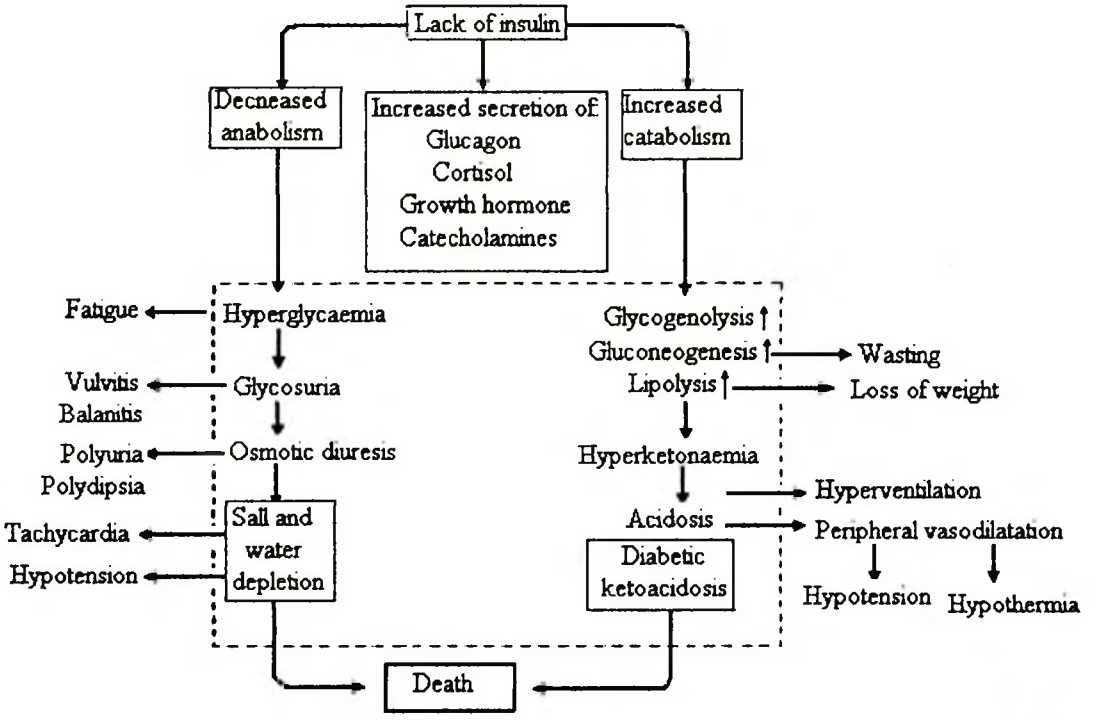
The incidence of type 2 diabetes mellitus is rising rapidly. More than half of the women who develop gestational diabetes mellitus (GDM), which represents approximately 90% of all cases of diabetes complicating pregnancy, will develop type 2 diabetes mellitus later in life. Diabetes mellitus increases the risk of important adverse outcomes of pregnancy. In women who are poorly controlled at the time of conception and during the early weeks of gestation, the incidence of spontaneous abortion and major congenital malformations are increased. Major congenital anomalies are the leading cause of perinatal mortality in pregnancies complicated by diabetes mellitus, occurring in 6-12% of all infants [37]

The proportion of total diabetes cases that were diagnosed increased from 41 to 83% (probability 99.9%) among individuals with BMI $\geq$5 kg/m^2.[38] [39] The crude prevalence of type 2 diabetes in a rural population of Bangladesh was 4.3% and IFG was 12.4%. The age-standardized prevalence of type 2 diabetes (95% CI) was 3.8% (3.12–4.49) and IFG was 13.0% (11.76–14.16). The subjects with higher family income had significantly

higher prevalence of type 2 diabetes (5.9 vs. 3.5%, p<0.001) and IFG (15.6 vs. 10.8%, p<0.001) than those with lower income. [22] [24] [40]

Age-adjusted (30-64 years) prevalence of NIDDM was higher in urban (7.97% with 95% CI 6.17-9.77) than in rural subjects (3.84%, CI 2.61-5.07), whereas impaired glucose tolerance (IGT) prevalence was higher in rural subjects. In either urban or rural areas, the highest prevalence of NIDDM was observed among the rich, and the lowest prevalence was observed among the poor socioeconomic classes. The rural rich had much higher prevalence of IGT than their urban counterpart (16.5 percent vs. 4.4 percent, CI 6.8-17.4). Increased age was an important risk factor for IGT and NIDDM in both rural and urban subjects. [22] [24] [39] [41]

2.2.2 Pathophysiology of diabetes mellitus:



Pathophysiological basis of diabetes mellitus. [24] [65]

2.2.3 *Pathogenesis of diabetic pregnancy:*

Pregnancy is a diabetogenic condition characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia. Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Insulin sensitivity is reduced by as much as 80%. Placental secretion of hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone, is a major contributor to the insulin-resistant state seen in pregnancy. The insulin resistance likely plays a role in ensuring that the fetus has an adequate supply of glucose by changing the maternal energy metabolism from carbohydrates to lipids. Women with GDM have a greater severity of insulin resistance compared to the insulin resistance seen in normal pregnancies. They also have an impairment of the compensatory increase in insulin secretion, particularly first-phase insulin secretion. This decrease in first-phase insulin release may be a marker for deterioration of β-cell function.[42] [43]

There are both fetal and maternal complications associated with GDM. Fetal complications include macrosomia, neonatal hypoglycemia, perinatal mortality, congenital malformation, hyperbilirubinemia, polycythemia, hypocalcaemia, and respiratory distress syndrome. Maternal factors associated with an increased incidence of macrosomia include hyperglycemia, high BMI, older age, and multi-parity. This excess in fetal growth can lead to increased fetal morbidity at delivery, such as shoulder dystocia, and an increased rate of cesarean deliveries. Neonatal hypoglycemia can occur within a few hours of delivery. This results from maternal hyperglycemia causing fetal hyperinsulinemia. Long-term complications to the offspring include an increased risk of glucose intolerance, diabetes, and obesity. Maternal complications associated with GDM include hypertension, preeclampsia, and an increased risk of cesarean delivery. [27]

2.2.4 *Diabetes mellitus and risk factors*

The correlation of a risk factor(s) with development of diabetes is never 100%. However, the greater the numbers of risk factors present in an individual, the greater the chance of that individual developing or having diabetes. Type 2 diabetes is more common in

individuals with a family history of the disease and in members of certain racial/ethnic groups. It occurs more frequently in women with prior GDM or polycystic ovary syndrome and in individuals with hypertension, dyslipidemia, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG). [21]

Age sex and waist-to-hip ratio for men were significant risk factors for both urban and rural subjects following fasting and 2-h post-glucose values adjusted for a number of confounding variables. Abnormal glucose values on the diagnostic OGTT or overt diabetes during pregnancy was the strongest predictive factor for diabetes (relative risk 3.92), and pre-pregnancy BMI was the predictive factor with the highest attributable fraction in the whole group (13.3%), women with GDM have an increased risk of diabetes and AGT. Age sex and waist-to-hip ratio for men were significant risk factors for both urban and rural subjects following fasting and 2-h post-glucose values adjusted for a number of confounding variables. Abnormal glucose values on the diagnostic OGTT or overt diabetes during pregnancy was the strongest predictive factor for diabetes (relative risk 3.92), and pre-pregnancy BMI was the predictive factor with the highest attributable fraction in the whole group (13.3%), women with GDM have an increased risk of diabetes and AGT. [44] [45]

The possibility that maternal vascular risk factors, potentially 'modifiable' before pregnancy, correlate with increased risk of preterm delivery and low birth weight, and thus fetal programming, requires further investigation. [46] Epidemiological evidence suggests that maternal psychosocial stress, strenuous physical activity and fasting are independent risk factors for preterm birth and low birth weight. [47] Although maternal nutritional deficiencies typically occur as a result of low dietary intakes of essential nutrients, nutritional deficiencies at the level of the concepts may be significant contributors to the occurrence of birth defects.[48] Obesity and overweight are common conditions in the developed countries and they carry many health consequences, including some reproductive disorders.[49] Perinatal mortality, intrauterine fetal death, and neonatal death increased with age.[50]

2.2.5 Effects of pregnancy on diabetes:

Pregnancy in diabetic women is associated with an increased perinatal mortality rate (that is, stillbirths and neonatal deaths within the first week of life), low birth weight and congenital malformation. Birth trauma is also more common due to a high incidence of excessively large, macrosomic babies. [26] Uncontrolled diabetes leads to more birth defects. Women who had diabetes before they got pregnant or who developed gestational diabetes with elevated fasting blood-glucose levels were three to four times more likely to have babies with birth defects than women who either did not have diabetes before pregnancy. [51]

Animals displaying maternal insulin deficiency have offspring who are insulin resistant without any evidence of iv glucose intolerance or diminished insulin secretion. [52] Maternal diabetes adversely affects pre-implantation embryo development and pregnancy outcomes. In addition, there may be dysfunctional or decreased communication in diabetic oocytes, as demonstrated by lower expression of connexin-43.[53] The prevalence and risk of complication of a population of Spanish pregnant women with GDM diagnosed complicated only with impaired glucose intolerance (IGT) (0.94%) showed a worst outcome. [54]

Normal weight women treated with diet therapy who achieved targeted levels of glycemic control had good outcomes, but obese women treated with diet therapy who achieved targeted levels of glycemic control, nevertheless, had a 2 to 3 fold higher risk for adverse pregnancy outcome when compared with overweight and normal weight patients with well-controlled GDM. Women with GDM who failed to achieve established levels of glycemic control had significantly higher adverse pregnancy outcomes.[55] This population of pregnant, untreated diabetic women, plasma glucose levels (either fasting or after various glucose loads) were independently but poorly correlated with birth weight; no more than 3% to 5% of birth weight variability could be explained by changes in glucose tolerance. Fasting plasma glucose was consistently but marginally better than the plasma glucose level 2 hours after 75-gm glucose load for predicting LGA neonates. The neonatal macrosomia is influenced by variables that are largely independent of plasma glucose concentrations.[56]

Status Indian non-pregnant females were three times as likely to be hospitalized as their non-status Indian counterparts. Under age 35 years there was no difference in risk. Older First Nations women have a higher risk of diabetes during pregnancy but this analysis cannot distinguish gestational diabetes from pre-existing Type 2 diabetes.[57] Maternal and fetal complications are increased when pregnancy is complicated by diabetes, and this may be further influenced by racial and cultural differences. Pregnancies complicated by type 2 diabetes in Indo-Asian and Caucasian women pose the greatest threat to successful pregnancy outcome.[58]

Fetal outcomes included early intrauterine deaths, stillbirths, neonatal/perinatal mortality and maternal outcomes included change in frequency of hypertension or severe proteinuria, serum creatinine data, and caesarean section rate were compared. Although the take-home baby rate was 90%, perinatal/neonatal mortality, congenital malformations and caesarean sections, in addition to maternal morbidity, were significantly higher in women with diabetic nephropathy than in the background population.[59] Women with IGT were at increased risk premature rupture of membranes, preterm birth breech presentation, and high birth weight adjusting for maternal age, pregravid BMI, hospital levels, and other confounding factors. The presence of IGT in pregnancy is predictive of poor pregnancy outcomes.[60]

The excessive or deficient release of some placental hormones in association with gestational diseases may reflect an abnormal differentiation of the placenta, an impaired fetal metabolism, or an adaptive response of the feto-placental unit to adverse conditions: Down's syndrome, fetal growth restriction, preeclampsia, preterm delivery, and diabetes mellitus.[61] Childhood obesity has contributed to an increased incidence of type 2 diabetes mellitus and metabolic syndrome (MS) among children. Intrauterine exposure to diabetes and size at birth are risk factors for type 2 diabetes mellitus. LGA offspring of diabetic mothers were at significant risk of developing MS in childhood. [62]

2.2.6 Effects of diabetes in pregnancy:

Two major forms of maternal diabetes may occur during pregnancy: preexisting or pre-gestational diabetes and gestational-onset or gestational diabetes mellitus (GDM. These

pregnancies are at risk for both maternal and fetal complications. Complications that arise from the effects of maternal diabetes on early fetal development (i.e. in the first trimester) include spontaneous abortions and major congenital malformations. Rates of both complications are highest in women with the most marked hyperglycemia during the first trimester. The most prominent fetal complications that can arise during the second and third trimesters are stillbirth and macrosomia (an excessively large infant). Stillbirths are now uncommon in diabetic pregnancies; congenital malformations and complications of maternal hypertensive disorders account for most of the 1.5-to 2-fold increase in perinatal mortality compared with non diabetic pregnancies.[63] [64]

Cundy and colleagues showed a threefold increased perinatal mortality in women with type 2 diabetes, mainly due to late stillbirths. The perinatal mortality rate was 2.5-fold greater than regional or national figures. The miscarriage rate in type 2 diabetes in the UK case series was 8.8 percent, almost doubling to 15.7 percent and half of the miscarriage occurred in the first trimester, in those with poor glycaemic control. Polyhydramnios was three times as likely compared to non-diabetics (9% compared to 3%), with infant mortality more likely in pregnancies affected by polyhydramnios. Postpartum haemorrhage was also much more common and appeared unrelated to macrosomia. Pregnancy-induced hypertension and/or pre-eclampsia were twice as common (20% compared to 10% in the background group). Delivery by caesarean section is common in women with type 2 diabetes, with a rate of 53% reported. Omori and colleagues identified a high rate of retinopathy (32%) and overt nephropathy (1.4%) in their series. Retinopathy is an independent predictor of poor fetal outcome. [65] [66]

2.2.7 Maternal and perinatal complications during pregnancy:

Diabetes mellitus is the most frequent metabolic pregnancy complication associated with an increased risk of maternal and neonatal mordidities: First trimester (pregestational diabetes): Spontaneous abortion, Congenital malformations, Ketoacidosis , Hypoglycemia. Second and third trimester (pregestational and gestational diabetes): Ketoacidosis, Hypoglycemia, Albuminuria and nephritic syndrome, Pregnancy-induced hypertension (hypertension associated with pregnancy), Preeclampsia, Polyhydramnios, Large-for-gestational-age fetus, Small-for-gestational-age fetus, Fetal death near term,

Miscarriage, Preterm delivery, Cesarean section. Neonatal complication: Large-for-gestational age (LGA macrosomia), Small-for- gestational age, Preterm newborn, Congenital malformations, Respiratory distress syndrome, Hypoglycemia, Neonatal jaundice, Polycythemia, Hypocalcemia[36] [67] [68]

There is increased maternal or neonatal morbidity in connection with impaired glucose tolerance (IGT) during pregnancy when the condition is not treated. The proportion of women who underwent cesarean section was significantly higher in the case subjects than in the control subjects and was independently associated with IGT. There is increased independent association between cesarean section rate, prematurity, LGA, and macrosomic infants born to mothers with untreated IGT.[36] [69] In the northeast England, perinatal mortality is five times higher and congenital malformation is four times higher for pregnancies in diabetic women than for those in women who do not have diabetes. The same is true in other regions in the United Kingdom. [70] Carpenter-Coustan, and GDM had a significantly higher risk of spontaneous preterm birth than pregnancies with normal screening. The risk of spontaneous preterm birth increased with increasing levels of pregnancy glycemia. This association was independent of perinatal complications that could have triggered early delivery.[71] [72] [73]

2.2.8 Diabetes mellitus and reproductive outcomes:

Pregnancy complicated by type 2 diabetes is a high-risk pregnancy. Associated with birth defects and high perinatal mortality to the same extent as in type1 diabetes. Maternal age and obesity are both associated with an increased risk of perinatal mortality. Pre-eclampsia is 2 to 3 times more common in women with type 2 diabetes than in non diabetic women, as quite high as in women with type 1 diabetes. [74] [75] Dunne has recently reported that women with type 2 diabetes have up to a 11 times greater risk of a congenital malformation compared with the general population. Perinatal mortality is substantially higher than in the general population, mainly owing to excess of late fetal death. Other maternal factors, including higher age, higher frequency of hypertension, low socioeconomic status are likely to contribute to the increased mortality rate.[76] [77] [78]

There is strong evidence that low birth weight is associated with glucose intolerance and diabetes in adults. Maternal factors are more important than feto-placental factors in determining glucose-insulin metabolism in the offspring. [79] [80] Both spontaneous and preterm deliveries are increased in pregestational diabetes. Type 2 diabetes was associated with a 3.4% congenital malformations..[81] In a Japanese study of women with pregestational diabetes in pregnancy, 5.8% of infants born to women with type 2 diabetes had major congenital anomalies compared with none of the infants born to women with type 1 diabetes. In another study of women in the UK, women with type 2 diabetes, most of whom were from the Indian subcontinent, also had twice the frequency of congenital malformations compared with women with type 1 diabetes (12.2% *vs* 6.1%).[82] [83] [84]

Post load glucose concentration at week 28 was associated with maternal ethnicity or altered the ethnic difference in birth weight after adjustment for duration of gestation and pregnancy outcome large-and small-for-gestational-age births. Maternal glucose was associated with infant birth weight to a similar extent within each ethnic group (1.5-2.0 g of birth weight per mg/dl of matemal glucose). A comparison of regression coefficients from models with and without glucose small but statistically significant effects of glucose on the ethnic difference in birth weight and the risk of large-for-gestational-age birth between African Americans and Whites. Maternal glucose concentration did not differ between Hispanics and Whites; consequently, glucose did not influence this ethnic difference in birth weight and pregnancy outcome. [85] [86] [87] [88]

Women with pre-gestational diabetes or gestational diabetes plus fasting hyperglycemia have a three-to four-fold increased risk of infant malformations, whereas women with mild gestational diabetes have malformation rates no different than the general non-diabetic obstetric population. It is generally accepted that increased severe malformations are the consequence of poorly controlled diabetes both pre-conceptional as well as early in pregnancy. It is also generally believed that women with gestational diabetes are not at risk for infant malformations, whereas those with pre-gestational diabetes have a three-to five-fold increased risk compared with the general obstetric population.[89] [90] [91]

Greater birth weight and length appear to offer a protective effect against glucose intolerance. Adult overweight or obesity enhances the risk associated with low birth

weight and length. The increased prevalence of type 2 diabetes that has been observed with very high birth weight has been attributed in part to gestational diabetes, resulting in large babies prone to diabetes later in life.[92] Increased maternal glucose concentration also was associated with an increased risk of large-for-gestation fetuses (p for trend<0.001) and a decreased risk of fetal growth restriction (p for trend<0.05). The association between glucose and gestation was inversed and significantly shortened when glucose concentrations were higher. Maternal complications increased twofold or more with high glucose concentrations and included concentration increased the risk of very preterm delivery almost 12-fold.[93] [94]

Prospective studies of pre-conception diabetes care have confirmed its positive impact on the incidence of malformations by improving glycaemic control. A pre-conception diabetes clinic may have a positive impact on neonatal morbidity. A systematic approach to pregnancy planning, avoiding unintended pregnancies through contraception, repeated emphasis by providers on the importance of pre-conception care and availability of pre-comprehensive diabetic management programme. [95] [96] [97]

Increased early pregnancy insulin resistance is independently associated with subsequent preeclampsia. First trimester SHBG levels may be a useful biomarker for pre-eclampsia, especially among lean women who otherwise would be perceived to be at low risk.[98] LBW was significantly associated with faster decrease in acute insulin response and increase in triglycerides with regard to age. The hyperbolic function between insulin sensitivity and β-cell function was retarded among children with LBW ($p<0.05$). In addition, there was a significant interaction between LBW and ethnicity in relation to fasting insulin ($p<0.05$) and visceral fat ($p<0.05$). LBW may predict the risk of the insulin resistance syndrome (IRS) and its progression over age in childhood, and this effect may be more pronounced among African-American children. [99] [100]

2.2.9 Gestational diabetes mellitus and reproductive outcomes:

Gestational diabetes mellitus occurs in 2 to 9 percent all pregnancies and is associated with substantial rates of maternal and perinatal complications. The rate of serious

perinatal outcomes among the infants (defined by one or more of the following: death, shoulder dystocia, bone fracture, and nerve palsy), was significantly lower in the intervention group than the routine-care group (1 percent vs. 4 percent; $p<0.01$, adjusted for maternal age, race or ethnic group, and parity. Significantly fewer infants in the intervention group were large for gestational age at birth, and significantly fewer had macrosomia (birth weight of 4 kg or greater). [101] [102] [103] The relationship between decreased maternal insulin sensitivity and fetal overgrowth particularly in obese women and women with gestational diabetes may help to explain the increased incidence of adolescent obesity and related glucose intolerance in the offspring. [104] [105] [106]

Gestational Diabetes indicated that increasing carbohydrate intolerance in women without GDM is associated with a graded increase in adverse maternal-fetal outcomes. Furthermore, IGT has been linked with increased rates of macrosomia, premature rupture of membranes, prematurity, breech presentation, and cesarian section.[107] [108] [109] Women with gestational diabetes mellitus (GDM) and their offspring are at increased risk of developing diabetes. Although increases in diabetes prevalence have been reported in the United States, it is unknown whether this trend is also occurring for GDM.[110] [111] Women with an early diagnosis of GDM, in the first half of pregnancy, represent a high-risk subgroup, with an increased incidence of obstetric complications, recurrent GDM in subsequent pregnancies, and future development of Type 2 diabetes. [112] [113] [114]

2.2.10 Maternal age, parity and reproductive outcomes

A comparison of pregnancy outcome was made on the basis of maternal age at delivery: 18-34 years, 35-40 years and women aged >40 years. Pregnant women aged 35-40 years were at increased risk of: gestational diabetes, placenta praevia; breech presentation; operative vaginal delivery; elective Caesarean section; emergency Caesarean section; postpartum haemorrhage; delivery before 32 weeks gestation; birth weight below the 5th centile; and stillbirth. Women aged >40 years had higher OR for the same risks. Pregnant women aged ≥35 years are at increased risk of complications in pregnancy compared with younger women. [115] [116] [117]

Meternal age influences the outcome of pregnancy and labour. Ten to fifteen percent of deliveries all over the world are from adolescent mothers. The adolescent age constitutes a high risk group of pregnancy when the maternal and foetal outcome is concerned. But early marriage is a prevailing custom in our country. As a result it has been found that abou.30 percent of adolescent girls are already mothers and another 6 percent is pregnant with their 1st child. Every year, 66 percent girls give birth before the age of 20 in Bangladesh.[118] Bangladesh has the highest proportion of girls under 20 years giving birth. A pregnant adolescent ''A child in a child'' has to meet the growing demands of her foetus in addition to her own demand, thus putting her in a stressful situation. She is at high risk and more vulnerable for complications. [118] [119]

2.3 Maternal nutrition (BMI) and reproductive outcomes

Diabetic mothers, who had LGA babies, had significantly higher pre-pregnancy body weight and BMI ($p<0.05$). [120] [121] [122] [123] There is strong epidemiological evidence of an association between maternal nutritional status, both during and prior to pregnancy (pre-pregnancy weight and weight gain during pregnancy), and birth weight and intrauterine growth retardation. Mothers with high parity are often more affected by malnutrition: as too many pregnancies or pregnancies too close together deplete the mother's stores and result in low birth weight babies.[1124] [125] Low birth weight babies have high morbidity and mortality rates especially in the first year of life. Malnourished mothers often fail to breast-feed their children successfully and hence there is a higher chance for the child to become malnourished due to early introduction of weaning of solid food. [126] [127] [128] [129] [130]

Maternal weight gain during pregnancy was not associated with risk of antepartum stillbirth. Maternal overweight condition increased the risk of antepartum stillbirth, especially term antepartum stillbirth, whereas weight gain during pregnancy was not associated with risk.[131] [132] [133] There is significant controversy as to whether or not stillbirth is increased in pregnancies prior to the onset of diabetes. An observed increase may be indicative of risks associated with untreated gestational diabetes. It is generally accepted that the risk of stillbirth in pregnancies that occur after the onset of diabetes has

been diminished by modern obstetric care. The risk of stillbirth was increased in both pre-diabetic and post-diabetic pregnancy.[134] The potential benefits of prenatal exercise include improved fitness, prevention of gestational diabetes, facilitation of labor, and reduced stress. Women whose occupations require prolonged standing, long working hours, and lifting heavy objects may be at a higher risk for delivering preterm or low birth weight infants. [135] [136] [137] [138]

A large number of epidemiological studies have demonstrated a direct relationship between birth weight and BMI attained in later life. The combination of lower birth weight and higher attained BMI is most strongly associated with later disease risk. [139] They faced with the seeming paradox of increased adiposity at both ends of the birth weight spectrum higher BMI with higher birth weight. Prevention of obesity starting in childhood is critical and can have lifelong, perhaps multigenerational. [140] [141] [142] [143]

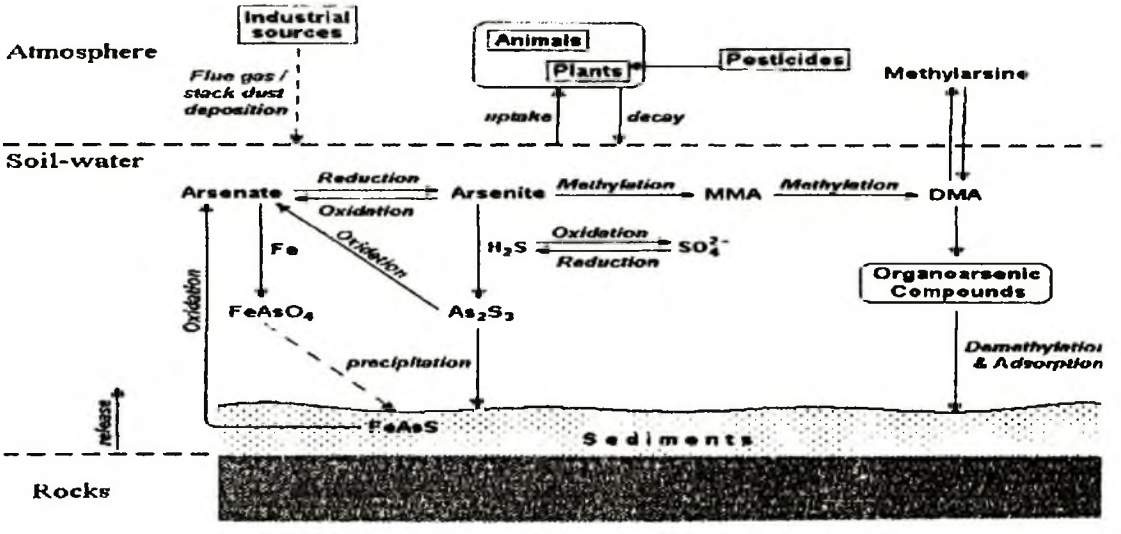
Maternal weight gain has been consistently linked to birth weight but, beyond maternal energy intake, no macronutrient has been associated with either of them. They have examined whether maternal energy-adjusted intake of macronutrients is associated with either maternal gain or birth-size parameters. Intake of neither energy nor any of the energy-generating nutrients was significantly associated with energy intake as energy adjusted intake of protein, lipids of animal origin and carbohydrates. Although maternal weight gain is strongly associated with size of the baby, the indicated nutritional associations with weight gain are not reflected in similar associations with birth-size parameters.[144] [145] [146] [147]

The nutrition situation of the growing children and pregnant and lactating women is very alarming in Bangladesh. Again 74 percent of the non-pregnant and nonlactating women were found to be anemic. Birth weight has now been accepted as an indirect indicator of nutritional status.[148] Birth weight is influenced by many factors, the most important of which is maternal nutrition during pregnancy. During pregnancy it is the mother who provides to the fetus with the nutrients necessary for its survival and development. Poor weight gain during gestation has been co-related to low birth weight. . [149] [150] [151]

2.4 *Natural sources and occurrence of arsenic:*

Arsenic is a naturally occurring ubiquitous element. It is an odorless, colorless, nearly tasteless element present in elemental, organic, and inorganic (trivalent and pentavalent) forms. The inorganic forms are more common sources of toxic exposure to arsenic, causing both acute and chronic effects on man, while the organic forms are generally thought to be much less toxic. The trivalent inorganic form of arsenic, arsenite [As (III)], and the pentavalent form, arsenate [As (V)], are both contaminants of groundwater and foods, but arsenite is the more toxic of the two. The mechanism of toxicity is uncertain, but generation of free radicals or interference in the glutathione pathway causing oxidative stress has been hypothesized. In nature, arsenic is frequently found in combination with other elements like sulfur, oxygen, and iron. The most common existing forms are orpiment (As2S3), realgar (AsS), arsenopyrite (FeAsS), arsenolite (As2O3) and lollingite (FeA+S2). These arsenic compounds commonly occur in gold, silver, copper, lead, zinc, cobalt, and tin ores. Smelting of these compounds can release large quantities of arsenic into the environment, causing unrecognized contamination of the surrounding air, water, soil, and vegetation.[152]

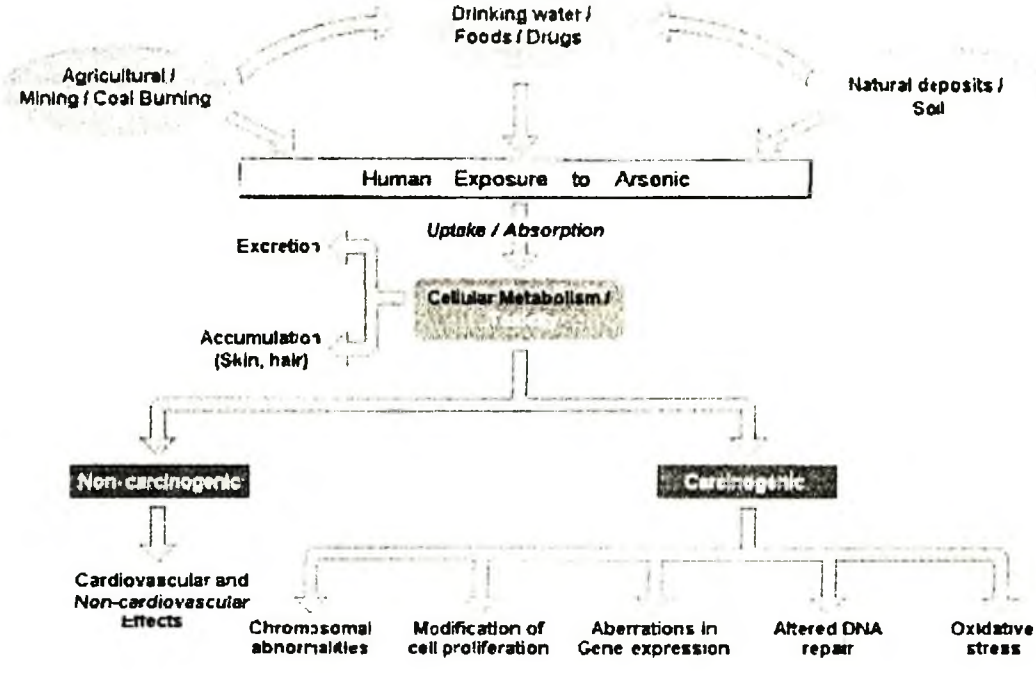
Arsenic cycle in the environment:



Inorganic arsenic is considered the most potential human carcinogen, and humans are exposed to it from soil, water, air and food. In the process of arsenic metabolism, inorganic arsenic is methylated to monomethyl arsenic acid and finally to dimethyl

arsenic acid, followed by excretion through urine. Thus, arsenic exposure may cause DNA hypomethylation due to continuous methyl depletion, facilitating aberrant gene expression that result in carcinogenesis. Further, though arsenic is non-mutagenic, it interacts synergistically with genotoxic agents in the production of mutations, and also induces chromosome abnormalities and cell proliferation. Few epidemiological investigations in the arsenic endemic regions of West Bengal (India) have established that inorganic arsenicals have the potential to cause skin and lung cancers in humans. [153]

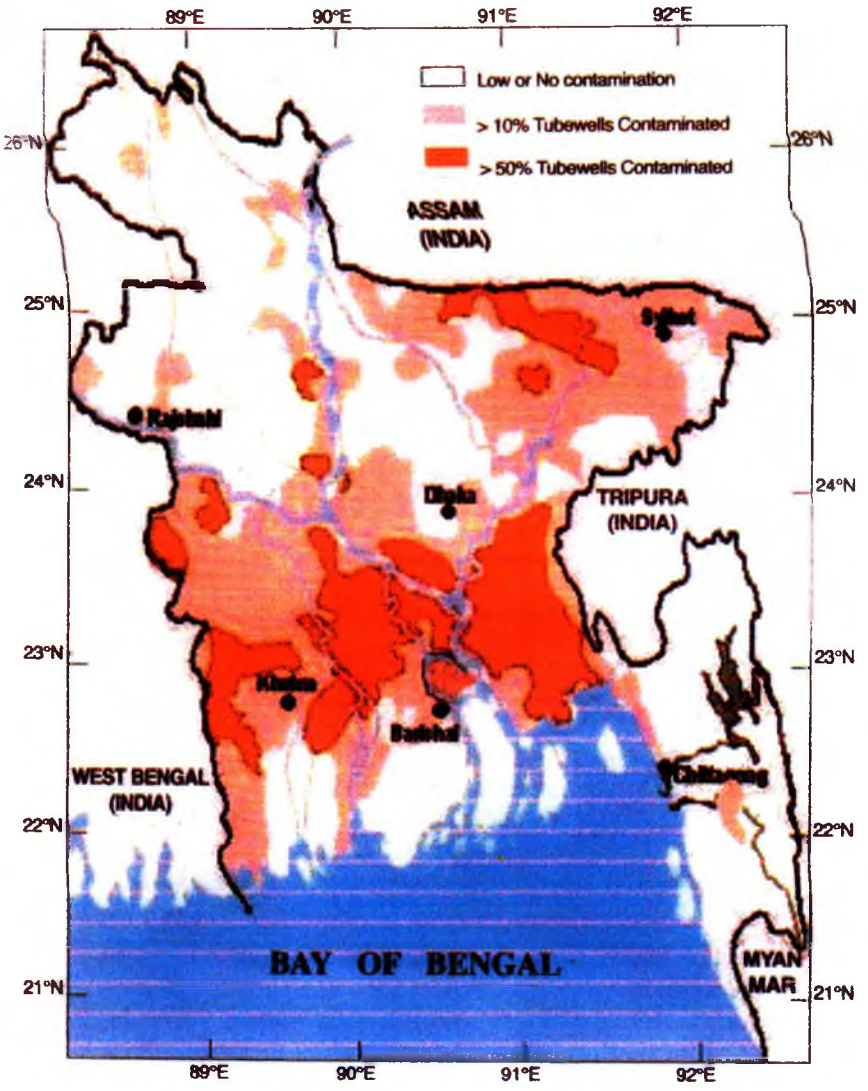
Sources of human exposure to arsenic and various modes of arsenic toxicity:



Sources of human exposure to arsenic and various modes of arsenic toxicity. Adapted from Azcue and Nriagu [1], Phillips [5] and Goering et al.

2.4.1 Global overview

Arsenic is the king of poisons and has plagued human being since the days of antiquity. Arsenic is both a cause of large scale environmental contamination and a serious health hazard. Many incidents of arsenic contamination in the environment and cases of victims are reported from various countries of the world. [154] Chronic arsenic poisoning due to contaminated ground water, which is a major source of drinking water, is an important



Arsenic contaminated areas in Bangladesh

form of xenobiotic insult, which has assumed worldwide importance over the past three decades. One of the worst afflicted areas is south-east Asia, mainly Gangetic West Bengal and Bangladesh, where contaminated shallow tube well water is responsible for the problem. [155]

Reliable data on exposure and health effects are rarely available, but it is clear that there are many countries in the world where arsenic in drinking water has been detected at concentration greater than the Guideline Value, 0.01 mg/L or the prevailing national standard. These include Argentina, Australia, Bangladesh, Chile, China, Hungary, India, Mexico, Peru, Thailand, and the United States of America. Countries where adverse health effects have been documented include Bangladesh, China, India (West Bengal), and the United States of America. [156]

Worldwide occurrences of arsenic contamination in water: [157]

Location	Potential exposed Population	Concentration (µg/L)	Environmental conditions	Source
Argentina	2,000,000	1-2,900	Natural; volcanic rocks and thermal spring	Groundwater
Bangladesh	>290,000,000	1-4.730	Natural, alluvia	Groundwater
Bolivia	50,000	-	Natural and anthropogenic	Surface water
China	>500	40-750	Natural; alluvial sediments	Groundwater
Chile	500,000	100-1,000	Natural and anthropogenic; basin lakes, thermal springs, mining	Surface water
Greece	150,000	-	Natural and anthropogenic; thermal springs and mining	Surface water
Hungary, Rumania	400,000	2-176	Natural; alluvial sediments; organics	Surface water
Inner Mongolia	>400,000	1-2,400	Natural; alluvial and lake sediments; high alkalinity	Groundwater
Mexico	400,000	8-620	Natural and anthropogenic; Volcanic sediments, mining	Surface water and Groundwater

Nepal	-	-	Natural, alluvia	Groundwater
Spain	>50,000	1-100	Natural; alluvial sediments	Surface water
Thailand	15,000	1-5,000	Anthropogenic, mining	Groundwater
Taiwan	>100,000	1-1.820	Natural	Groundwater
Vietnam	>1,000,000	1-3,050	Natural, alluvia	Groundwater
West Bengal, India	>1,000,000	10-3,880	Natural, alluvia	Groundwater

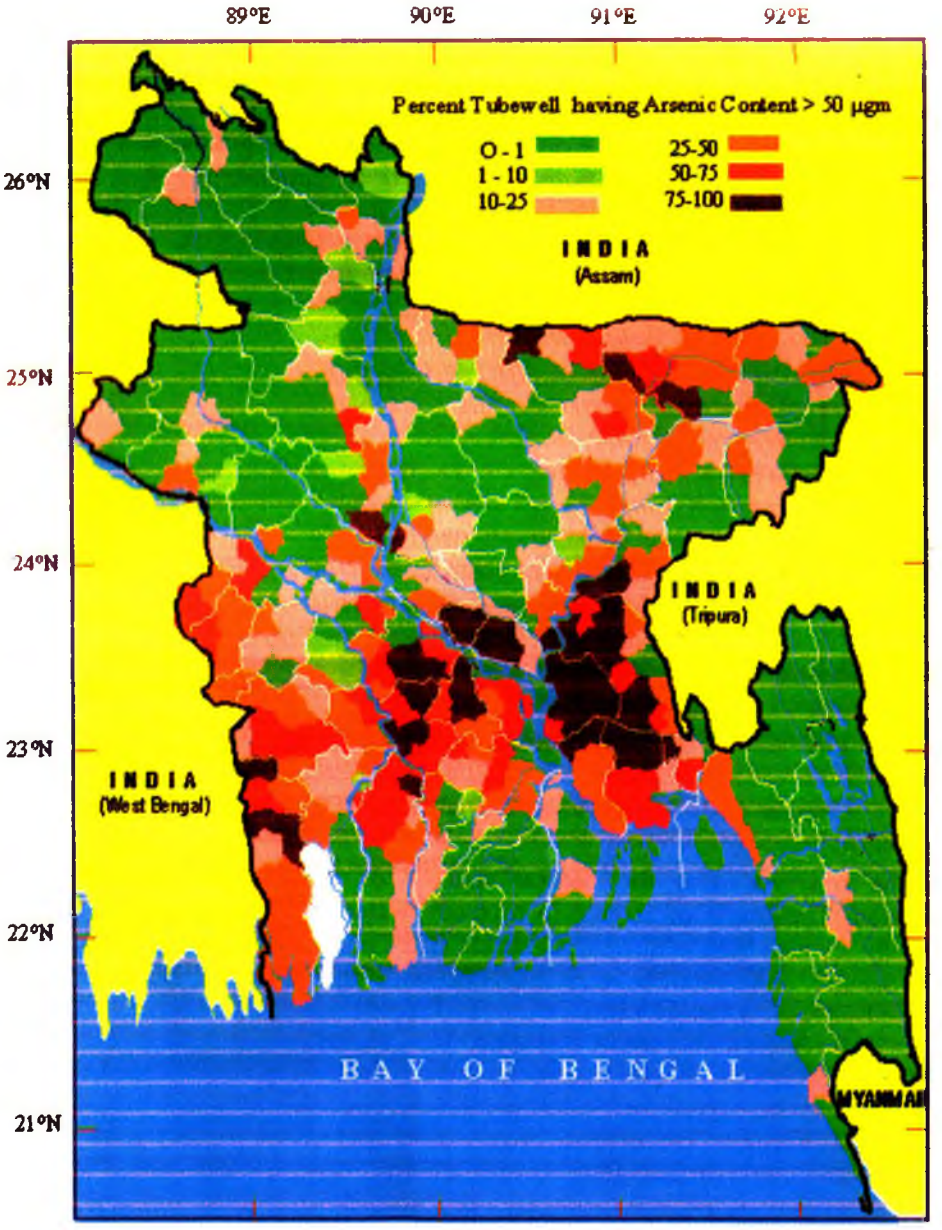
2.4.2 SEAR Countries and Bangladesh:

Globally, arsenic contamination in drinking water is a major public health issue. Groundwater is a major source of drinking water in many part of the world, especially the South East Asia Region Countries (SEAR). Arsenic contamination of groundwater has been reported in many SEAR countries including Bangladesh and India (Chatterjee et al., 1995; Ahmad, 2001; Shraim et al., 2002), Vietnam (Berg et al., 2001), Nepal (Tandukar and Neku, 2002), Taiwan (Chen et al., 1999), and PR China (Wang et al., 1993; Guo et al., 2001; Lin et al., 2002), where arsenic is from a natural source. [158]

Arsenic containing sediments and percolation of chemicals into soil as the result of dumping of garbage rich in chemicals into open landfills could be the possible source of arsenic in ground water of Delhi. Extensive survey and continuous monitoring is required to be made to assess the magnitude of problem and earlier intervention. Groundwater contamination with arsenic is a worldwide concern. The World Health Organization has identified many regions with groundwater levels of arsenic that greatly exceed the limit of 50 micrograms per liter. As many as 42 million people in 9 out of 18 districts in West Bengal, India are exposed to high arsenic levels in their water supply (there are some reports of arsenic levels as high as 3 milligrams per liter. [159]

2.5 Physical and chemical properties of arsenic

Arsenic is a metalloid widely distributed in the earth's crust and present in an average concentration of 2 mg per kg. It occurs in trace quantities in all rock, soil, water, and air. Arsenic can exist in four valency states: -3, 0, +3 and +5. Under reducing conditions,



Intensity of arsenic contaminated (>50 ug/L) tubewells in Bangladesh

arsenite (AsIII is the dominant form; arsenate (AsV) is generally the stable form in oxygenated environments. Elemental arsenic is not soluble in water. Arsenic salts exhibit a wide range of solubilities depending on PH and the ionic environment. Arsenic is present in more than 200 mineral species, the most common of which is arsenopyrite. It has ben estimated thatabout one third of the atmospheric flux of arsenic is of natural origin. Volcanic action is the most important natural source of arsenic, followed by low temperature voltalization. Inorganic arsenic of geological origin is found in ground water used as drinking water in several parts of the world including Bangladesh. [160]

2.6 Environmental level and human exposure of arsenic

Studies of populations outside the US exposed to arsenic in drinking water show increases in cancer only at relatively high concentrations, that is, concentrations in drinking water of several hundred micrograms per liter. Studies in the US of populations exposed to average concentrations in drinking water up to about 190 µg/l do not provide evidence of increased cancer. Consideration of arsenic's plausible mechanisms and evidence from epidemiological studies support the use of nonlinear methods, either via biologically based modeling or use of a margin-of-exposure analysis, to characterize arsenic risks. [161]

The British Geological Survey in 2001 estimated that 46% of all shallow tube wells in Bangladesh contained arsenic at concentrations exceeding the World Health Organization's guideline concentration of 0.01 mg/litre. An estimated 28-35 million people were thought to be exposed to arsenic in their drinking water at concentrations exceeding even Bangladesh's arsenic standard of 0.05 mg/litre. Many thousands of cases of chronic arsenic poisoning have now been identified, but the real magnitude of the health impact is still undefined. Doctors have a vital role both in the diagnosis and management of arsenicosis and in the mitigation of this major public health threat through educating their patients about options open to them to avoid the health effects of chronic poisoning. [162]

Bangladesh is located in the midst of one of the world's largest river systems. Although this vast amount of water provides a living for almost 1/3 of the country's population, the

water quality is poor and the abundance of this water does little to meet the drinking needs of the people. Hence, drinking water in Bangladesh is not largely a river based water purification system but instead, the most crucial source of drinking water remains groundwater. However, the discovery of "Arsenic" in groundwater in several areas of Bangladesh has aroused widespread concern from the last couple of years. The arsenic crisis in Bangladesh has been called the worst environmental catastrophe of the twentieth century. Arsenic contamination of groundwater in Bangladesh is widely accepted to be of geological origin, though the exact mechanisms remain poorly understood. Arsenic occurs in different forms, organic and inorganic, with different toxicity. Humans get affected by arsenic mainly through ingestion and probably the nutritional status is important in relation to the development of arsenicosis. [163]

2.7 Elimination of arsenic from the body:

Inorganic arsenic (In-As) is a well-known toxicant and carcinogen found naturally in surface and groundwater around the world. Exposure can cause skin lesions, adverse reproductive outcomes, and cancer. There are two main pathways of arsenic (As) metabolism in humans: the reduction reactions, and the oxidative methylation reactions, where methyl groups are attached to As compounds to form monomethyl arsenate (MMA) and dimethyl arsenate (DMA). MMA, DMA, and In-As are excreted in urine. Urinary levels of another metalloid, selenium (Se), have recently been shown to be associated with increased As excretion and altered metabolite distribution. Urinary Se levels were found to be correlated with urinary As levels in bivariate analysis ($r=0.68$, $p<0.01$).[146] Research results suggest that total arsenic in toenails is a reliable biomarker of As exposure, which correlates with As concentrations in drinking water. Toenails are easier to collect and store than other biomarkers, and there is a lower risk of external contamination with toenails than with hair and fingernails. Two studies also found good reproducibility between toenail TAs concentrations collected from patients 3-6 years apart suggesting that TAs in nails may be representative of long-term exposure (Garland et al., 1993; Karagas et al., 2001a). [164]

Arsenic exposure was estimated through water intake over 24 h. Arsenic excretion was assessed in the first morning void urine. Total arsenic concentrations and their species arsenate (As V), arsenite (As III), monomethyl arsenic (MMA), and dimethyl arsenic (DMA) were determined by HPLC/ICP-MS. Positive correlation between total arsenic intake by drinking water/day and the total arsenic concentration in urine ($r=0.50$, $p<0.001$) was found. There was a moderate correlation between arsenic exposure and urinary excretion of arsenic. There was considerable variation in metabolism of arsenic in the groups. These variations in metabolism could be attributed to polymorphisms of the methylation enzymes [165]

The study examined the associations between drinking water and urinary arsenic levels and skin lesions among residents of three contiguous villages in Bangladesh. The risk for skin lesions in relation to the exposure estimates based on urinary arsenic was elevated more than 3-fold, with the odds ratios for the highest versus the lowest quartiles being 3.6 (95% confidence interval, 1.2 to 12.1) for urinary total arsenic and 3.2 (95% confidence interval, 1.1 to 10.0) for urinary creatinine-adjusted total arsenic. The study suggests that arsenic exposure is associated with skin lesions in the Bangladesh population and that urinary arsenic may be a stronger predictor of skin lesions than arsenic in drinking water in this population. [166]

2.8 Placental transfer of arsenic:

Case reports of arsenic poisoning in pregnant women resulting in death of the fetus accompanied by toxic levels of arsenic in fetal organs and tissues demonstrate that arsenite (As_2O_3) readily passes through the placenta (Lugo et al. 1969; Bollinger et al. 1992). In a more recent study, Concha et al. (1998) reported that arsenic concentrations were similar in cord blood and maternal blood (~9μg/liter) of maternal-infant pairs exposed to drinking water containing high levels of arsenic (~200μg/liter). Another study of an unexposed population in the southern USA found that concentrations of arsenic in cord blood and maternal blood about (2μg/liter) were also similar, and suggests that arsenic readily crosses the placenta (Kagey et al. 1977).[167]

2.9 *Exposure of arsenic:*

Millions of people around the world are exposed to low doses of arsenic through drinking water. However, estimates of health effects associated with low-dose arsenic exposure have been extrapolated from high-dose studies. In Bangladesh, many persons have been exposed to a wide range of doses of arsenic from drinking water over a significant period of time. The researcher evaluated dose-response relations between arsenic exposure from drinking water and premalignant skin lesions by using baseline data. The effect seemed to be influenced by gender, age, and body mass index. This study reports a strong dose-response effect of arsenic exposure on skin lesion risk in Bangladesh. There was an increased risk even among the population consuming water containing less than 50μg/liter or arsenic-the currently permissible limit in Bangladesh and other countries, and in the United States until very recently. [168]

Women had significantly higher cumulative exposure to arsenic, while men had significantly higher prevalence of skin lesions (SMR 158, 95% CI 133 to 188). The highest prevalence occurred in 35-44 age groups for both sexes. Arsenic exposure and skin lesions had a positive association with socioeconomic groups and achieved educational level. The result showed sex, age, and socioeconomic differentials in both exposure and skin lesions. In the study, the highest prevalence of skin lesions was found among people 25-54 years of age, with a peak at 35-44 years. On average, those people had been using tube-well water for about 20 years. [169]

As skin manifestations are sensitive markers of arsenicosis, they examined the skin of adults and adolescents in two villages to elucidate the severity of arsenicosis. Three indicators, i.e. keratosis on the soles, keratosis on the palms, and melanosis and hypo-pigmentation on the trunk, were quantified for analysis. More than 50% of the villagers showed some skin manifestations due to arsenicosis. Keratosis on the soles was the most sensitive marker for the detection of arsenicosis at an early stage. Interestingly, the skin manifestations were more severe in males than in females. There was no correlation between the age and the severity of skin manifestations. Using skin manifestations, especially keratosis on the soles, as useful markers to detect and evaluate arsenicosis. [170]

The health effects of arsenic poisoning and to determine the relationship among duration and severity of skin lesions, exposure dose of arsenic, and nutritional status of people. The mean arsenic concentration in water was significantly associated with the severity of disease. Body mass index correlated inversely ($r=0.298$, $p<0.01$) with the duration of disease after controlling for age. The findings suggest the need to enhance public awareness on negative health effects of arsenic poisoning in rural Bangladesh. From a public-health perspective, effective intervention strategies need to be developed to curb the exposure, strengthen rapid diagnostic facilities, establish effective treatment facilities in rural areas, and improve the nutritional status of people. [171]

2.10 Reproductive toxicity of arsenic:

Chronic exposure to inorganic arsenic from drinking water is associated with different health effects, including skin, lung, bladder, and kidney cancer as well as vascular and possibly reproductive effects. In-As is metabolized through the process of methylation, resulting in the production and excretion of methylated species, mainly monomethyl arsenate (MMA) and dimethyl arsenate (DMA). Because a large percentage of the dose is excreted in urine, the distribution of urinary In-As, MMA, and DMA is considered a useful indicator of methylation patterns in human populations. Several factors affect these patterns, including sex and exposure level. The total urinary arsenic increased with increasing weeks of gestation. This increase was mainly due to an increase in DMA, resulting in lower percentages of In-As and MMA and a higher percentage of DMA. The findings indicate that among women exposed to moderate arsenic from drinking water during pregnancy, changes occur in the pattern of urinary arsenic excretion and metabolite distribution. The toxicologic significance of this effect is not clear. Nevertheless, the study suggests that arsenic metabolism changes throughout the course of pregnancy, which in turn may have toxicologic effects on the developing fetus.[172]

2.10.1 Embryogenecity:

Although arsenic is a well-established human carcinogen, the underlying carcinogenic mechanism(s) is not known. The effects of free radical scavenging enzymes on the cytotoxic and mutagenic potential of arsenic were examined using the A_L cells.

Concurrent treatment of cells with either superoxide dismutase or catalase reduced both the cytotoxicity and mutagenicity of arsenite by an average of 2–3 fold, respectively. Using immunoperoxidase staining with a monoclonal antibody specific for 8-hydroxy-2′-deoxyguanosine (8-HDG), They demonstrated that arsenic induced oxidative DNA damage in A_L cells. This induction was significantly reduced in the presence of the antioxidant enzymes. Furthermore, reducing the intracellular levels of non-protein sulfhydryds (mainly glutathione) using buthionine S-R-Sulfoximine increased the total mutant yield by more than 3-fold as well as the proportion of mutants with multilocus deletions. Taken together, data provide clear evidence that reactive oxygen species play an important causal role in the genotoxicity of arsenic in mammalian cells. Arsenic was found to affect the T cell sub population [173]

2.10.2 Teratogenicity:

Arsenic (inorganic oxides) were listed under Proposition 65 as known to the state to cause reproductive toxicity (developmental toxicity). For purposes of Proposition 65, arsenic (As) oxides include arsenate and arsenite salts, arsenic trioxide, arsenic pentoxide, arsenic acid, arsenous acid and other arsenic compounds that dissociate to the oxyanion species. The Proposition 65 listing of arsenic (inorganic oxides) was based on a finding by the Developmental and Reproductive Toxicant (DART) Identification Committee, the Proposition 65 State's qualified experts for reproductive toxicity, that the chemicals had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental toxicity. As part of its deliberations, the Committee was provided with the document "Evidence on Developmental and Reproductive Toxicity of Arsenic," [174]

2.11 Arsenicosis and diabetes mellitus (type 2)

Although a relationship between ingested arsenic and diabetes mellitus and hypertension has so far only been reported in a limited number of studies from Taiwan, Sweden and now in Bangladesh (Lai et al., 1994; Chen et al., 1995; Rahman and Axelson, 1995; Rahman et al., 1996a,b), it appears likely that there is a causal relationship. Nonetheless,

the strength of the current findings in terms of the high prevalence ratios, along with the plausibility of finding corresponding from Taiwan, that diabetes mellitus and hypertension are effects that may indeed result from ingestion of inorganic arsenic. However, the mechanism underlying the ability of inorganic arsenic to induce these disorders is still unclear. Various sources of exposure should be taken into consideration in further investigations of the indicated effects of arsenic. [175]

Diabetes prevalence in arseniasis hyperendemic villages in Taiwan has been reported to be significantly higher than in the general population. The findings are consistent with their previous cross-sectional observation that ingested inorganic arsenic is diabetogenic in human beings. [176] Data from a previous study on arsenic exposure and mortality at a copper smelter in Sweden were reexamined to investigate a possible association between diabetes mellitus and arsenic exposure. The authors conclude that the findings of this study provide some support for the suggestion that arsenic exposure could be an important factor in the development of diabetes mellitus. [177]

According to the Environmental Protection Agency (EPA), exposure to low concentrations of arsenic over many years can leads to diabetes, anemia, reproductive disorders, and cancers of the skin, bladder, lungs, and prostate. The current congressional standard for the presence of arsenic in water is limited to no more than 50 parts per billion. However, the EPA hopes to lower this standard to no more than 5 parts per billion. This information is particularly timely in light of recent research into the correlation between arsenic intake and the development of diabetes in populations in Argentina, Bangladesh, India, Mexico, Thailand, and Taiwan. [178]

In Bangladesh, a large part of the population has been drinking water contaminated with arsenic at concentrations >0.05 mg/l. The study assessed whether arsenic exposure is a risk factor for diabetes mellitus as indicated in a few earlier studies. Arsenic in drinking water is known to occur in Bangladesh, and in 1996, two of the authors conducted a survey of the prevalence of diabetes mellitus among subjects with keratosis taken as exposed to arsenic and unexposed individuals. Diabetes mellitus was determined by history of symptoms, previously diagnosed diabetes, glucosuria, and blood sugar level after glucose intake. The crude prevalence ratio for diabetes mellitus among keratotic

subjects exposed to arsenic was 4.4 (95% confidence interval 2.5–7.7) and increased to 5.2 (95% confidence interval 2.5-10.5) after adjustment for age, sex, and body mass index. The result corroborates earlier studies and suggests that arsenic exposure is a risk factor for diabetes mellitus. [179]

2.12 Nutritional and other risk factors of arsenicosis:

The nutritional status of the subject, which may modify the toxicity of certain environmental chemicals. In fact, in the West Bengal study mentioned, it was suggested that malnourished individuals, having less than 80% of the standard body weight, were more susceptible to chronic arsenic toxicity. The impact of a malnourished status on arsenic toxicity in the present subjects was not clear. It has been repeatedly suggested that the deficiency of certain trace elements may affect the manifestations of As toxicity in human populations, especially in developing countries where inadequate nutrient supply is more likely. Despite such a suggestion, has no status of arsenic-affected populations in developing countries. Arsenic as a preliminary step for elucidating the potential role of trace elements in chronic As toxicity, they have determined the urinary levels of selenium (Se) and iodine. [180]

There has been widespread speculation about whether nutritional deficiencies increase the susceptibility to arsenic health effects. The study was conducted in West Bengal, India, which along with Bangladesh constitutes the largest population in the world exposed to arsenic from drinking water to investigate whether dietary micronutrient and macronutrient intake modulates the well-established human risk of arsenic-induced skin lesions, including alterations in skin pigmentation and keratoses. Conditional logistic regression suggested that the strongest associations were with low calcium, low animal protein, low folate, and low fiber intake. Nutrient intake was not related to arsenic exposure. They conclude that low intake of calcium, animal protein, folate, and fiber may increase susceptibility to arsenic-caused skin lesions. [181]

The evidence that poor nutritional status may increase in individual's susceptibility to chronic arsenic toxicity, or alternatively that arsenicosis may contribute to poor nutritional status. The role of nutritional factors on arsenic metabolism and toxicity is not

clear. Limited studies have indicated that poor nutritional status may increase the risk of arsenic related health effects. Overall, increase in the prevalence of keratoses, suggesting that malnutrition may increase the susceptibility for arsenic toxicity (Mazumder et al. 1998). Thus, a high proportion of individuals are likely to be deficient in energy, protein and micronutrients, which may affect their susceptibility to arsenicosis. [182]

2.13 Effects of arsenic on human health:

The first population based study considering the different patterns of skin lesions in Bangladesh concludes that men had a higher risk of developing melanosis or keratosis than women. [183] Melanosis was common (97%) among patients but about two-thirds (68.7%) of the patients were suffering from keratosis. Melanosis was significantly associated with younger patients. Keratosis was also significantly associated with older age. Duration of arsenic symptoms was significantly associated with older age. Marital status was significantly associated with keratosis and longer duration of arsenic symptoms. Mazumder et al. (1998) found that older age was relatively higher risk of keratosis. Duration of consuming tube-well water was also significantly higher for married person as compared to single. After adjusting the effect of and duration of consuming tube-well water on duration of arsenic symptoms, they found that the skin manifestations were more severe in males than in females.[184]

The overall prevalence of skin cancer was as high as 6.1%, showing an increase with age in both men and women. There was a significant dose-response relation between skin cancer prevalence and chronic arsenic exposure as indexed by duration of residence in the endemic area, duration of consumption of high-arsenic artesian well water, average arsenic exposure in parts per million (ppm) and cumulative arsenic exposure in p.p.m.-years. Undernourishment, indexed by a high consumption of dried sweet potato as a staple food, was also significantly associated with an increased prevalence of arsenic-induced skin cancer. All these risk factors remained statistically significant in the multiple logistic regression analysis. Consistent with animal experiments, the findings imply that liver function and nutritional status may affect the metabolism of inorganic arsenic and the development of subsequent skin cancers. [185]

Arsenic-an antidote to a Global Poison. Through the centuries, this "king of poisons" was a common means of homicide. And yet, no toxicologist would deny that chronic arsenic exposure places people at risk for a host of adverse health effects, from skin and internal cancers (of the bladder, kidney, liver, lung, colon, uterus, prostate, and stomach) to diabetes mellitus and vascular, reproductive, developmental, and neurological effects. Studies have shown arsenic to be a potent endocrine disruptor, altering hormone-mediated cell signaling at extremely low concentrations. [186]

2.14 Arsenicosis and reproductive outcomes:

Chronic arsenic exposure has been associated with a range of neurologic, vascular, dermatologic, and carcinogenic effects. However, limited research has been directed at the association of arsenic exposure and human reproductive health outcomes. The data indicate an elevation of the late fetal, neonatal, and post-neonatal mortality rates for specific time periods, which generally coincide with the period of highest arsenic concentration in the drinking water. The findings from this investigation may support a role for arsenic exposure in increasing the risk of late fetal and infant mortality. [187]

To identify the pregnancy outcomes, A group of women of reproductive age (15-49 years) who were chronically exposed to arsenic through drinking water and compared pregnancy outcomes of women of reproductive age (15-49 years) who were not exposed to arsenic-contaminated water. Adverse pregnancy outcomes in terms of spontaneous abortion, stillbirth, and preterm birth rates were significantly higher in the exposed group than those in the nonexposed group ($p<0.005$, $p<0.005$, and $p<0.005$, respectively). As revealed in this study, contamination is also a threat to healthy and safe pregnancy outcomes.[188]

Delivery outcome was compared between different municipalities arranged according to the degree of arsenic pollution. Congenital malformations observed at birth or during the first week of life, a significantly high odds ratio for stillbirths is seen for arsenic. Only a limited number of exposures has been studied and other pollutants and other pregnancy outcomes, e.g., miscarriages, may be of importance. In spite of this, clear correlation

between outcome and arsenic exposure and mortality could be of some biological significance.[189] Epidemiological studies have pointed to the existence of other non-cancer health effects are noted as well, such as spontaneous abortions and stillbirths. These inferences may or may not be proven, due to lack of adequate epidemiological data relating to their prevalence. [190]

2.15 Social aspect of arsenic crisis:

Women are significantly more likely than men to think that arsenic related disease is hereditary or contagious. This idea in itself, of course, has powerful implications for marriage arrangement and other social relationships, as whole families might be stigmatized by the arsenic related illness of one or more members.[191] Besides its toxicity, groundwater arsenic contamination creates widespread social problems for its victims and their families in Bangladesh. There is, for instance, a tendency to ostracise arsenic-affected people, arsenicosis being thought of as a contagious disease. Within the community, arsenic-affected people are barred from social activities and often face rejection, even by their immediate family members. Women with visible arsenicosis symptoms are unable to get married and some affected housewives are divorced by their husbands. Children with symptoms are not sent to school in an effort to hide the problem. They found that patients' experiences reveal severe negative social impacts. This involves living with social uncertainty, social injustice, social isolation and problematic family issues. [192]

The prevalence of arsenicosis was associated with age, sex, education and the economic status of the household. Multivariate analysis identified age and economic status as significant predictors of arsenicosis controlling for education and gender. A clear understanding of the socio-economic distribution of arsenicosis in different demographic and socio-economic groups will be useful in identifying the high-risk groups from arsenic-affected communities. This research has indicated the potential health effects of arsenic poisoning in a poor rural community. The estimated prevalence clearly indicates that arsenicosis has already become a serious public health threat in the affected communities.[193]

2.16 Conclusions:

This chapter has attempted to provide a comprehensive review the factors known to be associated with arsenicosis, non-arsenicosis, diabetes mellitus and their reproductive outcomes and there is consistence evidence that those with national and international findings. The adverse reproductive outcomes among arsenic exposed and non-exposed groups were identified and compared. The international maternal and fetal mortality and morbidity of adverse pregnancy outcomes can be justified by considering the effect of arsenic exposure and diabetes mellitus. There are also other factors that have a different impact on reproductive outcomes.

There is a lack of clarity amongst the term used in the associated research fields and there is a range of challenge is a common theme, although the research can also take place with different settings, objectives, and emphasis. The research findings has led to questioning of whether these research still achieve the study objectives. Research undertaken in the field of arsenicosis and has been limited to mainly focusing on reproductive outcomes but need has been identified to undertake research that links reproductive outcomes, chronic exposure of arsenic and prevalence of diabetes mellitus. The studies with data on exposure of arsenic and reproductive outcomes are inadequate to fully achieving the contribution of chronic exposure of arsenic in drinking water and adverse pregnancy outcomes and other risk factors influences the adverse reproductive outcomes is the main goal of this research project.

CHAPTER-3

METHODS AND MATERIALS

Chapter-3

Methods and Materials

3.1 Introduction:

In this chapter we shall discuss the research design, data, methods and materials that are being used in this study. We first formulate the research hypothesis and the research objectives which have already been detailed in the introduction to this thesis (chapter-1) that guide us to complete every steps of research effectively. These are reproduced here to throw some light on the material and methods developed for quantitative and qualitative research. This chapter divided into 27 broad sections. In section 3.5 we discussed the reasons for selecting the study areas were purposive due to well established highly arsenic endemic areas in Bangladesh. Pre-tested semi-structured interview questionnaire (3.14) were used for data collection which was valid and reliable. We organized both human and material resources for data collection in the most efficient way (3.16) and we could minimize errors and delays (3.23). The findings of this study presented and interpreted (3.22) with recognition of its limitations (3.26). Ensuring quality of data (3.24), checked and verification started from the field followed by subsequent steps of analysis and interpretation. This chapter closes with a discussion of the conclusion (3.27).

3.2 Justification for the paradigm and methodology:

Justification for the methodology in terms of research problem, our research background in this regard and the literature review on previous research and our world view provides supportive evidence between arsenic in drinking water exposure and adverse reproductive outcome. However, We designed a cross sectional comparative study as the main methodology reflected the use of both quantitative and qualitative approaches. The nature of this research showing the strengths and weakness of research process and phenomological

paradigm as a basis for discussing choice of methodology used. Some quantitative and qualitative analysis was undertaken using statistical z-tests, chi-square tests, Correlation coefficient, ANOVA, multiple logistic regression for qualitative and linear regression for both qualitative and quantitative analysis comparing prevalence of diabetes mellitus and difference in pregnancy outcome of arsenic exposed and nonexposed mother.

3.3 Study Design:

The cross sectional comparative study was carried out to compare the prevalence of diabetes mellitus among mother of reproductive ages (15-49 years) having arsenicosis and non-arsenicosis living in areas with and those without exposure to arsenic in drinking water. The prevalence of diabetes mellitus and their reproductive outcome of these groups were compared along with their socio-demographic characteristics.

3.4 Study Period:

A total period of four and a half years started from May 2003 to October 2007.

3.5 Study areas:

Four upazillas of two districts were selected on the basis of survey of arsenic found in drinking water. Laksham and Muradnagar of Comilla district situated nearly 150 km south-east of Dhaka city. Selection of these areas were purposive due to well established highly arsenic endemic areas in Bangladesh. These study places were suitable because of proper contrast of exposure within the study places. Most of the tube-wells in the study places were known to have arsenic concentrations of >0.05mg/l. Dhunat of Bogra district located about 200 km north-west of Dhaka city and Trisal of Mymensingh district situated nearly 100 km north of Dhaka city were selected as arsenic free areas of Bangladesh and matched with the characteristics of arsenic exposed and nonexposed groups.

3.6 Study Population:

Mother of reproductive age (15-49 years) who previously had at least one outcome of pregnancy and who had lived in the study places throughout their lifetime and who had used

the same tube-well water for more than 2 years as long as it had been existed were considered as study population.

3.7 Sample Size Calculation:

The sample size calculated on the basis of assumption. The formula for calculating the sample size depends on the types of outcome (dependent variable), the design of the study and the results of previous study. The sample size has been calculated using the formula given by scientist Bland (2000): [161]

$$n = \frac{f(\alpha,p)p_1(1-p) + p_2(1-p_2))}{(p_1-p_2)^2}$$

where:

n = desired sample size, are equal for both case and control

p_1 = 0.05. Average prevalence rate in arsenic exposed area of arsenicosis patients given by (Ahmed et al. (1999) 10 percent of which 0.05 percent men and 0.05 percent women. That is $p_1 = 0.05$

p_2 = 0.01. Prevalence rate in non-exposed areas (arsenic free area) indicated by p is unknown. So the prevalence rate p_2=0.01 is taken hypothetically.

P = 90 percent (power of the test statistic

α = 0.05 (level of significance)

α,p = 10.5 (Bland (2000) have shown that (α,p)=10.5 when P= 90 percent and α= 0.05.

n = 377 (we took 400)

We have tested the difference between three sub samples (two in exposed and another non-exposed) regarding a proportion and can assume an equal number of cases ($n^1 + n^2 + n^3 = n$) in three sub sample. So we took 400 arsenicosis and 400 non-arsenicosis from exposed group and 400 from nonexosed group. Thus the total sample size 1200 mother were investigated.

3.8 Procedure of Selection of Sample:

According to nature and purpose of the study the study population was divided into two groups-exposed and nonexposed. The exposed group was further categorized into arsenicosis

and non-arsenicosis subgroups. Selection of sample was purposive and the sample collected from all mothers during study period who met the eligible criteria. To eliminate the selection bias, the investigator had no control over allocation of participants. Every individual would be the representative of reference population and characteristics related with variables to generalize the findings of the study to reference population.

Group-A (Arsenicosis):

Mother from selected sample during ecological survey conducted by UNICEF, Community Hospital, DPHE, WHO, British Geological Survey and other investigator diagnosed as arsenicosis mothers who were exposed to arsenic contaminated drinking water (>0.05mg/l) for at least more than 2 years and had clinical manifestations of arsenicosis.

Group-B (Nonarsenicosis):

Controls would be selected in an appropriate manner. Mothers who were exposed to arsenic contaminated drinking water (>0.05mg/l) for at least >2 years but without any clinical manifestations of arsenicosis.

Group-C (Nonexposed):

Mothers who were not exposed to arsenic contaminated water above recommended limit >0.02mg/l and without having arsenicosis manifestations would be treated as control.

Arsenicosis mother were enrolled to ensure definite arsenic exposure and concentration of arsenic in that particular tube-well water were examined through UNICEF provided arsenic measuring kit. The sample reasonably represents a homogenous mixture according to population characteristics would be the rural population in context of Bangladesh. The subjects in control group-1 (non-arsenicosis) and control group-2 (non-exposed group) were matched for age, parity, education, age of marriage and socio-economic status (SES). We enlisted the individuals fulfilling the criteria for inclusion in the study through house to house visits. Mothers were enrolled after providing informed consent and receiving an explanation of the purpose and nature of the study and obtained her verbal consent to participate. We interviewed the required number of respondents until the desired number of sample met.

3.9 Eligibility Criteria:

3.9.1 Inclusion Criteria:

All mothers of reproductive ages (15-49 years) and who had at least one outcome of pregnancy lived in the study places and who had used the same tube-well water more than 2 years available at the time of study, willingly cooperate and voluntarily gave their informed consents were considered eligible for the study.

3.9.2 Exclusion Criteria:

Mothers did not have the knowledge to understand the nature and purpose of the study, severely ill, weak, debilitated and mentally retarded and the mother refused to participate in an interview were excluded from the study.

3.10 Measuring arsenic concentration:

We collected water samples directly from tube-wells (one tube-well served each cluster) and concentrations of arsenic in drinking water were all measured by UNICEF provided Arsenic Measuring Kit. The available data for exposure assessment came from various sources including previous study, an official report, and an unpublished report of water analysis performed by other national and international organizations (WHO, UNICEF, World Bank, British Geological Survey, Community Hospital) were compared. As shown elsewhere, there is considerable variation in arsenic concentration even between adjacent wells and probably also overtime. Assuming that the current levels of arsenic in the well water were also the representative level of the past. Arsenic levels may have been different in the past, however, but there is no reliable information is available on this subject.

3.11 Diagnosis of Arsenicosis:

Each and every respondent underwent a thorough physical examination by two experienced study physician who had considerable experience in diagnosing arsenical skin lesions through a detailed and structured method was used to examine the skin manifestation-keratosis, melanosis and rain drop pigmentation, keratosis, hyper-pigmentation or hypo-pigmentation occurs anywhere in the body, often as a raindrop-like pigmentation or a diffuse dappling of dark brown, specially marked in the trunk, buttock and upper thigh. Hypo-

pigmentation follows the same distribution and depigmented spots may be present even in the absence of hyper-pigmentation. Keratosis is characterized diffuse bilateral thickening of palms or soles with or without nodules of various shapes and sizes, most often on the thinner eminence and the lateral borders of palms and fingers. For each subject, consensus diagnosis was made through decision between study physician and compared with diagnosis confirmed by WHO, UNICEF, British Geological Survey (BGS), Community Hospital and used by other previous study. The interviews and medical examinations were performed at a door-to-door visit and each mother was examined for skin lesions.

3.12 Diagnosis of Diabetes Mellitus:

According to World Health Organization (1999) Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision, and weight loss were possible symptoms of diabetes. All were also examined for hyperglycemia after overnight fasting and 2 hours after 75gm glucose. Samples were examined for glucose by glucose peroxidase enzymatic method (BM-Test Glucose, Boehringer Mannheim GmbH, Mannheim, Germany).

Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia [2] [211]

	Glucose concentration, mmol l^{-1} (mg dl^{-1})			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes Mellitus:				
Fasting	6.1 (110)	6.1 (110)	7.0 (126)	7.0 (126)
2-h post glucose load	10.0 180)	11.1(200)	11.1 (200)	12.2 (220)
Impaired Glucose Tolerance (IGT):				
Fasting	6.1 (110)	6.1 (110)	7.0 (126)	7.0 (126)
2-h post glucose load	>6.7 (>120) 10.0 (180)	>7.8(>140) 11.1 (200)	>7.8(>140) 11.1(200)	8.9 (160) 12.2(220)
Impaired Fasting Glycaemia (IFG):				
Fasting	5.6 (100) 6.1 (110)	5.6 (100) 6.1 (110)	6.1 (110) 7.0 (126)	6.1 (110) 7.0 (126)
2-h post glucose load	6.7 (120)	7.8 (140)	7.8 (140)	8.9 (160)

3.13 Steps in Designing a Questionnaire:

The quality of research depends to a large extent on the quality of the data collection tools. A crucial part of good research design concerns making sure that the questionnaire design addresses the needs of the research. The strength of the analysis depends on good quality data that in turn stems from good design of the data collection instrument, i.e. the questionnaire, and of the data collection procedures. Once the decision has been made to use these tools, the following steps applied to designing a questionnaire:

3.13.1 Content of the Questionnaire:

Considered research objectives and variables as a starting point and decided what questions would be needed to measure or to define variables and reach research objectives. Somehow we need to ensure that the questions asked were the right ones-is a key aspect that needs to be addressed by the researcher. To define the aims and fulfilling these aims would then drive the design of the questionnaire and help select questions that were relevant, concise and efficient. We were careful to make the mistake of asking too many questions. Clear and concise questionnaires could help getting the best response. We would reconsider the variables we have chosen and, if necessary, added, dropped or changed some variable.

3.13.2 Formulating questions:

Formulate one or more questions that would provide the information needed for each variable. Took care that questions were specific and precise enough so that different respondents didn't interpret them differently. The question therefore, as a rule, has to be broken up into different parts and made so specific that all informants focused on the same thing. In this section we have concentrated on interactive usually face-to-face interviews. Before examining the steps in designing a questionnaire, we needed to review the types of questions used in interviews. Such as:

- Closed Questions
    - Limited Choice:
    - Multiple Choice:
- Partially Closed:
- Factual Questions

- Opinion or Motivational Questions
- Behavioural Questions
- Hypothetical Questions
- Classification or Demographic Questions
- Knowledge Questions

3.13.3 Question Wording and Response Categories:

Some general rules can be stated on question wording:

- Be concise and unambiguous
- Avoid questions involving negatives
- Ask for precise answers
- Avoid leading questions
- Used simple and easy language
- Double-Barrelled Questions (Multiple Concepts in one Question)
- Unbalanced Questions
- Recall/Memory Error
- Intrusive (Sensitive) Questions
- Attitude Strength
- Acquiescence
- Adequate Response Categories
- Number of Response Options
- Don't Know Category

3.13.4 Sequence and Layout of the Questionnaire:

There are different views on sequencing of questions. The sequence of questions must be logical for the informant and allow, as much as possible, for a natural conversation, even in more structured interviews. At the beginning of the interview a limited number of questions concerning background variables, age, education, marital status might be asked. Start with an interesting but non-controversial question that is directly related to the subject of the study. Pose more sensitive questions as late as possible in the interview. This type of beginning

would help to raise the informants interest and lessen suspicions concerning the purpose of the interview. Designed our interview schedule (questionnaire) to be 'informant friendly'.

Lay out the questions and answer choices attractively and neatly. When we finalized the questionnaire, be sure that a separate, introductory page was attached to each questionnaire, explaining the purpose of the study, requesting the informant's consent to be interviewed and assuring confidentiality of the data obtained. Each questionnaire has a heading and space to insert the number, date and location of the interview, the name of the informant and added the name of the interviewer, to facilitate quality control. Sufficient space was provided for answers to categories such as 'other' and for comments on pre-categorized questions. Boxes for pre-categorized answers were placed in a consistent manner on the right half of the page. The right margin of the page would be reserved for boxes intended for computer codes.

3.13.5 Translating Questionnaires:

The interviews would be conducted with the questionnaire translated into Bengali in order to standardize the way questions would be asked. After having it translated we have retranslated into the original language by a different person. We could then compare the two versions for differences and make decisions concerning the final phrasing of difficult concepts. We used Bengali versions of the questionnaire for respondents that make the respondent felt free to answer all questions closest to their best meaning. Hence, our questionnaire would not only be informant-but also 'researcher friendly'.

3.13.6 Testing Questionnaire:

It was important to test each of these aspects of questionnaire design with a group of respondents before finalizing the questionnaire. Designing a good questionnaire we did several drafts. In the first draft we have concentrated on the content. In the second, we looked critically at the formulation and sequencing of the questions. Then we scrutinized the format of the questionnaire. Finally we did a test-run to check whether the questionnaire gave us the information we required and whether interviewers as well as respondents felt at ease with it. Usually the questionnaire would need some further adaptation before we could use it for actual data collection. When necessary, the form could then be modified and retested until respondents could complete it accurately and quickly with a minimum of errors.

3.13.7 Run a Pilot Survey:

Before conducting the research, the investigator should at least know how effective a research tool (interview questionnaire) was used. Pre testing of the questionnaire was necessary to test the validity and reliability of the questionnaire. The instrument was applied on mothers (age group 15-49 years) for reliability and appropriateness of its lingual meaning, wording construct and the meaning of the items to the respondents. Tested the questionnaire on a small sample of our subjects minimum 10% of the study sample (n = 40) was taken for response in pilot study. The aim here was to detect any flaws in our questioning and corrected these prior to the main survey. The piloting enabled us to convert an open-ended question into a closed question by determining the range of possible answers. We may also be able to perform a trial analysis on pilot sample and hence tested out all analysis procedures. Having done our pilot survey, we could make amendments that would help to maximize response rate and minimize error rate on answers.

3.13.8 Validity Test:

Measurement of the content Validity referred to the validation of the study. A draft questionnaire was constructed and being sent to the 6 experts of relevant field to see the feasibility and relevance of the questionnaire. Each item was examined and given score for every item. The score were tabulated and the item correlation calculated by using the formula:

$$\mathbf{IC = \Sigma R/N}$$

Every item has the score more than 0.5 except six items has the score 0.5 and only one item has score less than 0.5. These items were corrected and re-written. So, the item correlation of the questionnaire was valid, and could be used in this study.

- R = Total score of that item.
- N = Number of experts.
- Score +1 = Relatively valid items.
- Score 0 = Not sure and
- Score - 1 = Relatively irrelevant.
- **IC > 0.5 ⟶ Acceptable.**

3.13.9 Reliability Test:

Reliability is the accuracy, dependability, stability, consistency and predictability of a measuring instrument. In this study, dichotomous scale, multiple options, continuous and categorical response of arsenicosis and nonarsenicosis mother was used. Internal consistency was done by Cronbach alpha statistic, which was appropriate for reliability test. The reliability coefficient (RC) was more than 0.8, the items were highly reliable. Before data collection test-retest was done for stability of the test in the study site.

RC > 0.8 ⟶ Highly Reliable.

3.14 Training Research Assistants:

Before any data were actually collected, first to determine what will be done, and who will do it. In this study, some information, however, of a more difficult in nature that mothers were conservative and felt shy, unwilling, reluctant or unable to gave accurate information. Question may have to be carefully handled by well trained and experienced female interviewers that the mothers were greatly at ease and felt more comfort and they talked more freely about a topic and data could be obtained in an easier or better way. Regardless of who they were, or what role they would play, all research assistants would participate in some type of orientation training that explained the nature and purpose of the study and the role they would play in it. After training they would be able to understand exactly what they were going to do and how they could do it

3.14.1 Theoretical training:

Research assistants and other team members must be thoroughly familiar with the objectives of the research project and the methodology. Therefore, it was recommended that they were provided with copies of the research protocol and that the most relevant sections be discussed thoroughly, including:

- Statement of the problem
- Objectives
- Data collection tools to be used

- Sampling procedures
- Plan for data collection and Plan for data analysis.

It was important at this stage that the research assistants got an ample opportunity to ask questions. Research assistants would be taught basic interview techniques, such as asking questions in a neutral manner; not showing by words or expression what answers one expects, not showing agreement, disagreement or surprise, without sifting or interpreting them. Finally, clear instructions were given as well, concerning how an interviewer would introduce herself to the interviewee, what to say concerning the purpose of the study, how to ask for consent, and how to close the interview.

3.14.2 Practical training

Practical training in interviewing was essential. It was provided in two stages:

Role-plays: Firstly, role-plays could be performed, during which one trainee assumed the role of the interviewer and another played the interviewee. Other trainees and the trainers (researchers) would observed carefully what happened and gave constructive feedback right after the role-play. Then roles could be changed, until each trainee has had a chance to practice each type of interview at least once.

Field test: Secondly, a field test would be conducted, which would serve two purposes: the training of the entire research team including research assistants, and a further test of the data collection tools. A test of the tools was essential when a previous field-test resulted in important changes and/or when the questionnaire were translated into a local language after the first field test. When the research assistants were involved in the proper phrasing of questions this would definitely strengthen their interest and commitment.

3.14.3 Allocation of interviewers tasks:

During the fieldwork. interviewers or research assistants worked independently or together with the researchers. When they went out independently they have to carried out the following tasks:

- Did the sampling in the field for individuals to be interviewed within households?

- Gave a clear introduction to the interviewee concerning the purpose and procedures of the interview and ask for permission to interview.
- Researchers trained research assistants so they could carry out their tasks and performed the interviews accurately and correctly, according to the procedures developed by the researchers.

3.14.4 Supervision of research assistants:

Even when research assistants were used, responsibility for the research remains with the research team as a whole. To guarantee the quality of the data collected, it was important to supervise the research assistant's performance, especially at the beginning of the data collection period. When they were going out into the field independently, plans could be made to accompany them on selected visits and/or to question a small sample of the interviewees as a 'control group' concerning key aspects of the interview. As a further quality control check it was important that an interviewer's name appears standard on each questionnaire so that it was possible to ask for clarification if certain information was not clear or inconsistent.

3.15 Data Collection Procedure:

3.15.1 Plan for Data Collection:

Data collection is a crucial stage in the planning and implementation of a study. If the data collection has been superficial, biased or incomplete, data analysis becomes difficult, and the research report will be of poor quality. A plan for data collection developed so that we have a clear overview of what tasks have to be carried out, who would perform these works, and the duration of these tasks. We could organize both human and material resources for data collection in the most efficient way and we could minimize errors and delays. We have to describe typical problems that may arise during data collection and how they could be solved.

3.15.2 Main stages in the data collection process:

Three main stages can be distinguished:

1. Permission to proceed:

Researcher obtained permission to proceed at the various levels. Consent obtained from the relevant authorities, individuals and the community in which the research was carried out. Research proposals have to be screened for scientific and ethical integrity by Bangladesh Medical Research Council (BMRC) and Ethical Review Committee of NIPSOM.

2. Data Collection:

When collecting our data, we have to consider logistics: who would collect what, when and with what resources and ensuring quality control. We allocated tasks for data collection, listed these tasks then identified who could best implement each of these tasks. We considered the time required to reach the study areas, the time required to locate the study units and the number of visits required per study unit. We calculated the number of interviews that could be carried out per person per day and the number of days needed to carry out the interviews. Our research team of 3 person conducted 5 interviews per day, and completed 12 months required (400/5 = 80 days = 4 months as 20 working days per month x 3 groups) to complete 1200 interviews, measured concentration of arsenic in drinking water and glycemic status (fasting and 75gm glucose 2 hours after).

Pre-tested structured interview questionnaire were used to collect relevant information regarding demographics, socio-economic status and other reproductive events, drinking water sources and pattern of well water used. Every mother underwent a thorough physical examination by one of the study physician and clinical data including the presence of melanosis, keratosis, rain drop pigmentation were collected. The study obtained interview data and drinking water samples from the study participants. Water samples were collected directly from the tube-wells (one tube-well covered each cluster). We collected information on the respondents lifetime reproductive history which included the number of pregnancies, live births, pre-term births, stillbirths, neonatal deaths, spontaneous and induced abortion, menstrual regulation (MR), and congenital abnormality. Standing height and body weight were measured with the subjects having light clothes and not wearing shoes. Individual body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

3. Data Handling:

Once the data have been collected and checked for completeness and accuracy, a clear procedure has been developed for handling and storing them. At some stages questionnaires

have to be numbered and this would be done at the time of the interview. Usually each questionnaire used would get its own number starting from 1. The author was responsible for storing data and the place where it would be stored.

3.15.3 Data-collection techniques:

Data-collection techniques allowed us to systematically collected information about our objects of the study and the settings in which they occurred. During data collection we have to be systematic otherwise it would be difficult to answer our research questions in a conclusive way. Various data collection techniques could be used such as:

3.15.3.1 Using available information:

The large amount of data that has already been collected from relevant sources: DPHE, WHO, UNICEF, NIPSOM, British Geological Survey (BGS), Community Hospital and from other researcher) at the various levels of health and health-related services might be a study in itself.

3.15.3.2 Face to face Interview:

Personal interview was carried out by research assistant through semi structured interview questionnaire and supervised by author and two other competent supervisors. Answers to the questions posed during an interview recorded by writing them down during the interview itself. The information obtained from the interview included residential history, history of water consumption including water source and duration of use of drinking water from a particular tube-well and reproductive history, prevalence of diabetes mellitus, height and weight of the respondents.

3.15.3.3 Arsenic Mapping:

Mapping is a valuable technique for visually displaying relationships and resources or situation analyses. It could be used to know the placement of wells, distance of the homes from the wells, other water supply systems etc. It gave researchers a good overview of the physical situation and might help to highlight relationships hitherto unrecognized. Mapping a community was also very useful and often indispensable as a pre-stage to sampling. With the help of this mapping highly arsenic contaminated pockets were efficiently targeted. This

piece of information was useful to target not only the vulnerable areas but also to demonstrate suitable safe water options for the mother.

3.16 Data compilation by computer:

The computer can do all kinds of analysis and the results could be printed. It was important to decide whether each of the tables, graphs, and statistical tests that could be produced makes sense and would be used in our report. That is why we planned the data analysis and introduced data into a computer costs time and money. The author and the computer analyst and statistician responsible for computer analysis consulted very early in the study, as soon as the questionnaire and dummy tables were finalized. In fact the research team worked closely with the throughout the design and the implementation of the study. Computer compilation consists of the following steps:

Choosing an appropriate program: In this study we choose the most widely used an appropriate computer program-an advanced Statistical Package for Social Sciences (SPSS) and Epi-info-a database software.

Data entry: To enter data into the computer we developed a data entry format, depending on the program we were using and did the analysis through SPSS and Epi-info program. The information on the data collection instrument were coded and recoded relating to each subject in the study and introduced into the computer in the form of the relevant code.

Verification: During data entry, mistakes were definitely creeping in. The computer was instructed to identify and printed out all subjects exactly as it has been entered, so the printout could be checked visually for obvious errors. Computer verification had built in giving the appropriate commands to identify errors.

Programming: We used competent statistician to analyze data and consulted how many subjects were to be analyzed and which groups were to be compared, whether any variables were to be re-coded or calculated, and for which variables we needed straight tabulations and which variables we would like to cross-tabulate in the questionnaire and which statistical test could be used in this study.

3.17 Data Processing & Summarization:

3.17.1 Data Processing:

Data processing and analysis started in the field, with checking for completeness of the data and performing quality control check. Data of small samples processed and analyzed as soon as it was collected. When internal inconsistencies or contradictions occurred, eliminated inconsistant data from further analysis When the data were ready for processing we applied a systematic approach to the summarization, analysis and presentation stages.

3.17.2 Data Summarization:

Whenever we collected significant quantities of data it became essential to summarize the data in some way. Analysis began with basic data summarization and presentation techniques using statistical techniques, using graphical techniques, or using a combination of both. Summary statistics were a set of mathematical methods we used to extract further information from observed data.

3.18 Data Management:

Data management steps involve reading data from external files, merging separate files together, making transformations or recoding, or creating new variables for analysis. Original data files left unchanged; let the program itself calculated new variables rather than store the original and computed values in the external data file. Data management procedures include: documentation and storage, data editing, data entry and data clearing. Prior to data analysis, internal consistency of the collected information was checked by graphing and calculation

3.19 Data Analysis Procedure:

Data analysis is the process of transforming raw data into useable information that is often presented in the form of a final report. Analysis is the principal tool for obtaining information from the data. Choose an analytical method that was appropriate for the question being investigated. When making comparisons between two groups of individuals, controlled for extraneous factors. When significant differences between the groups were found as a result of

statistical tests, then considered alternative plausible explanations for the differences. Consulted with experts both on the subject matter and on the statistical methods, before beginning to write report, when preparing the outline, considered such questions as: "what issues I was addressing, what data I was using, could I eliminate any irrelevant data, what analytical methods were appropriate, what results did I want to highlight, and what were my interesting findings?" During analysis, we calculated stillbirth, live birth, pre-term birth, neonatal death, abortion, miscarriage and congenital anomalies using the total number of live births as the denominator. Subsequently, we compared these reproductive events in the exposed (both arsenicosis and non-arsenicosis) and non-exposed groups.

Statistical Considerations:

A statistical analysis should clearly state the research objectives and list the most important tasks. Beyond these essential steps, this plan would also provide us with a detailed description of exactly what we wanted to do and why. Wrote out the details on paper with plenty of visual aids showing what results could look like. Create mock versions of tables or graphs we would eventually include our final report. From that point, the data we have collected, as well as appropriate analysis procedures, would become much more obvious:

Descriptive statistics:

Descriptive statistics, which aims to describe (by summarization) the structure of data, comprise those methods concerned with describing a set of data so as to yield meaningful information, creating summary values. Descriptive statistics gave us the average for each sample. Means, standard deviations for quantitative data, absolute or relative frequencies for qualitative data. These statistical parameters described the distribution characteristics of the variables being examined in samples derived from the study populations.

Inferential statistics:

Inferential statistics allowed us to estimate the average volume of all the population from which these are a sample. It also aimed to derive conclusions about a large group (the population) from measurements on a smaller sub-group (a sample). Significance level (P-

value) to make inferences (chance we reject the null hypothesis/accept the research hypothesis when the latter is, in fact, false).

The presence of differences in the mean and median values was assessed using a one way analysis of variance (ANOVA) for continuous variables, general association (Chi-square) statistic for categorical variables. Bivariate analysis were performed to determine if reproductive outcomes and select covariates varied across arsenic exposure categories. Prevalence ratio with 95% confidence interval, odds ratio (OR) and relative risk (RR) was calculated by Epi-Info software package. To evaluate the associations between independent variables (arsenic concentrations in water) and reproductive outcome (dependent variables) Pearson's correlation and z-test were used. Logistic regression models were used for assessing whether any associations existed between arsenic exposure and selected outcome of interest reproductive outcome and diabetes mellitus. Variables known to be independently associated with reproductive outcome such as maternal age, parity, use of contraceptives, duration of drinking water, BMI, etc. were forced into all generalized equation models. Other potential covariates-ANC, INC, PNC, place of delivery, person conducted delivery, were initially placed in the models and then dropped if they did not change the adjusted odds ratio (OR) of exposure of interest (arsenic) by more than 5 percent level.

3.20 The Data Presentation Process:

In this section we introduced to the basic methods by which we communicate our ideas and results, both to other researcher and to the rest of the population. Many reports rely on narrative information to present most, if not all, of the necessary information. Narrative information presented by tables and/or figures, diagrams, maps, charts and statistical inferences.

3.21 Ensuring quality of data:

It was extremely important that the data we have collected are of good quality, that was, reliable, valid and there was no variation in the information. Otherwise we would come up with false or misleading conclusions. Research assistants were not placed under too much stress requiring too many interviews a day paying per interview instead of per day. Arranged

for on-going supervision by competent supervisors following guidelines developed for supervisory tasks. Quality could be assured to check whether the questionnaire was filled in completely before finishing each interview, asked the supervisor to check at the end of each day during the data collection period whether the questionnaires were filled in completely. When inconsistency was clearly due to a mistake made by the researcher/research assistant, it might still be possible to check with the person who conducted the interview and corrected the answer. If the inconsistency was less clearly a mistake in recording, it might be possible to return to the respondent and asked for clarification. For computer data analysis, quality control checks of data must also include a verification of how the data has been transformed into codes and subsequently entered into the computer.

Researchers reviewed the data during the data analysis stage to check whether data were complete and consistent. The study was also monitored by researcher during data collection and conducted reliability check for 10 percent of completed questionnaire. Before and during data processing, however, the information would be checked again for completeness and internal consistency. If a questionnaire has not been filled in completely we would have missing data for some of variables. When there were many missing data in a particular questionnaire, and it was not possible to correct information that was clearly inconsistent, we decided to exclude the whole questionnaire from further processing and analysis as it would affect the validity of the study.

3.22 Confidentiality and Ethics:

As we develop our data collection techniques, we need to consider whether our research procedures were likely to cause any physical or emotional harm. It was strictly maintained by keeping informants right to privacy by posing sensitive questions or by gaining access to records which may contain personal data; concealed observation would therefore always be crosschecked or discussed with other researchers with respect to ethical admissibility; not to allow personal information to be made public which informants would want to be kept private, and showing respect certain cultural values, traditions or taboos valued by our informants.

Several methods for dealing with these issues might be recommended: Nature and purpose of the study explained before interviewing, obtained informed consent before the interview begins (Informed Consent Form –Appendix-3), not exploring sensitive issues before a good relationship has been established with the informant, ensuring the confidentiality of the data obtained and well trained health and family planning female personnel were assisted the researcher during data collection. The study received ethical clearance from Bangladesh Medical Research Council (BMRC) and Nationl Institute of Preventive and Social Medicine (NIPSOM).

3.23 Study Limitations and delimitations:

Several potential limitation and biases of this study must be considered. The findings of this study interpreted with recognition of its limitations and delimitations.

1. The major limitation of this study was that it was cross sectional, and convenience sampling used, a random sampling could not be obtained. The retrospective information raises some important issues which would be better addressed in prospective cohort study.
2. Medical records were not available, the accuracy of specific diagnosis registered in database also has not been extensively checked and depends on mother's memory for all self reported cases (recall bias). However, overall rates of adverse maternal and fetal outcomes in this data set were limited to a certain extent.
3. Because of observational nature of our data we could not entirely exclude the possibility that important confounders were omitted from the analysis or the adjustment for confounders were not completed, thus there was a chance of residual confounding in this study which may influence the reproductive outcome.

4. At the time of enrollment high risk mother and the mother who obtained prenatal care, confounding factors such as race, parity, BMI, education, marital status, smoking, pre-existing medical conditions, previous adverse pregnancy outcome and use of assisted reproductive health care were not excluded from the study.
5. The present study included prevalent cases and thus may be susceptible to survival bias and skin lesions may be confused with other skin diseases as the diagnosis was not confirmed by histopathology of skin.

6. Many respondents drunk water from a single well making well water arsenic concentration a shared characteristics correlated errors arising from shared wells. We assume that the arsenic levels of tube wells at the time of interviewing were the same as in the past may have introduced non differential measurement errors.

3.24 Conclusion of this chapter:

In this chapter we have discussed the data, methods and materials used in this research. Cross sectional comparative study were carried out using both quantitative and qualitative methodology for data analysis. Selection of the study places were purposive due to well established highly arsenic endemic areas in Bangladesh and most of the tube-wells in the study places were known to have arsenic concentrations of more than 0.05mg/l. Mother of reproductive age (15-49 years) who previously had at least one outcome of pregnancy were interviewed through pre-tested structured questionnaire by trained interviewer. We could organize both human and material resources for data collection in the most efficient way and we could minimize errors and delays. In this study we used the most widely used an appropriate computer program-an advanced Statistical Package for Social Sciences (SPSS) and Epi-info-a database software. During analysis, z-test, chi-square test, parametric and non-parametric test and multiple logistic regression (MLR) were used to study prevalence of diabetes mellitus and difference of reproductive outcome in the exposed (both arsenicosis and non-arsenicosis) and non-exposed groups. Hence, this chapter lays the foundation for the research which will be elaborated in the ensuing chapter of this thesis.

Chapter-4

Results and Findings

4.1 Introduction:

A total of 1200 mother of which 400 mother with arsenicosis (case), 400 mother with nonarsenicosis (control-1) in exposed group and 400 mother in nonexposed group (control-2) were interviewed with semi-structured questionnaire. Privacy, confidentiality and anonymity were strictly maintained and the respondent felt free to discuss their reproductive events closest to their best meaning. Response rate were excellent and reproductive histories were ascertained. The general and reproductive events of the study sample are summarized below:

Table 1: Characteristics of mother and comparison by groups:

Mean of socio-demographic characteristic			Multiple comparison		
Variable	Groups	Mean±SD	(I) Group	(J) Group	Sig.
Age	Arsenicosis	33.53±7.55	Arsenicosis	Non Arsenicosis	.000*
				Nonexposed	.000*
	Non Arsenicosis	30.04±6.75	Non Arsenicosis	Arsenicosis	.000*
				Nonexposed	.225
	Nonexposed	29.45±6.17	Nonexposed	Arsenicosis	.000*
				Non Arsenicosis	.225
Income	Arsenicosis	3592.75±1935	Arsenicosis	Non Arsenicosis	.904
				Nonexposed	.841
	Non Arsenicosis	3566.75±1877	Non Arsenicosis	Arsenicosis	.904
				Nonexposed	.748
	Nonexposed	3636.06±4555	Nonexposed	Arsenicosis	.841
				Non Arsenicosis	.748
Age of menarche	**Arsenicosis**	12.87±0.98	Arsenicosis	Non Arsenicosis	.001*
				Nonexposed	.426
	Non Arsenicosis	12.65±0.98	Non Arsenicosis	Arsenicosis	.001*
				Nonexposed	.000*
	Nonexposed	12.93±0.82	Nonexposed	Arsenicosis	.426
				Non Arsenicosis	.000*

**** The mean difference is significant at the 0.05 level.***

Table-1 reveals that the mean age of arsenicosis affected mother, nonarsenicosis mother and mother of nonexposed group were 33.53 (SD±7.55) years, 30.04 (SD±6.82) years and 29.45 (SD±6.17) years respectively. The mean income in different groups were Taka 3592.75 (SD±1935), Taka 3566.75 (SD±1877) and Taka 3636.06 (SD±4555) respectively. Mean age of menarche was 12.87 (SD±0.98) yeas of arsenicosis group, 12.65 (SD±0.98) years of nonarsenicosis in exposed group and 12.93 (SD±0.82) years in nonexposed group respectively.

Table-2: Characteristics of mother and comparison by groups:

Mean of socio-demographic characteristics			Multiple comparison		
Variables	Groups	Mean±SD	(I) Group	(J) Group	Sig.
Body Mass Index (BMI)	Arsenicosis	20.18±2.85	Arsenicosis	Arsenicosis	.255
				Nonexposed	.001*
	Non Arsenicosis	20.40±2.47	Non Arsenicosis	Arsenicosis	.255
				Non Arsenicosis	.000*
	Nonexposed	19.52±2.94	Nonexposed	Arsenicosis	.001*
				Nonexposed	.000*
Mid arm circumference (MAC)	Arsenicosis	24.12±2.42	Arsenicosis	Non Arsenicosis	.508
				Nonexposed	.000*
	Non Arsenicosis	24.23±2.22	:Non Arsenicosis	Arsenicosis	.508
				Nonexposed	.000*
	Nonexposed	23.20±2.65	Nonexposed	Arsenicosis	.000*
				Non Arsenicosis	.000*
Age of marriage	Arsenicosis	16.70±1.86	Arsenicosis	Non Arsenicosis	.001*
				Nonexposed	.000*
	Non Arsenicosis	17.15±1.61	Non Arsenicosis	Arsenicosis	.001*
				Nonexposed	.000*
	Nonexposed	16.03±2.28	Unexposed	Arsenicosis	.000*
				Non Arsenicosis	.000*

**** The mean difference is significant at the 0.05 level.***

Table-2 reveals that mean body mass index (BMI) was 20.18 (SD± 2.852) of arsenicosis group, 20.40 (SD±2.47) of nonarsenicosis in exposed group and 19.52 (SD±2.944) in nonexposed group. Mean mid arm circumference (MAC) of arsenicosis mother was 24.23 (SD±2.22), nonarsenicosis 24.12 (SD±2.42) in exposed group and 23.20 (SD±2.65) in nonexposed group. Mean age of marriage was 16.70 (SD±1.86) years of arsenicosis, 17.15 (SD±1.61) years of nonarsenicosis in exposed group while 16.03 (SD±2.28) years in nonexposed group.

Figure 1: Duration of drinking water by exposed and nonexposed group:

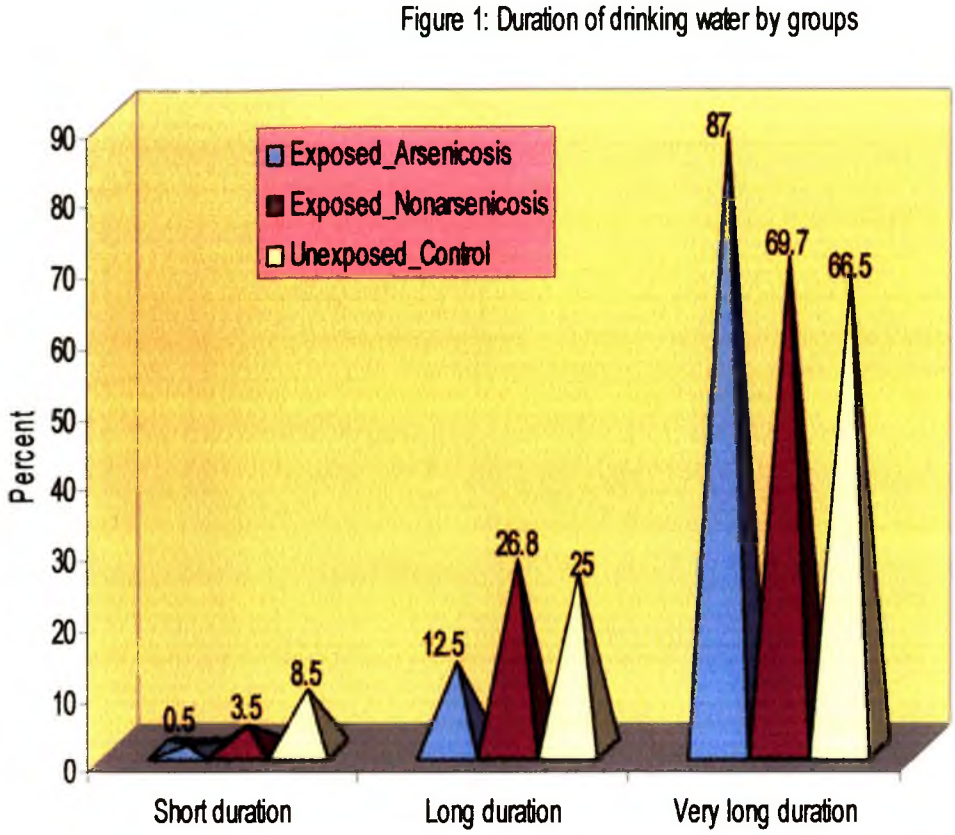


Figure 1 shows that 87.0 percent mother of arsenicosis, 69.7 percent mother of nonarsenicosis and 66.5 percent mother in nonexposed group had a long duration (more than 2 years) of drinking arsenic contaminated water. Mean duration of drinking water were 12.98 (SD±5.91) years, 9.93 (SD±2.85) years and 9.92 (SD±2.85) years in different groups respectively.

Figure 2: Sign and symptoms of arsenicosis mother:

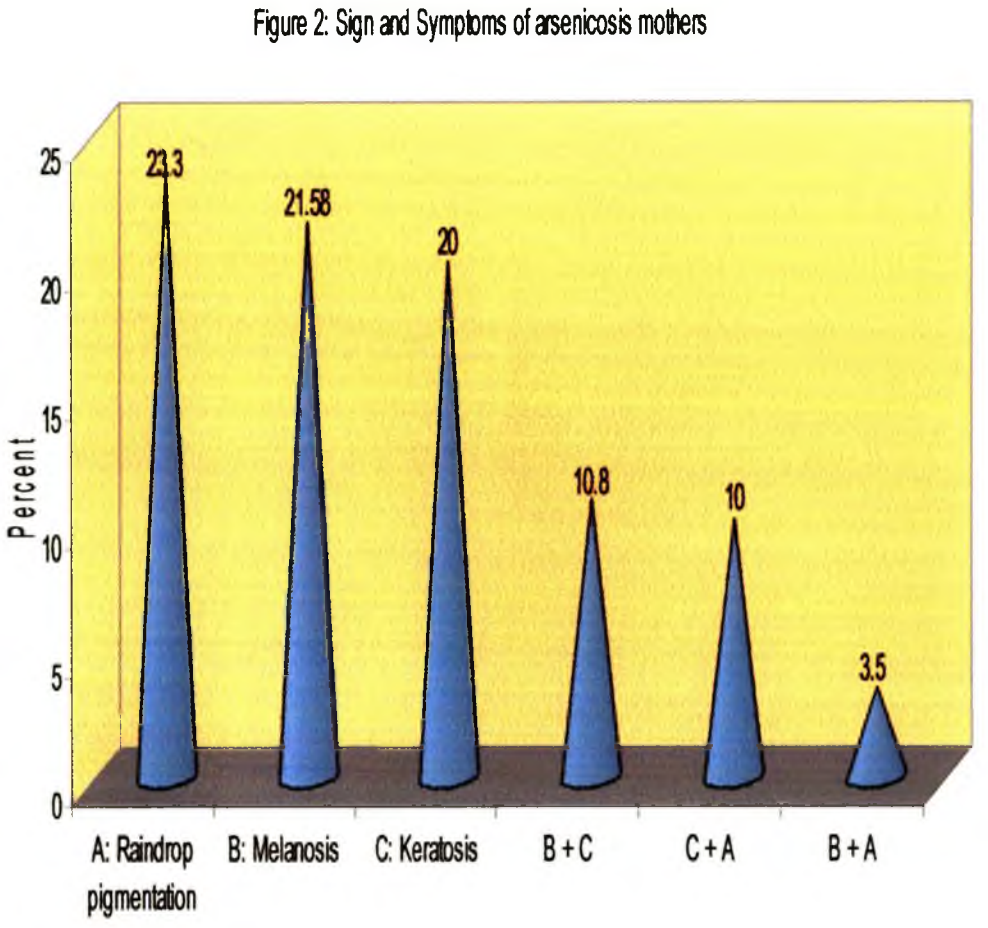


Figure 2 reveals that arsenicosis affected mother had 23.3 percent raindrop pigmentation, 21.58 percent melanosis and 20 percent keratosis, and 10.8 percent melanosis+keratosis, 10.0 percent had keratosis+raindrop pigmentation and 3.5 percent melanosis+raindrop pigmentation.

Figure 3 Duration of sign and symptoms of arsenicosis mother:

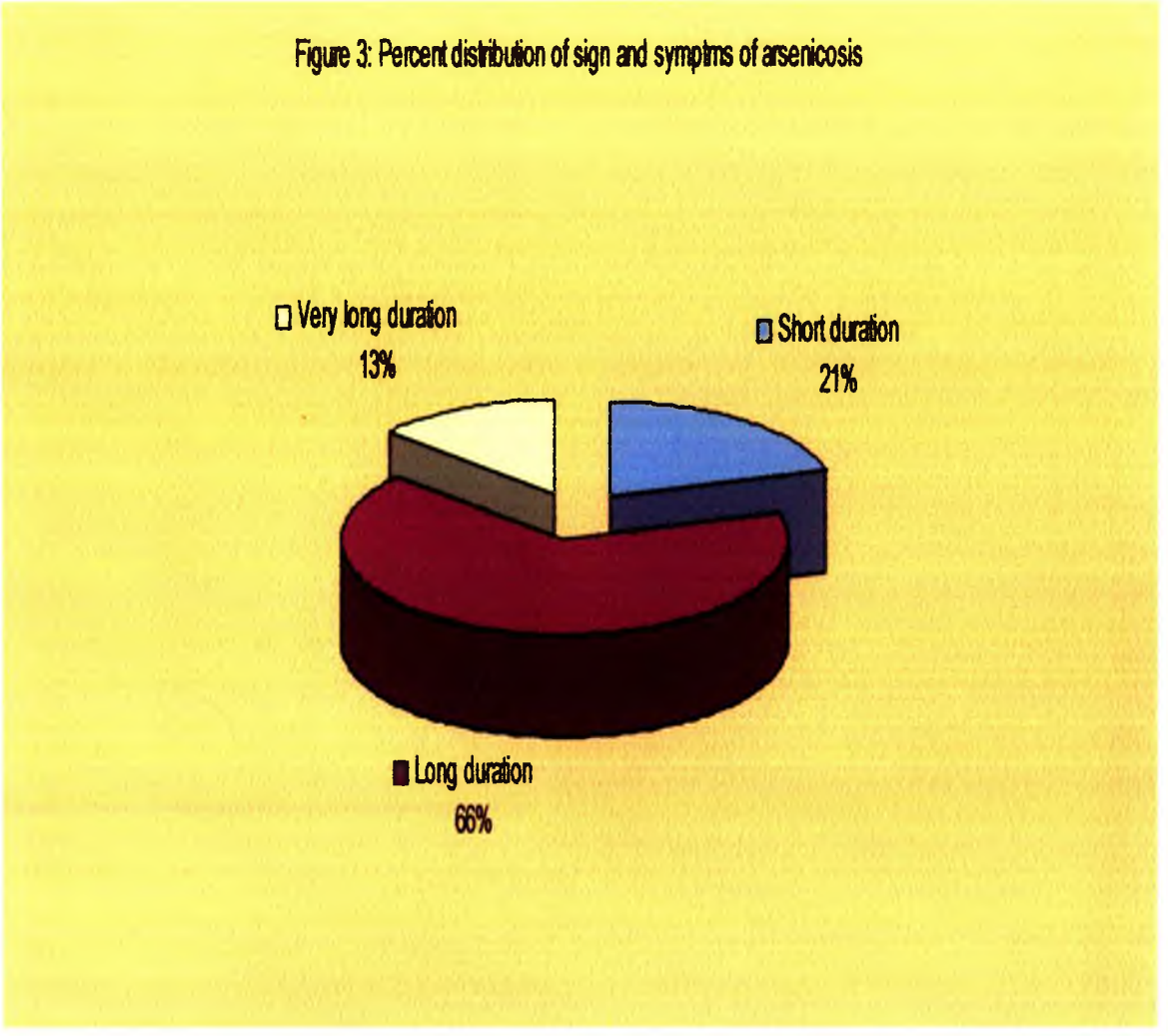


Figure 3 Shows that 66 percent mother had long duration, 21 percent had short duration and 13 percent had very long duration of sign/symptoms of arsenicosis.

Table 3: Distribution of the mother with regards to fasting blood glucose level:

Fasting glucose level	Exposed		Nonexposed group
	Arsenicosis	Nonarsenicosis	
Normal	331 (82.7)	346 (86.5)	340 (85.0)
Impaired Fasting Glucose (IFG)	43 (10.8)	38 (9.5)	44 (11.0)
Diabetes Mellitus (DM)	26 (6.5)	16 (4.0)	16 (4.0)
Total	400 (100.0)	400 (100.0)	400 (100.0)

Percentage in the parenthesis

Table-3 shows that Impaired Fasting Glucose (IFG) were 10.8 percent mother of arsenicosis, 9.5 percent mother of nonarsenicosis in exposed and 11.0 percent mother in nonexposed group. Suffering from Diabetes Mellitus (DM) were 6.5 percent, 4.0 percent and 4.0 percent in three groups respectively. The rest had normal level of fasting blood glucose.

Table-4: Distribution of mother with blood glucose level 2 hrs after 75gm glucose:

Glucose 2HA 75gm glucose	Exposed		Nonexposed
	Arsenicosis	Nonarsenicosis	Control group
Normal	325 (81.3)	342 (85.4)	346 (86.5)
Impaired Fasting Glucose (IFG)	47 (11.7)	41 (10.3)	39 (9.7)
Diabetes Mellitus (DM)	28 (7.0)	17 (4.3)	15 (3.8)
Total	400 (100.0)	400 (100.0)	400 (100.0)

Percentage in the parenthesis

Table 4 shows that 81.3 percent arsenicosis, 85.4 percent of nonarsenicosis in exposed and 86.3 percent in nonexposed group had normal blood glucose level 2 hours after 75gm glucose. The rest 11.7 percent, 10.3 percent and 9.8 percent were IFG and 7.0 percent, 4.3 percent and 4 percent were DM respectively in arsenicosis, nonarsenicosis and nonexposed groups respectively.

Table 5: Distribution of mother regarding Gestational Diabetes Mellitus (GDM):

Variables of DM	Exposed		Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed
	Arsenicosis N (%)	Nonarsenicosis N (%)	Control group N (%)	Chi-square (λ^2 Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Time of suffering: During pregnancy	8 (2.0)	8 (2.0)	5 (1.3)	$\lambda^2 = 0.04$ p=0.839 OR = 0.94 0.24<OR<0.70 RR = 0.97 0.53<RR<1.76	$\lambda^2 = 0.14$ p=0.708 OR = 1.60 0.36<OR<7.29** RR = 1.23 0.71<RR<2.14
Not during pregnancy	16 (4.0)	15 (3.8)	16 (4.0)		

** Percentage in the parenthesis*

Table 5 reveals that, Gestational Diabetes Mellitus (GDM) was found 2.0 percent in arsenicosis, 2.0 percent in nonarsenicosis in exposed and 1.3 percent in nonexposed groups. Gestational diabetes (GDM) in arsenicosis were positively associated with nonexposed group (OR=1.60; CI 0.36-7.29).

Table 6: Arsenic level in tube well water by classification of blood glucose level:

Variable	Blood glucose level	Arsenicosis		Nonarsenicosis	
		N (%)	Mean±SD	N (%)	Mean±SD
Fasting blood glucose level	Normal	331 (82.7)	327.19±63.13	346 (86.5)	266.57±63.60
	IFG	43 (10.8)	332.56±71.45	38 (9.5)	275.58±69.33
	DM	26 (6.5)	334.62±74.52	16 (4.0)	270.00±70.71
	Total	400 (100)	328.25±64.71	400 (100)	267.75±64.58
Blood glucose level 2 hours after 75gm glucose	Normal	325 (81.3)	327.55±62.67	342 (85.4)	267.69±64.41
	IGT	47 (11.7)	330.00±78.90	41 (10.3)	268.52±68.15
	DM	28 (7.0)	333.33±62.02	17 (4.3)	275.58±69.33
	Total	400 (100)	328.25±64.71	400 (100)	267.65±69.35

** Percentage in the parenthesis*

Table 6 shows that average arsenic level in tube well water of arsenicosis group gradually increased across the classification of fasting blood glucose level and blood glucose level 2 hours after 75gm glucose. No trend was found in the nonarsenicosis group.

Figure 4: Distribution of mother getting treatment of Diabetes Mellitus:

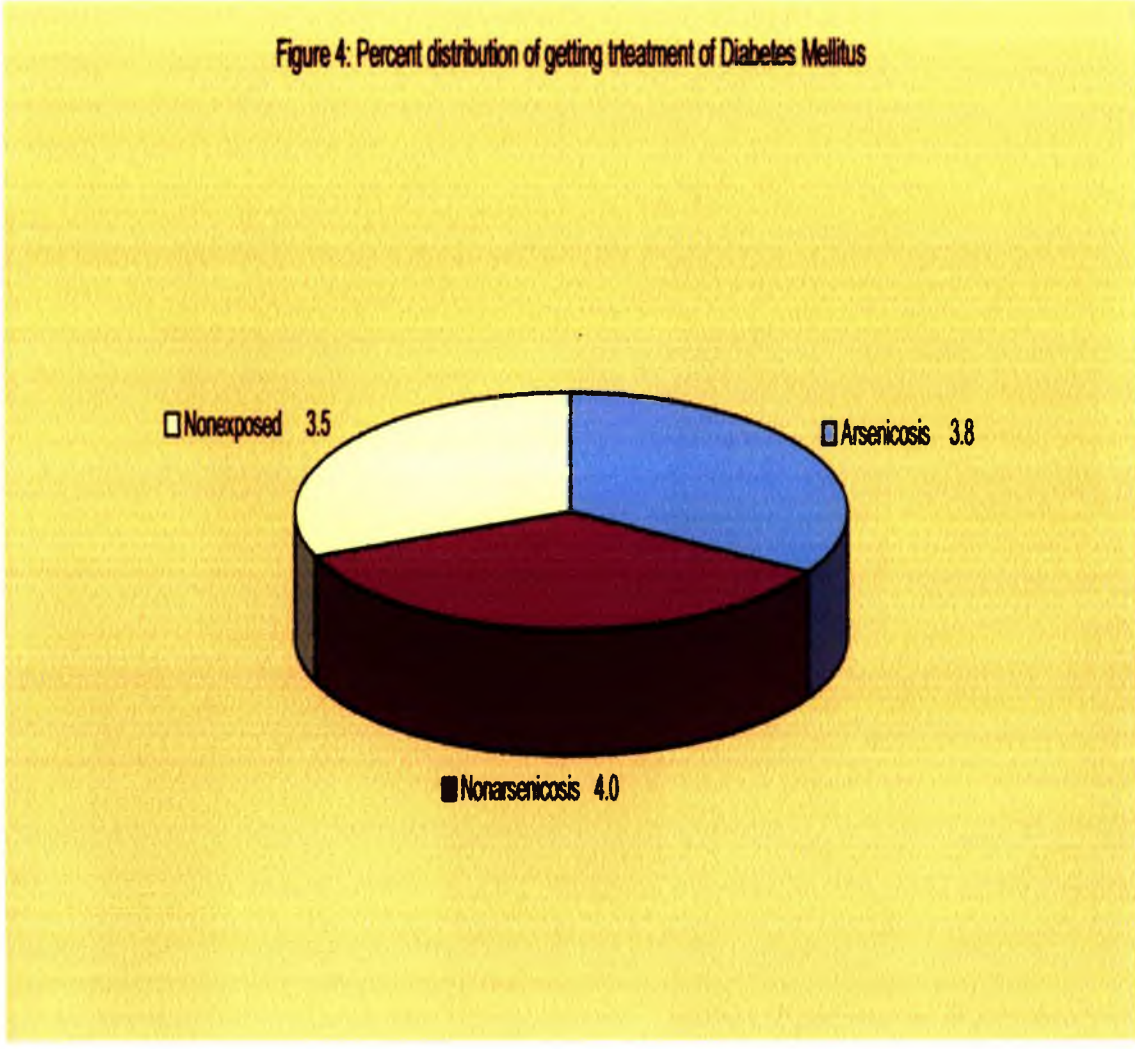


Figure 4 shows that 3.8 percent arsenicosis affected mother, 4.0 percent nonarsenicosis mother in exposed group and 3.5 percent mother in nonexposed group were getting treatment of Diabetes Mellitus (DM).

Figure 5: Distribution of mother getting type of treatment of Diabetes Mellitus:

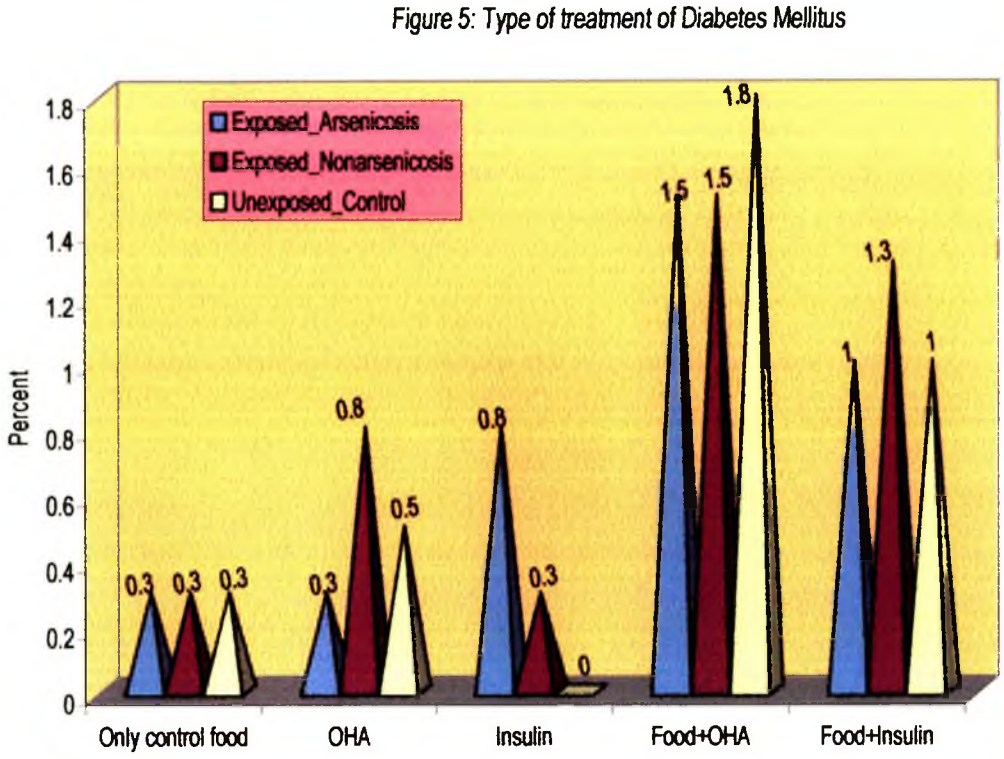


Figure 5 shows that various types of treatment of DM by groups. Most of DM patients were getting Food and OHA was found higher 18 percent in nonexposed group while 15 percent in both arsenicosis and nonarsenicosis group.

Table 7: Average blood glucose level and multiple comparison by groups:

Mean of blood glucose level			Multiple comparison		
Variables	Groups	Mean ± SD	(I) Group	(J) Group	Sig.
Fasting blood glucose	Arsenicosis	5.33±1.41	Arsenicosis	Non Arsenicosis	.004*
				Nonexposed: Control	.021*
	Non Arsenicosis	5.08±1.07	Non Arsenicosis	Arsenicosis	.004*
				Nonexposed: Control	.581
	Nonexposed Control	5.13±1.17	Nonexposed Control	Arsenicosis	.021*
				Non Arsenicosis	.581
Blood glucose after 75gm glucose intake	Arsenicosis	6.40±2.05	Arsenicosis	Non Arsenicosis	.283
				Nonexposed Control	.336
	Non Arsenicosis	6.25±1.99	Non Arsenicosis	Arsenicosis	.283
				Nonexposed: Control	.042*
	Nonexposed Control	6.23±1.74	Nonexposed Control	Arsenicosis	.336
				Non Arsenicosis	.042*

** The mean difference is significant at the 0.05 level.*

Table 7 shows that average fasting blood glucose level 5.33±1.41 of arsenicosis group were significantly higher when compared with that of 5.08±1.07 and 5.13±1.17 of nonarsenicosis and nonexposed group respectively ($p<0.05$). Average blood glucose level after 75gm glucose intake 6.40±2.05 of arsenicosis, 6.25±1.99 of nonarsenicosis in exposed group was significantly higher when compared with 6.23±1.74 of nonexposed group ($p<0.05$).

Table-8: Fasting blood glucose level and multiple comparisons by age group:

Average FBG level by age groups			Multiple comparison		
Groups	Age group	Mean±SD	(I) Group	(J) Group	Sig.
Arsenicosis	Age<20 years	5.060±.347	age<20 years	20-29 years	.959
				≥ 30 years	.406
	20-29 years	5.084±.081	20-29 years	age<20 years	.959
				≥ 30 years	.028*
	≥ 30 years	5.437±.093	≥ 30 years	age<20 years	.406
				20-29 years	.028*
Non Arsenicosis (control)	Age<20 years	4.533±.238	age<20 years	20-29 years	.217
				≥ 30 years	.196
	20-29 years	5.081±.072	20-29 years	age<20 years	.217
				≥ 30 years	.799
	≥ 30 years	5.109±1.081	≥ 30 years	age<20 years	.196
				20-29 years	.799
Nonexposed (Control)	Age<20 years	4.380±.195	age<20 years	20-29 years	.208
				≥ 30 years	.904
	20-29 years	4.904±.062	20-29 years	age<20 years	.208
				≥ 30 years	.000*
	≥ 30 years	5.335±1.098	≥ 30 years	age<20 years	.904
				20-29 years	.000*

**** The mean difference is significant at the .05 level.***

Table 8 shows that age group of exposed group and nonexposed group gradually increased as average fasting blood glucose level increase. Average FBG level 5.437±1.578 of exposed arsenicosis by age ≥30 years was significantly higher than that of 5.084±.842 by age 20-29 years ($p<0.05$). In nonexposed group, average FBG level 5.335±1.406 by age ≥30 years was significantly higher than that of 4.904±.850 by age group 20-29 years ($p<0.001$).

Table 9: Average blood glucose after 75gm glucose intake and multiple comparisons by age group:

Average BG level by age group			Multiple comparison		
Groups	Age group	Mean±SE	(I) Group	(J) Group	Sig.
Arsenicosis	age<20 years	5.720±.237	age<20 years	20-29 years	.642
				≥ 30 years	.198
	20-29 years	6.034±.063	20-29 years	age<20 years	.642
				≥ 30 years	.022*
	≥ 30 years	6.568±.158	≥ 30 years	age<20 years	.198
				20-29 years	.022*
Non Arsenicosis	age<20 years	5.600±.277	age<20 years	20-29 years	.435
				≥ 30 years	.402
	20-29 years	6.246±.131	20-29 years	age<20 years	.435
				≥ 30 years	.807
	≥ 30 years	6.295±.158	≥ 30 years	age<20 years	.402
				20-29 years	.807
Nonexposed (Control)	age<20 years	5.490±.237	age<20 years	20-29 years	.557
				≥ 30 years	.475
	20-29 years	6.164±.063	20-29 years	age<20 years	.557
				≥ 30 years	.000*
	≥ 30 years	6.886±.158	≥ 30 years	age<20 years	.475
				20-29 years	.000*

** The mean difference is significant at the .05 level.*

Table 9 shows that age group of exposed and nonexposed group gradually increased as average blood glucose after 75gm glucose intake increase. Average blood glucose after 75gm glucose level 6.568±.158 of exposed arsenicosis by age ≥30 years was significantly higher than that of 6.034±.063 by age 20-29 years ($p<0.05$). In nonexposed group, average blood glucose after 75gm glucose level 6.886±.158 by age ≥30 years was significantly higher than that of 6.164±.063 by age group 20-29 years ($p<0.001$).

Figure 6: Co-morbidity pattern of diabetes mellitus by groups:

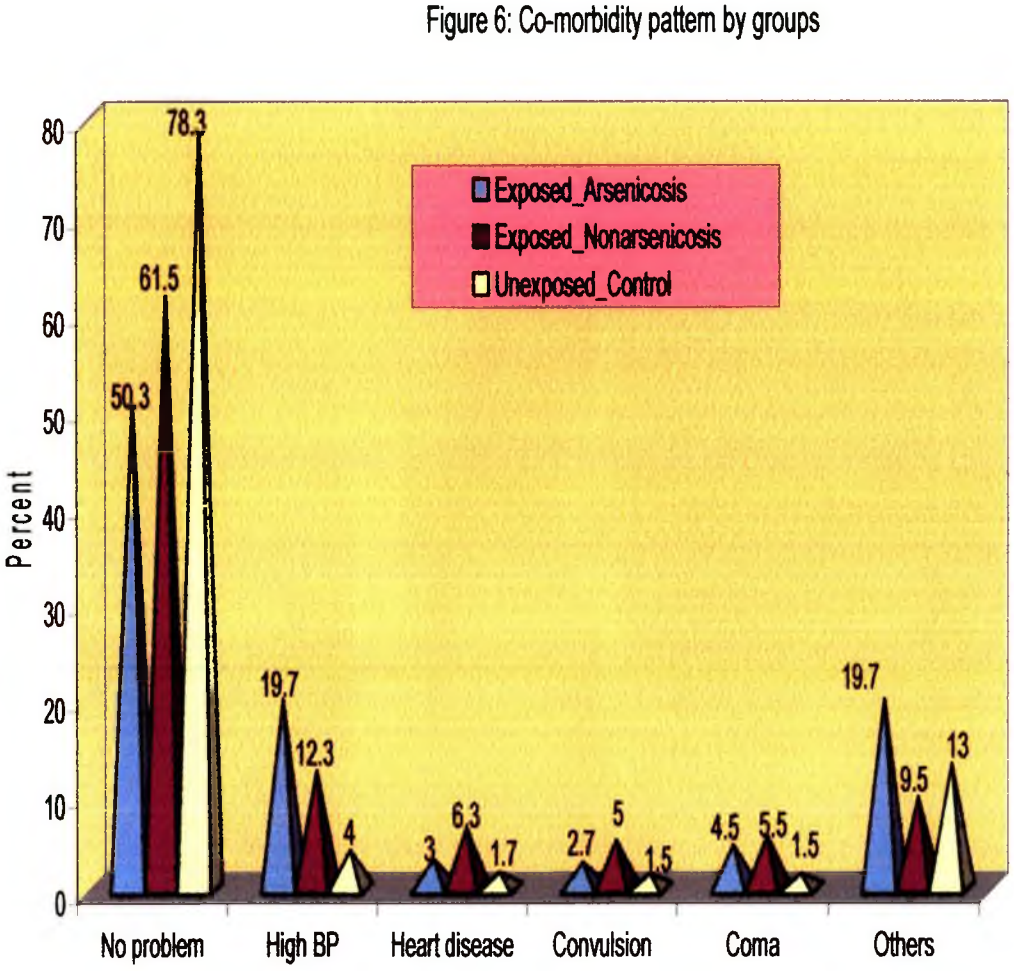


Figure 6 reveals that 49.7 percent mother of arsenicosis, 38.6 percent mother of nonarsenicosis and 21.7 percent mother of nonexposed group had been suffering from co-morbidity of diabetes mellitus. The incidence of co-morbidity of DM was significantly higher in exposed group than nonexposed group ($p<0.000$).

Figure 7: Distribution of mother by contraceptive methods used:

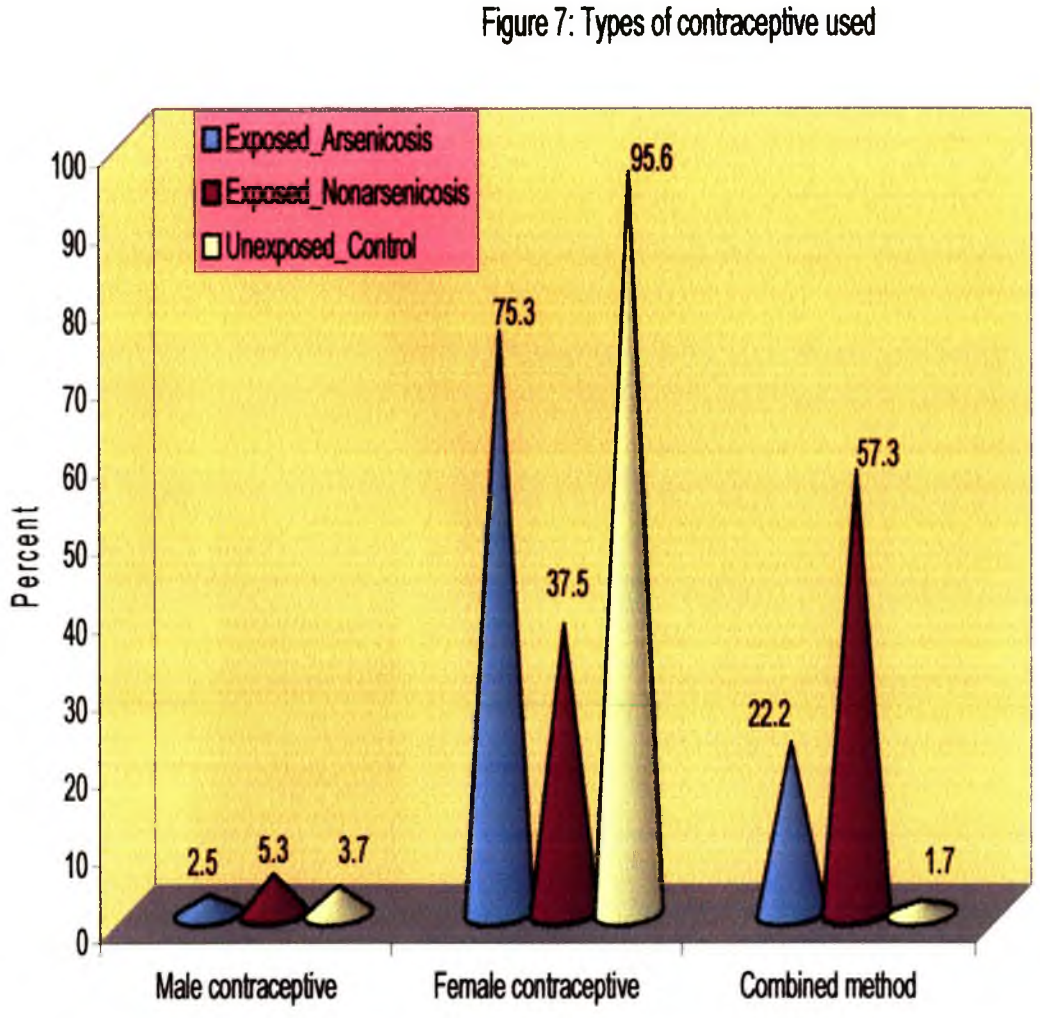


Figure 7 shows that 75.3 percent mother of arsenicosis, 37.5 percent mother of nonarsenicosis in exposed and 95.6 percent mother of nonexposed group used female contraceptive method. Combined methods used 22.2 percent, 57.3 percent and 1.7 percent mother while only 2.5 percent, 5.3 percent and 3.7 percent used male contraceptive in different groups respectively.

Figure 8: Reasons for nonuse of contraceptives in different groups:

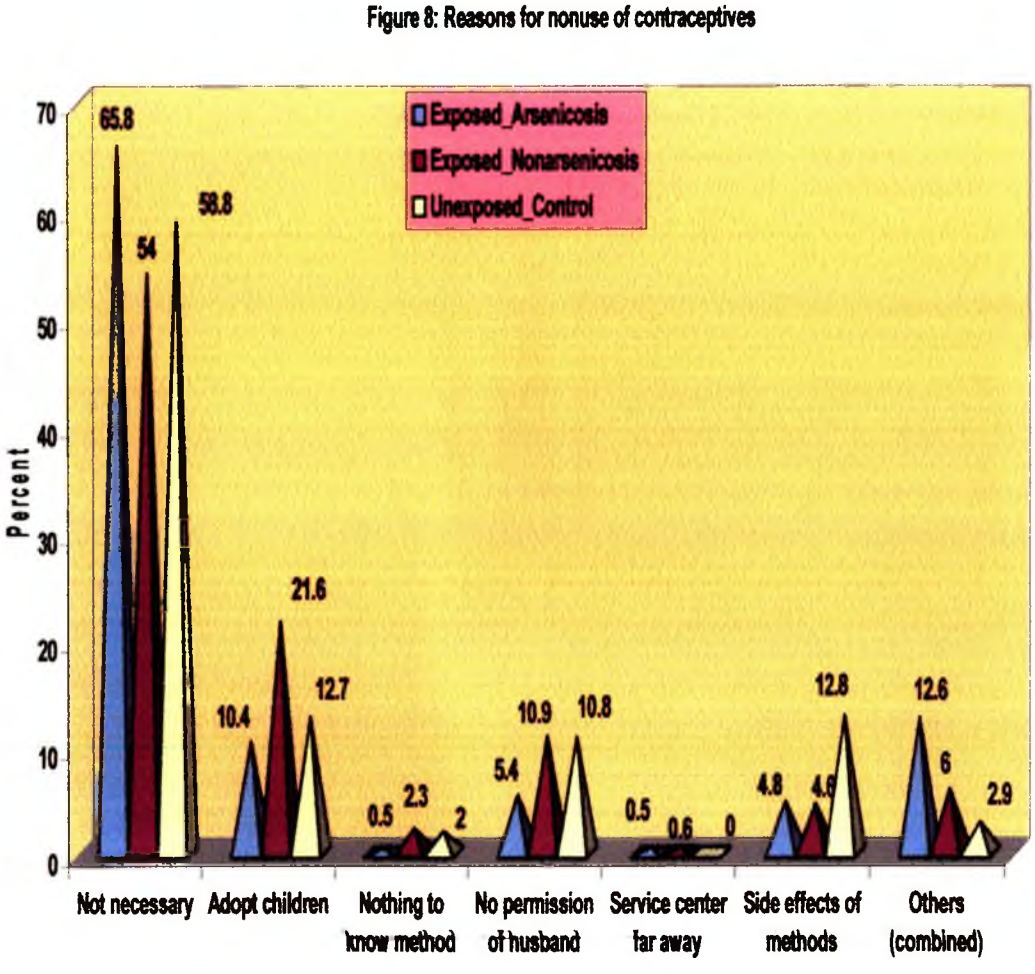


Figure 8 represents that 65.8 percent mother of arsenicosis, 54.0 percent mother of nonarsenicosis in exposed and 58.8 percent mother in nonexposed group said that they had no need to use any contraceptive method while 5.4 percent, 10.9 percent and 10.8 percent mother in different groups did not use contraceptive, as they had no permission from their husband. They also said that, 10.4 percent, 21.4 percent and 12.7 percent mother in different groups wanted to adopt children.

Figure 9 Distribution of the mother by their decision regarding family planning:

Figure 9: Distribution of the mother by their decisiobs regarding family planning

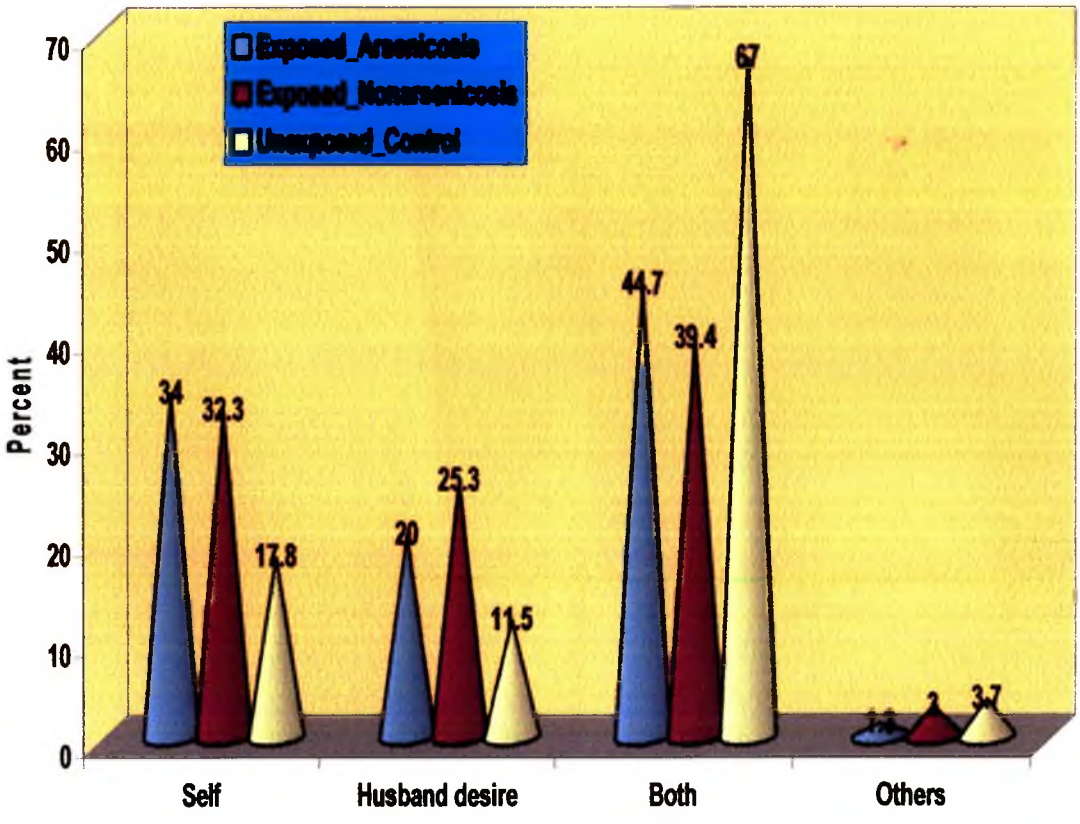


Figure 9 reveals that 34.0 percent mother of arsenicosis, 32.3 percent mother of nonarsenicosis in exposed and 17.8 percent mother in nonexposed group had taken decision regarding family planning by their self. The decision was taken by their husband 20.0 percent, 25.3 percent and 11.5 percent when by both husband and wife 44.7 percent, 39.4 percent and 67.0 percent in different groups respectively.

Table 10: Distribution of the mother by their health problem during pregnancy:

Health problems	Exposed		Nonexposed
	Arsenicosis	Nonarsenicosis	Control group
No health problem	209 (52.3) z-score=2.76 p=.006*	194 (48.5) zscore=2.78p=.0051*	252 (63.0) z-score=2.78p=.0051*
High blood pressure	20 (5.0) z-score=0.44 p=0.660	29 (7.3) z-score=0.21 p=0.834	26 (6.5) z-score=0.19 p=0.849
Diabetes mellitus	24 (6.0) z-score=0.31 p=0.757	23 (5.8) z-score=0.42 p=0.675	21 (5.3) z-score=0.33 p=0.741
Convulsion	3 (0.8) z-score=0.24 p=0.810	11 (2.8) z-score=0.53 p=0.569	5 (1.3) z-score=0.46 p=0.646
Headache Vomiting	20 (5.0) z-score=0.44 p=0.660	51 (12.8) z-score=0.19 p=0.849	41 (10.3) z-score=0.01 p=0.992
Oedema leg	16 (4.0) z-score=0.51 p=0.610	17 (5.3) z-score=0.35 p=0.726	25 (6.3) z-score=0.20 p=0.841
High fever	16 (4.0) z-score=0.51 p=0.610	6 (1.5) z-score=0.63 p=0.529	7 (1.8) z-score=0.44 p=0.660
Abortion	22 (5.5) z-score=0.33 p=0.741	17 (64.3) z-score=0.24 p=0.810	6 (1.5) z-score=0.35 p=0.726
Miscarriage	31 (7.8) z-score=0.32 p=0.749	21 (5.3) z-score=0.35 p=0.726	8 (2.0) z-score=0.36 p=0.719
Combined	62 (16.6) z-score=0.34 p=0.734	27 (6.9) z-score=0.24 p=0.810	2 0(5.0) z-score=0.51 p=0.610

**** Significant at 5 percent level***

Table 10 shows that 7.0 percent mother of arsenicosis, 4.3 percent mother of nonarsenicosis in exposed group and 3.8 percent mother in nonexposed group had diabetes mellitus. It was also found that 5.6 percent, 6.8 percent and 3.5 percent mother had abortion and 6.8 percent, 5.3 percent and 3.3 percent mother had miscarriage in different groups respectively. No health problem was found to be significant in exposed group 52.3 percent than in nonexposed group 63.0 percent ($p<0.005$).

Table 11: Decision of mother regarding pregnancy in exposed and nonexposed group:

Decision regarding pregnancy	Exposed		Unexposed
	Arsenicosis	Nonarsenicosis	Control group
Nothing to do	128 (32.0)	132 (33.0)	55 (13.7)
Try to stop birth (failure)	45 (11.3)	41 (10.3)	179 (44.8)
Again try to stop birth (success)	6 (1.5)	11 (2.7)	10 (2.5)
Adopt children	80 (20.0)	92 (23.0)	96 (24.0)
Do not know	78 (19.5)	79 (19.7)	56 (14.0)
Others	63 (15.7)	45 (11.3)	4 (1.0)
Total	400 (100.0)	400 (100.0)	400 (100.0)

**Percentage in the parenthesis*

Table 11 reveals that 12.8 percent mother of arsenicosis, 13.0 percent mother of nonarsenicosis in exposed group and 47.3 percent mother in nounexposed group tried to stop their birth. It was also observed that 32.0 percent, 33.0 percent and 13.7 percent mother of different groups said that nothing to do if they got pregnant. On the other hand 20.0 percent, 23.0 percent and 24.0 percent mothers of different groups respectively wanted to continue pregnancy (adopt more children).

Table 12: Distribution of mother according to their place of delivery:

Place of delivery and nature of abortion	Exposed		Unexposed
	Arsenic sis	Nonarsenicosis	Control group
Home delivery	380 (95.0)	371 (92.7)	384 (96.0)
Hospital delivery	20 (5.0)	29 (7.3)	16 (4.0)
Spontaneous abortion	35 (8.8)	26 (6.5)	12 (3.0)
Induced abortion	2 (0.5)	1 (0.3)	2 (0.5)

**Percentage in the parenthesis*

Table 12 reveals that 95.0 percent mother of arsenicosis, 92.7 percent mother of nonarsenicosis in exposed and 96.0 percent mother in nonexposed group had delivered their baby at home. It was also found that 8.8 percent, 6.5 percent, 3.0 percent mother had occurred spontaneous abortion and 0.5 percent, 0.3 percent, 0.5 percent mother occurred induced abortion in different groups respectively.

Figure 10: Person conducted delivery in exposed and nonexposed groups:

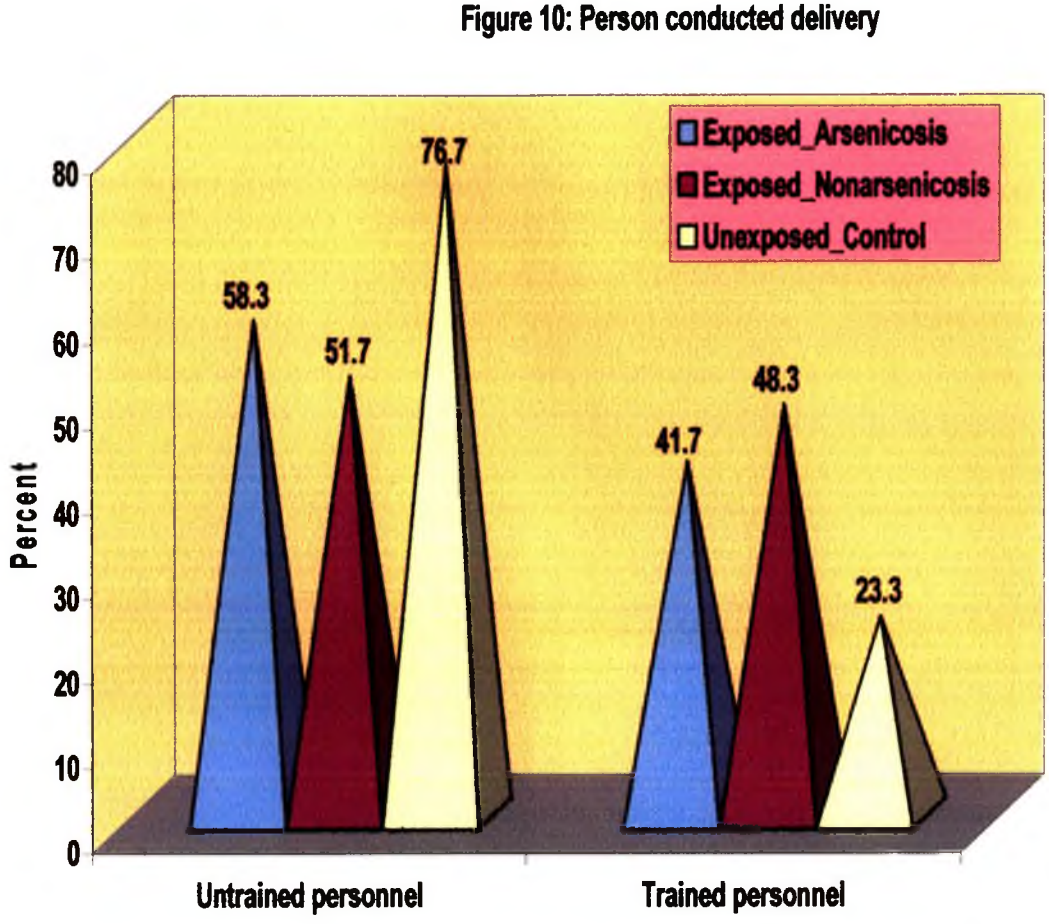


Figure 10 reveals that 41.7 percent mother of arsenicosis, 48.3 percent mother of nonarsenicosis in exposed group and 23.3 percent mother in nonexposed group conducted their delivery by trained personnel. Delivery conducted by trained personnel in exposed group is higher than nonexposed group.

Table-13: Reproductive outcome of mother in exposed and nonexposed group:

Reproductive outcome	Exposed		Nonexposed
	Arsenicosis	Nonarsenicosis	
Alive child	283 (70.8)	311 (77.8)	361 (90.3)
Neonatal death	16 (4.0)	14 (3.5)	8 (2.1)
Stillbirth	17 (4.3)	15 (3.8)	9 (2.3)
Premature	26 (6.5)	19 (4.8)	7 (1.8)
Handicapped	5 (1.3)	3 (0.8)	1 (0.3)
Miscarriage	31 (7.8)	21 (5.3)	8 (2.0)
Abortion	22 (5.5)	17 (4.3)	6 (1.5)
Total	400 (100.0)	400 (100.0)	400 (100.0)

* ***Percentage in the parenthesis***

Table-13: Reveals that, 70.8 percent mother with arsenicosis and 77.8 percent mother with nonarsenicosis in the exposed group, while 90.3 percent mother in the nonexposed group delivered alive child. Neonatal death 4.0 percent, 3.5 percent and 2.1 percent; Stillbirth 4.3 percent 3.8 percent and 2.3 percent; Premature 6.5 percent, 4.8 percent and 1.8 percent; Handicapped 1.3 percent 0.8 percent 0.3 percent; Miscarriage 7.8 percent. 5.3 percent and 2.0 percent; Abortion 5.5 percent, 4.3 percent and 1.5 percent in different groups respectively.

Table-14: Reproductive outcome of diabetic mother in exposed and nonexposed group:

Reproductive outcome	Exposed		DM in Nonexposed n=16
	DM in Arsenicosis n=28	DM in Nonarsenicosis n=17	
Diabetes mellitus	28 (7.0)	17 (4.3)	16 (4.0)
Alive child	22 (78.5)	12 (70.5)	13 (81.3)
Neonatal death	1 (3.6)	2 (11.8)	1 (6.3)
Stillbirth	0 (0.0)	0 (0.0)	1 (6.3)
Premature	1 (3.6)	1 (5.9)	0 (0.0)
Handicapped	1 (3.6)	0 (0.0)	0 (0.0)
Miscarriage	2 (7.1)	2 (11.8)	1 (6.3)
Abortion	1 (3.6)	0 (0.0)	0 (0.0)
Total	28 (7.0) (100.0)	17 (4.3) (100.0)	16 (4.0) (100.0)

** Percentage in the parenthesis*

Table-14 shows that, 78.5 percent mother with arsenicosis and 70.5 percent mother with nonarsenicosis in the exposed group, while 81.3 percent mother in the nonexposed group delivered alive child. Neonatal death 3.6 percent, 11.8 percent and 6.3 percent; Stillbirth 0.0 percent 0.0 percent and 6.3 percent; Premature 3.6 percent, 5.9 percent and 0.0 percent; Handicapped 3.6 percent 0.0 percent 0.0 percent; Miscarriage 7.1 percent. 11.8 percent and 6.3 percent; Abortion 3.6 percent, 0.0 percent and 0.0 percent in different groups respectively.

Table 15: Reproductive outcome and average arsenic level in tube well water:

Reproductive outcome	Arsenicosis		Nonarsenicosis	
	N (%)	Mean ± SD	N (%)	Mean ± SD
Living	283 (70.7)	327.56±64.82	311 (77.7)	266.40±64.42
Neonatal death	16 (4.0)	337.50±71.88	14 (3.5)	292.86±75.59*
Still birth	17 (4.3)	329.41±77.17	15 (3.7)	270.00±67.61
Premature	26 (6.5)	323.08±65.16	19 (4.7)	265.79±60.21
Handicapped	5 (1.3)	320.00±44.72	3 (0.8)	216.67±57.74
Miscarriage	31 (7.7)	322.58±56.03	21 (5.3)	269.05±60.16
Abortion	22 (5.5)	345.45±67.10*	17 (4.3)	279.41±68.60
Total	400 (100.0)	328.25±64.71	400 (100.0)	267.75±64.58

** Percentage in the parenthesis*

Table 15 shows that mean arsenic level was 328.25±64.71 in arsenicosis and 267.75±64.58 in nonarsenicosis group. Arsenic level 345.45±67.10 in arsenicosis group was found higher whose pregnancy outcome was spontaneous abortion. In exposed nonarsenicosis group, arsenic level 292.86±75.59 was found higher whose pregnancy outcome was neonatal death.

Figure 11: Linear trend of adverse reproductive outcome by number of pregnancy:

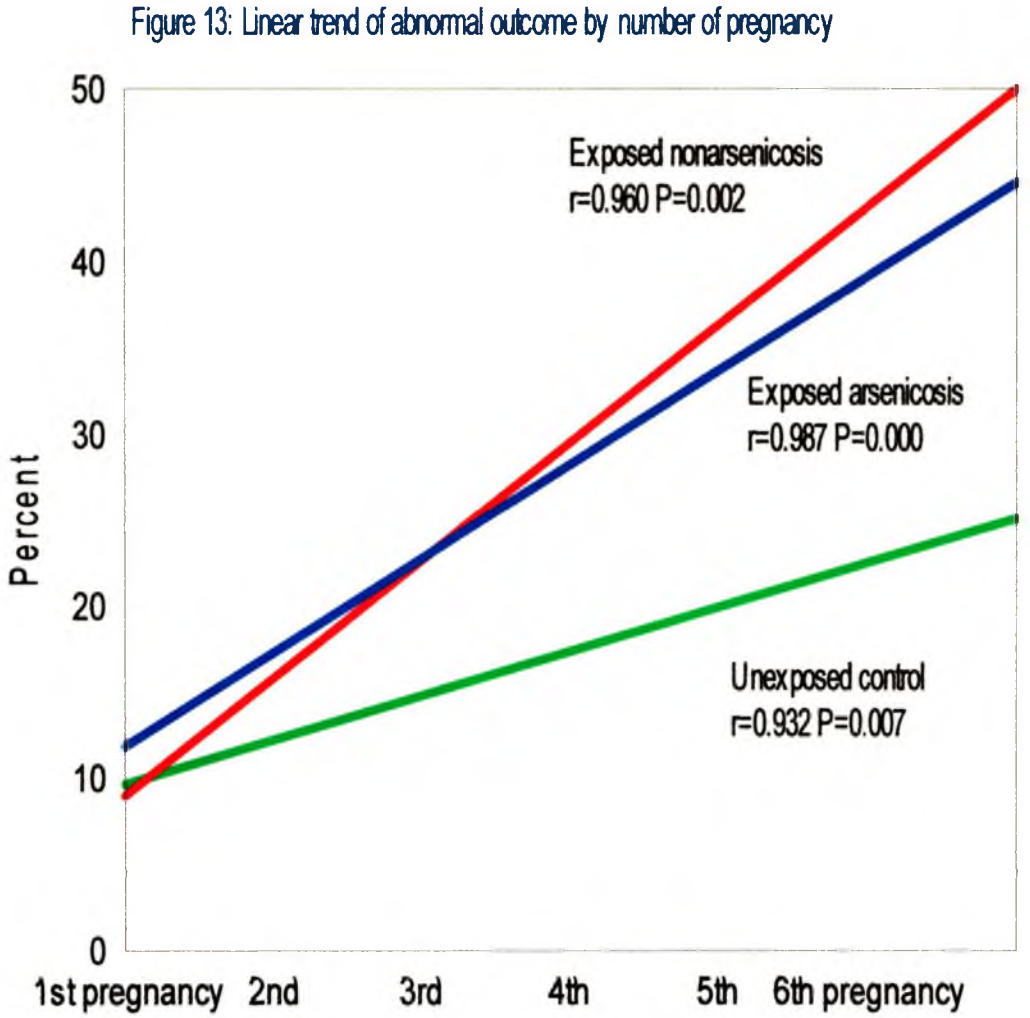


Figure 11 reveals that adverse outcome of pregnancy increases when number of pregnancy increases. Degree of relationship of exposed group was higher than that of nonexposed group ($p<0.001$).

Figure 12: Arsenic level in tube-well water and reproductive outcome:

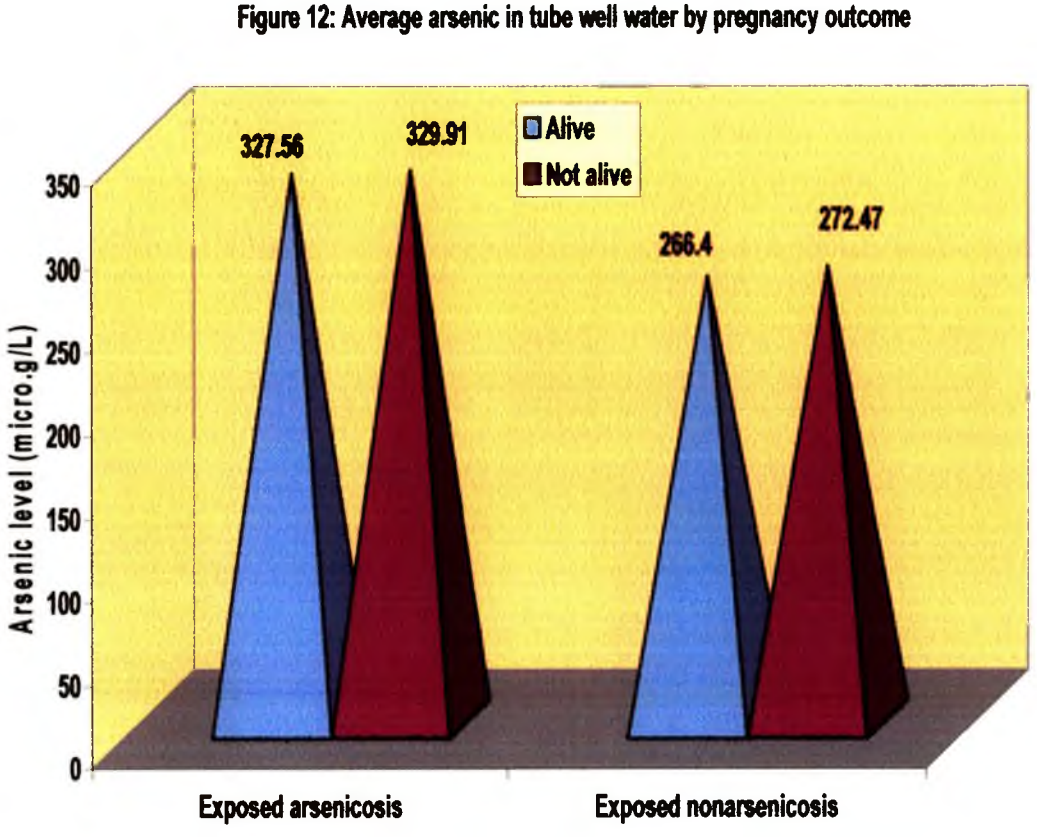


Figure 12 shows average arsenic level was 329.91 higher than the average arsenic level 327.66 whose reproductive outcome was not alive in arsenicosis group while arsenic level was 372.47 higher than 266.4 whose reproductive outcome was not alive in nonarsenicosis group.

Figure 13: Comparison of pregnancy outcome in different groups:

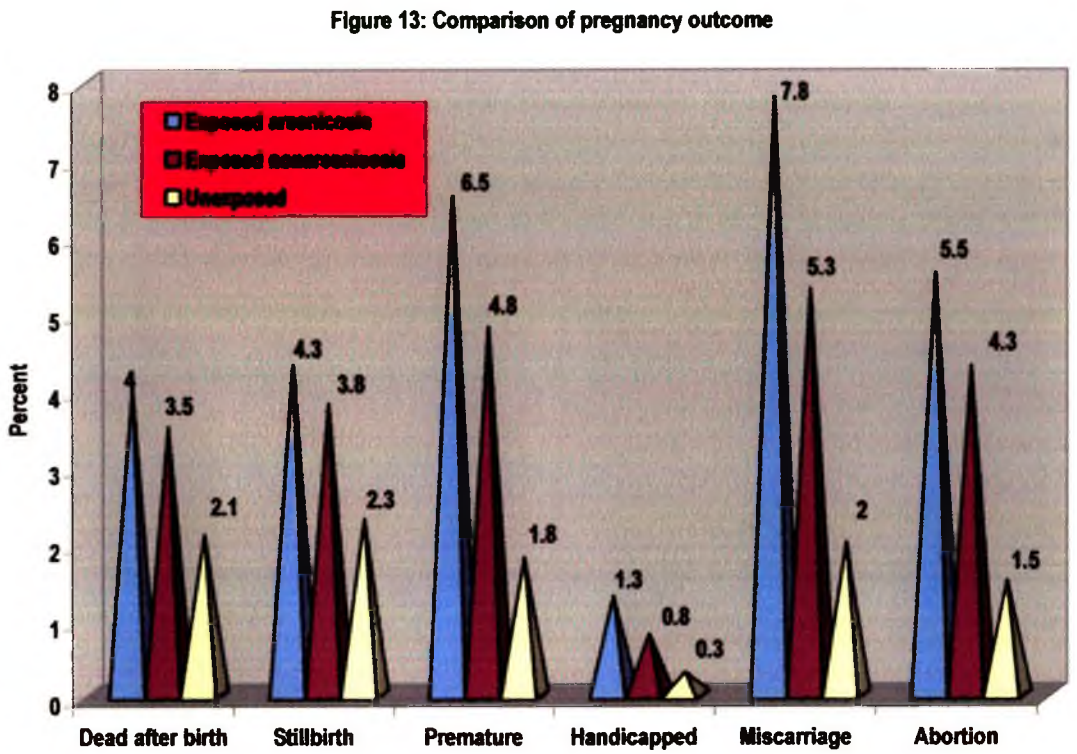


Figure 13 reveals that adverse pregnancy outcome: Neonatal death, stillbirth, preterm birth, handicapped, miscarriage and abortion is higher in arsenicosis and nonarsenicosis in exposed group than nonexposed group.

Table 16: Distribution of the mother with problems for never received PNC:

Problems for never received PNC	Exposed		Nonexposed
	Arsenicosis	Nonarsenicosis	Control group
No problem	231 (57.7)	220 (55.0)	295 (73.7)
Familial constrain	82 (20.5)	87 (21.7)	16 (4.0)
Nobody to accompany	9 (2.3)	6 (1.5)	7 (1.7)
Service center faraway	9 (2.3)	22 (5.5)	9 (2.3)
Nobody look after children	4 (1.0)	13 (3.3)	7 (1.7)
Do not know where to go	20 (5.0)	16 (4.0)	33 (8.3)
Non availability of medicine	34 (8.5)	34 (8.5)	32 (8.0)
Others	11 (2.7)	2 (0.5)	1 (0.3)
Total	400 (100.0)	400 (100.0)	400 (100.0)

Percentage in the parenthesis

Table 16 reveals that 20.5 percent mother of arsenicosis, 21.7 percent mother of nonarsenicosis in exposed and 4.0 percent mother in nonexposed group had never received PNC due to familial constrain, 5.0 percent, 4.0 percent and 8.3 percent do not know where to go, 8.5 percent, 8.5 percent and 8.0 percent due to non availability of medicine in different groups respectively.

Table 17: Distribution of mother faced health problems during postnatal period:

Health problems during PNC	Exposed		Nonexposed
	Arsenicosis	Nonarsenicosis	Control group
Profuse bleeding	34 (8.5) z-score=0.11 p=0.912	45 (11.3) z-score=0.37 p=0.711	22 (5.5) z-score=0.11 p=0.912
Pain lower abdomen	76 (19.0) z-score=1.77 p=0.077	93 (23.3) z-score=2.04* p=0.04	65 (16.3) z-score=2.18* p=0.029
High fever	27 (6.8) z-score=0.16 p=0.873	31 (7.8) z-score=0.12 p=0.905	8 (2.0) z-score=0.56 p=0.576
Infection (PID)	11 (2.8) z-score=0.79 p=0.430	15 (3.8) z-score=0.68 p=0.497	2 (0.5) z-score=0.85 p=0.395
Foul smell discharge	5 (1.3) z-score=1.03 p=0.303	2 (0.5) z-score=1.14 p=0.254	4 (1.0) z-score=0.75 p=0.453
Illness of children	15 (3.8) z-score=0.64 p=0.660	16 (4.0) z-score=0.65 p=0.516	19 (4.8) z-score=0.02 p=0.984
Problem of breast feedings	19 (4.8) z-score=0.48 p=0.631	24 (6.0) z-score=0.65 p=0.516	30 (7.5) z-score=0.49 p=0.246
Others (combined)	62 (15.5) z-score=1.22 p=0.223	51 (12.8) z-score=0.37 p=0.711	7 (1.8) z-score=0.60 p=0.549

Significant at 5% level

Table 17 shows that 62.5 percent mother of arsenicosis, 69.5 percent mother of nonarsenicosis in exposed and 39.4 percent mother in nonexposed group had ever faced reproductive health problems during postnatal period. Pain in the lower abdomen of nonarsenicosis and nonexposed group were statistically significant ($p<0.05$).

Table 18: Arsenicosis affected mother facing different types of social problems:

Social problem	Arsenicosis	
	Frequency	Percent
No problem	336	84.0
Marriage related	11	2.6
Education related	3	0.8
Job related	7	1.8
Meet with others	24	6.0
Collection of arsenic free water	5	1.3
Neglect as a curse of God	14	3.5
Total	400	100.0

Table 18 shows that 84.0 percent mother with arsenicosis faced no social problems whereas 16.0 percent mother faced different types of social problems due to arsenicosis such as: marriage, education, job, meeting with others, collection of arsenic free water and neglect as a curse of God.

Table 19: Association of socio-demographic characteristic with exposed and nonexposed mother:

Variables	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) P Value Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio(OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Age group 15-30 Years	147 (36.7	253 (63.3)	244 (61.0)	λ^2 = 12.54 p=0.000 S OR =0.64 0.50<OR<0.82 RR=0.86 0.80<RR<0.93	λ^2 = 55.13 p=0.000 S OR=0.34 0.15<OR<0.45 RR=0.58 0.50<RR<0.67	λ^2 = 46.10 P=0.000 S OR=0.37 0.28<OR<0.50 RR=0.61 0.52<RR<0.71
31-49 Years	253 (63.3)	147(36.7)	156 (39.0)			
Mothers Education Illiterate	163 (40.8)	161 (40.3)	184 (46.0)	λ^2 = 3.08; p=0.079 OR=0.80; 0.62<OR<1.03 RR =0.93; 0.85<RR<1.01	λ^2 = 0.01 p=0.94 OR=1.01 0.76<OR<1.37 RR=1.02 0.88<RR<1.16	λ^2=2.04 p=0.153 OR=0.81 0.60<OR<1.08 RR=0.90 0.78<RR<1.04
Literate	237 (59.3)	239 (59.7)	216 (54.0)			
Husbands education Illiterate	147 (36.8)	173 (43.3)	216 (54.0)	λ^2 = 20.58 p=0.000 S OR= 0.570.44<OR<0.73 RR= 0.83 0.76<RR<0.90	λ^2 = 3.26 p=0.071 OR=0.76 0.57<OR<1.02 RR=0.87 0.75<RR<1.01	λ^2=23.22 p=0.000 S OR=0.49 0.37<OR<0.66 RR=0.70 0.60<RR<0.81
Literate	253 (63.3)	227 (56.7)	184 (46.0)			
Mothers Occupation Housewives	378 (94.5)	359 (89.8)	392 (98.0)	λ^2 = 15.5 p=0.000 S OR=0.24 0.10<OR<0.52 RR=0.74 0.67<RR<0.81	λ^2 = 5.58 p=0.018 S OR=1.96 1.11<OR<3.48 RR=1.47 1.04<RR<2.07	λ^2 = 5.85 p=0.015 S OR=0.35 0.14<OR<0.84 RR=0.67 0.53<RR<0.84
Service	22 (5.5)	41 (10.3)	8 (2.0)			
Husbands ocupation Unemployed	10 (2.5)	6 (1.5)	4 (1.0)	λ^2 = 1.07 p=0.300 OR=2.02 0.63<OR<7.2* RR=1.20 0.96<RR<1.56	λ^2=0.57 p=0.448 OR=0.68 0.56<OR<5.26 RR=1.26 0.85<RR<1.85	λ^2 = 1.82 p=0.177 OR=2.58 0.73<OR<9.68 RR=1.44 1.03<RR<2.02
Service	390 (97.5)	394 (98.5)	396 (99.0)			

** Percentage in the parenthesis*

Table 19 shows that the incidence of arsenicosis was significantly higher in the age group 31-49 years than in the lower age group 15-30 years (λ^2=12.54; p=0.001, OR=0.64; 0.50<OR<0.82, RR=0.86; 0.80<RR<0.93), arsenicosis than nonarsenicosis (p<0.001) and arsenicosis and nonexposed (p=0.001) It was observed that mother's occupation was significantly associated with arsenicosis (p<0.001) in exposed group than nonexposed group, arsenicosis than nonarsenicosis (p<0.05) and arsenicosis and nonexposed (p=0.05). Housewives were 1.96 times higher risk in arsenicosis than nonarsenicosis. Unemployed group of husband was positively associated with arsenicosis λ^2 = 1.82 (OR=2.58 0.73<OR<9.68 RR=1.44 1.03<RR<2.02). Odds ratio (OR) showed that unemployed group was positively associated with arsenicosis. Relative risk (RR) showed that unemployed group had 1.44 times higher risk to form arsenicosis than service holder.

Table 20: Association of socio-demographic characteristic with exposed and non-exposed groups:

Variables	Exposed		Nonexposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) pValue Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) p Value Odds Ratio(OR) Relative Risk (RR)	Chi-square (λ^2) p Value Odds Ratio (OR) and Relative Risk (RR)
Income				λ^2 = 11.01 p=0.001 S	λ^2=0.01 p=0.935	λ^2=9.0 p=0.002 S
Poor class	295 (73.8)	297 (74.3)	331 82.3)	OR=0.59 0.43<OR<0.81	OR=0.97 0.70<OR<1.35	OR=0.59 0.41<OR<0.84
Middle-higher	105 (26.2)	103 (25.8)	69 (17.3)	RR=0.85 0.79<RR<0.93	RR=0.99 0.84<RR<1.15	RR=0.78 0.67<RR<0.90
Mediaexposed				λ^2 = 11.22 p=0.000 S	λ^2=35.32 p=0.000 S	λ^2 = 28.84 p=0.000 S
Nothing	201 (50.3)	164 (41.0)	249 (62.3)	OR= 0.610.46<OR<0.82	OR=0.42 0.31<OR<9.57	OR=0.51 0.40<OR<0.66
Have media	199 (49.7)	236 (59.0)	151 (37.7)	RR=0.79 0.68<RR<0.90	RR=0.65 0.56<RR<0.75	RR=0.80 0.74<RR<0.87
Religion:				λ^2 = 0.18 p=0.777	λ^2 =0.08 p=0.772	λ^2 = 0.12 p=0.704
Islam	376 (94.0)	376 (94.0)	373 (93.3)	OR=1.18 0.62<OR<2.08	OR = 1.13 0.62<OR<2.08	OR=1.13 0.68<OR<1.89
Others	24 (6.0)	24 (6.0)	27 (6.7)	RR=1.09 0.79<RR<1.44	RR = 1.07 0.79<RR<1.14	RR=1.04 0.88<RR<1.24

**** 95 percent confidence limits implies that there is only a 5 percent chance that the ranges of the mentioned factors excluded the percentage of population.***

Table 20 found that 73.8 percent mother of arsenicosis, 74.3 percent mother of nonarsenicosis in exposed and 82.3 percent mother in nonexposed group were in poor class. Income was significantly associated with exposed and nonexposed group ($p<0.005$). Most of the mothers 94.0 percent of arsenicosis, 94.0 percent of nonarsenicosis in exposed and 93.3 percent of nonexposed group were Muslims. Odds ratio and relative risk (OR=1.0, RR=1.0) showed that Muslim and non Muslims had equal chance to form arsenicosis.

Table 21: Association of height, weight and BMI with exposed and nonexposed groups:

Variables	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) RelativeRisk (RR)	Chi-square (λ^2 Odds Ratio (OF Relative Risk (I
Height(cm) ≤150	302 (75.5)	280 (70.0)	255 (63.7)	λ^2=9.82 p=0.001 S OR=1.52 1.16<OR<1.98 RR=1.16 1.05<RR<1.27	λ^2 = 2.78 p=0.015 S OR = 1.32 0.95<OR<1.83 RR = 1.51 0.98<RR<1.36	λ^2=2.51 p=0.000 S OR = 1.75 1.28<OR<2.41 RR = 1.34 1.13<RR<1.60	λ^2=3.25 p=0.0 OR = 1.33 0.98<OR<1.80 RR = 1.16 0.99<RR<1.35
>150	98 (24.5)	120 (30.0	145 (36.3)				
Weight(kg) ≤ 50	338 (84.5)	351 (87.7)	358 (89.5)	λ^2=2.44 p=0.118 OR = 0.73 0.49<OR<1.08 RR = 0.91 0.82<RR<1.01	λ^2 = 1.51 P=0.219 OR = 0.76 0.50<OR<1.16 RR = 0.88 0.73<RR<1.05	λ^2=3.99 p=0.045 S OR = 0.64 0.41<OR<0.99 RR = 0.81 0.68<RR<0.97	λ^2 = 0.45 p=0.5 OR = 0.84 0.53<OR<1.33 RR = 0.92 0.75<RR<1.13
>50	62 (15.5)	49 (12.3)	42 10.5)				
BMI: < 18.5	114 (28.5)	178 (44.5)	236 (59.0)	λ^2=53.0 p=0.000 S OR = 0.40 0.31<OR<0.51 RR = 0.73 0.67<RR<0.80	λ^2= 17.10 p=.000 S OR = 0.53 0.37<OR<0.67 RR = 0.72 0.59<RR<0.82	λ^2 = 74.37 p=.000 S OR = 0.28 0.20<OR<0.38 RR = 0.51 0.43<RR<0.61	λ^2=16.26p=.00 OR = 0.56 0.42<OR<0.74 RR = 0.75 0.65<RR<0.86
≥ 18.5	286 (71.5)	222 (55.5)	164 (41.0)				

** Percentage in the parenthesis*

Table 21 height measurement showed that 75.5 percent mother of arsenicosis, 70.0 percent mother of nonarsenicosis in exposed group while 63.7 percent mother in nonexposed group had ≤150cm was significantly associated with exposed and nonexposed group ($p<0.005$). arsenicosis and nonarsenicosis group ($p<0.05$) and arsenicosis and nonexposed groups ($p<0.001$). Weight measurement showed that 84.5 percent mother of arsenicosis, 87.7 percent mother of nonarsenicosis in exposed group and 89.5 percent mother in nonexposed group had weight less than 50 kg. Weight ≤50 kg was significantly associated with arsenicosis and nonexposed group ($p<0.001$) Calculated BMI showed that 28.5 percent mother of arsenicosis, 44.5 percent of nonarsenicosis in exposed group and 59.0 percent in nonexposed group had BMI <18.5. BMI was significantly associated with exposed and nonexposed group ($p<0.001$). arsenicosis and nonexposed group ($p<0.001$) and nonarsenicosis and nonexposed group($p<0.001$).

Table 22: Association of drinking and cooking water wit exposed and nonexposed group:

Source of drinking and cooking water	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Drinking water: Same Tube-well	105 (26.3)	103 (25.7)	386 (96.5)	λ^2=527.4p=0.000S OR = 0.01 0.01<OR<0.02 RR = 0.36 0.32<RR<0.40	λ^2= 0.01 p=0.935 OR = 1.03 0.74<OR<1.43 RR = 1.01 0.87<RR<1.19	λ = 92.02 p=0.000 S OR = 0.27 0.01<OR<0.02 RR = 0.43 0.19<RR<0.27	λ^2=418.33 p=0.000S OR = 0.01 0.01<OR<0.02 RR = 0.22 0.19<RR<0.26
Alternative sources	295 (73.7)	297 (74.3)	14 (3.5)				
Cooking water: Same Tube-well	74 (18.5)	67 (16.7)	387 (96.7)	λ^2=674.36p=0.00S OR = 0.01 0.00<OR<0.01 RR = 0.27 0.24<RR<0.31	λ^2=1.51p=0.219 OR = 0.76 0.50<OR<1.16 RR = 0.88 0.73<RR<1.05	λ^2 = 3.99 p=0.045 S OR = 0.64 0.77<OR<1.65 RR = 0.81 0.89<RR<1.26	λ^2=518.25 p=0.000S OR = 0.01 0.0<OR<0.01 RR = 0.15 0.12<RR<0.19
Alternative sources	326 (81.5)	333 (83.3)	13 (3.3)				

Percentage in the parenthesis

Table 22 reveals that 26.3 percent mother of arsenicosis and 25.7 percent mother of nonarsenicosis in exposed group still drinking arsenic contaminated water from the same tube well. Similarly 18.5 percent mother of arsenicosis and 16.7 percent mother of nonarsenicosis in the exposed group still using arsenic contaminated water from the same tube well for cooking purpose. On the other hand 96.5 percent mother drinking arsenic free water and 96.7 percent mother using water for cooking purpose from the same tube well in nonexposed group. Source of drinking and cooking water were significantly associated with exposed and nonexposed, arsenicosis and nonexposed group ($p<0.05$) and nonarsenicosis and nonexposed group ($p<0.05$).

Table 23: Association of fasting blood glucose level with arsenic exposed and nonexposed groups:

Fasting glucose level	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
IFG and DM	69 (17.3)	54 (13.5)	60 (15.0)	$\lambda^2 = 0.01$ p=0.932 OR = 1.03 0.73<OR<1.46 RR = 1.01 0.90<RR<1.13	$\lambda^2 = 1.88$ p=0.169 OR = 1.34 0.89<OR<2.00 RR = 1.15 0.96<RR<1.37	$\lambda^2 = 0.59$ p=0.441 OR = 1.18 0.80<OR<1.75 RR = 1.08 0.91<RR<1.30	$\lambda^2 = 0.26$ p=0.613 OR = 0.88 0.58<OR<1.34 RR = 0.94 0.76<RR<1.16
Normal	331 (82.7)	346 (86.5)	340 (85.0)				

** Percentage in the parenthesis*

Table 23 shows that, 17.3 percent of arsenicosis and 13.5 percent of nonarsenicosis mother in exposed group while 15.0 percent mother in nonexposed group were found impaired fasting glucose (IFG) and diabetes mellitus (DM). No association was found between exposed and nonexposed group of mother.

Table 24: Assoeiation of blood glucose level 2 hours after 75gm glucose with arsenic exposed and nonexposed group:

Glucose 2HA 75gm glucose	Exposed		Non exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2), Odds Ratio (OR), Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
IFG and DM	75 (18.7)	58 (14.6)	55 (13.7)	λ^2 = 1.46 p=0.227 OR = 1.25 0.88<OR<1.78 RR = 1.07 0.97<RR<1.19	λ^2 = 2.31 p=0.128 OR = 1.36 0.92<OR<2.01 RR = 1.16 0.98<RR<1.37	λ^2 =3.32 p=0.040S OR = 1.45 0.97<OR<2.15 RR = 1.19 1.01<RR<1.40	λ^2 = 0.04 p=0.831 OR = 1.06 0.70<OR<1.61 RR = 1.03 0.85<RR<1.25
Normal	325 (81.3)	342 (85.4)	345 (86.3)				

** Percentage in the parenthesis*

Table 24 shows that IFG and DM were 18.7 percent mother with arsenicosis, 14.6 percent mother with nonarsenicosis in exposed group while 13.7 percent in nonexposed group. Blood glucose level 2 hours after 75gm glucose was significantly associated with arsenicosis and nonexposed group. Odds ratio and relative risk showed that IFG and DM was positively associated with arsenic exposure ($p<0.05$; OR=1.45; RR=1.19).

Table 25: Association of age of marriage with exposed and nonexposed groups:

Age of marriage	Exposed		Unexposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2), Odds Ratio (OR), Relative Risk (RR)	Chi-square (λ^2)Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2), Odds Ratio (OR), Relative Risk (RR)
< 18 Years	340 (85.0)	340 (85.0)	366 (91.5)	λ^2 = 9.5 p=0.002 S OR = 0.53 0.35<OR<0.80 RR = 0.83 0.76<RR<0.92	λ^2 = 0.01 p=0.921 OR = 1.0 0.67<OR<1.50 RR = 1.0 0.82<RR<1.21	λ^2 = 7.53 p=0.006 S OR = 0.53 0.33<OR<0.84 RR = 0.75 0.64<RR<0.89	λ^2=7.53 p=0.006 S OR = 0.53 0.33<OR<0.84 RR = 0.75 0.64<RR<0.89
≥ 18 Years	60 (15.0)	60 (15.0)	34 (8.5)				

* *Percentage in the parenthesis*

Table 25 reveals that 85.0 percent mother of arsenicosis, 85.0 percent mother of nonarsenicosis in exposed group and 91.5 percent mother in nonexposed group got married before they reach 18 years of age. The mean age was 16.7±1.86, 17.2±1.61 and 16.0±2.30 years in different groups respectively. Marriage age was significantly associated with exposed and nonexposd group ($p<0.005$), arsenicosis and nonexposed group ($p<0.005$), and nonarsenicosis and nonexposed group ($p<0.005$).

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Table 26: Association of age of menarche with exposed and nonexposed groups:

Age of menarche	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
>12 Years	137 (34.3)	196 (49.0)	115 (28.7)	λ=18.35 p=0.000 S OR = 1.77 1.35<OR<2.31	λ^2 =17.31 p=0.000 S OR = 0.54 0.40<OR<0.73	λ^2=2.55 p=0.109 OR = 1.29 0.95<OR<1.76	λ^2=33.67p=0.000 S OR = 2.38 1.76<OR<3.22
≤ 12	263 (65.7)	204 (51.0)	285 (71.3)	RR = 1.20 1.11<RR<1.29	RR = 0.73 0.63<RR<0.85	RR = 1.13 0.98<RR<1.31	RR = 1.51 1.32<RR<1.73

** Percentage in the parenthesis*

Table 26 shows that 65.7 percent mother of arsenicosis, 51.0 percent mother of nonarsenicosis in exposed group while 71.3 percent mother in nonexposed group had started their menstruation on or before 12 years of age The mean age of menarche were 12.9±0.98, 12.7±0.98 and 12.9±0.82 years in different groups respectively. Chi-square test (λ^2=17.31, showed that age of menarche was significantly associated with exposed and nonexposed (λ^2=18.35; p<0.001, OR=1.77; 1.35<OR<2.31, RR=1.20; 1.11<RR<1.29) arsenicosis and nonarsenicosis (p<0.001) nonarsenicosis group and nonexposed (λ^2=33.67; p<0.001, OR=2.38; 1.76<OR<3.22, RR=1.51; 1.32<RR<1.73)

Table 27: Association of menstrual problems with exposed and nonexposed groups:

Menstrual problems	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Noexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Irregular	129 (32.3)	125 (31.3)	130 (32.5)	λ^2 =0.04 p=0.843 OR = 0.97 0.74<OR<1.26	λ^2 = 0.05 p=0.819 OR = 1.05 0.70<OR<1.30	λ^2 =0.0 p=1.0 OR = 0.99 0.74<OR<1.38	λ^2 = 0.09 p=0.761 OR = 0.94 0.69<OR<1.29
Regular	271 (67.7)	275 (68.7)	270 (67.5)	RR = 0.99 0.91<RR<1.08	RR = 1.02 0.84<RR<1.13	RR = 0.99 0.78<RR<1.17	RR = 0.97 0.84<RR<1.13

** Percentage in the parenthesis*

Table 27 shows that 32.3 percent mother of arsenicosis, 31.3 percent mother of nonarsenicosis in exposed group and 32.5 percent mother in the nonexposed group had irregular menstruation. Chi-square test, Odds ratio and Relative risk showed that menstrual problem was not significantly associated with arsenicosis and nonarsenicosis group, and arsenicosis and nonexposed group.

Table 28: Association of contraceptive use with exposed and nonexposed groups:

Use of Contraceptive	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR) Z-value	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR) Z-value	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR) Z-value	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR) Z-value
Not used contraceptive	196 (49.0)	180 (45.0)	104 (26.0)	λ^2=48.13 p=.000S OR = 2.52 1.92<OR<3.31 RR = 1.33 1.23<RR<1.44 Z=7.47 p=0.000 S	λ^2 = 1.13 p=0.287 OR = 1.17 0.88<OR<1.57 RR = 1.18 0.94<RR<1.24 Z=1.13 p=0.258	λ^2 =44.17 p=0.000 S OR = 2.73 2.10<OR<3.72 RR = 1.60 1.40<RR<1.83 Z=6.92 p=0.000 S	λ^2=30.71p=0.000S OR = 2.33 1.71<OR<3.17 RR = 1.49 1.30<RR<1.70 Z=5.72 p=0.000 S
Used contraceptive	204 (51.0)	220 (55.0)	296 (74.0)				

** Percentage in the parenthesis*

Table 28 reveals that 51.0 percent mother of arsenicosis, 55.0 percent mother of nonarsenicosis in exposed group while 74.0 percent mother of nonexposed group used contraceptives. Use of contraceptive in nonexposed group was significantly higher (Z=6.93, p<0.001) than that of exposed arsenicosis group λ^2=48.13; p<000S; OR=2.52; 1.92<OR<3.31; RR=1.33; 1.23<RR<1.44; Z=7.47 p<0.001). Use of contraceptive was significantly associated with exposed arsenicosis and nonexposed group showed that exposure (not use of contraceptive) was positively associated with arsenicosis. Relative risk (1.60) showed that exposure had 1.60 times higher risk to form arsenicosis than nonexposed group (use of contraceptive) (λ^2=44.17; p<0.001, OR=2.73; 2.10<OR<3.72, RR=1.60; 1.40<RR<1.83, Z=6.92; p<0.001).

Table 29: Association of pregnancy with exposed and nonexposed groups:

Pregnant	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Unexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Yes	28 (7.0)	33 (8.3)	23 (5.7)	λ^2 =0.40 p=0.452 OR = 1.21 0.72<OR<2.05 RR = 1.06 0.92<RR<1.21	λ^2 = 0.28 p=0.594 OR = 0.84 0.48<OR<1.46 RR = 0.91 0.69<RR<1.21	λ^2 =0.34 p=0.562 OR = 1.23 0.67<OR<2.26 RR = 1.11 0.85<RR<1.43	λ^2 = 1.56 p=0.212 OR = 1.47 0.82<OR<2.65 RR = 1.19 0.95<RR<1.50
No	372 (93.0)	367 (91.7)	377 (94.3)				

** Percentage in the parenthesis*

Table 29 shows that 7.0 percent mother of arsenicosis, 8.3 percent mother of nonarsenicosis and 5.8 percent mother in exposed group were found to be pregnant. Based on the Chi-square test it was found that pregnancy was not significantly associated with exposed and nonexposed group ($p>0.05$).

Table 30: Association of birth order with exposed and nonexposed groups:

Birth order	Exposed		Nonexposed	Exposed And Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
> 2	293 (73.3)	249 (62.3)	232 (58.0)	Z=3.28 p=0.001 S λ^2=10.65p=0.001S OR = 1.52 1.18<OR<1.96 RR = 1.16 1.06<RR<1.26	Z=3.35 p=0.0009 S λ^2 = 0.58 p=0.001 S OR = 1.66 1.22<OR<2.27 RR = 1.30 1.11<RR<1.54	Z=4.62 p=0.0000 S λ^2 =19.95 p=0.000 S OR = 1.98 1.46<OR<2.70 RR = 1.43 1.21<RR<1.69	Z=1.24 p=0.2150 λ^2 = 1.33 p=0.247 OR = 1.19 0.89<OR<1.60 RR = 1.09 0.95<RR<1.26
≤ 2	107 (26.7)	151 (37.7)	168 (42.0)				

* Percentage in the parenthesis

Table 30 shows that 26.7 percent mother of arsenicosis, 37.7 percent mother of nonarsenicosis and 42.0 percent mother in nonexposed group had their birth order 2 or less than 2. Birth order more than two 73.3 percent of arsenicosis were significantly higher than that of 62.8 percent of nonarsenicosis in exposed group and 58.0 percent in nonexposed group ($p<0.001$) respectively. It was found that birth order was significantly associated with exposed arsenicosis and nonexposed group ($p<0.001$). Odds ratio (OR=1.66) showed that in exposed group (birth order >2) was positively associated with arsenicosis. Relative risk (RR=1.30) showed that exposure had 1.30 times higher risk to form arsenicosis than nonexposure. It was also found that birth order was significantly associated with arsenicosis and nonexposed group ($p<0.001$).

Table 31: Association of ever visit ANC with exposed and nonexposed groups:

Received ANC	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
No	310 (77.5)	302 (75.5)	326 (81.5)	Z=1.40 p=0.162 λ^2 =3.62 p=0.057 OR = 0.74 0.54<OR<1.101 RR = 0.91 0.83<RR<0.99	Z=0.67 p=0.503 λ^2 = 0.34 p=0.559 OR = 1.12 0.86<OR<1.57 RR = 1.06 0.89<RR<1.25	Z=1.40 p=0.162 λ^2 =1.73 p=0.188 OR = 0.78 0.55<OR<1.12 RR = 0.89 0.89<RR<1.04	Z=0.67 p=0.503 λ^2 = 03392 p=0.047 OR = 0.70 0.49<OR<1.00 RR = 0.84 0.72<RR<0.98
Yes	90 (22.5)	98 (24.5)	74 (18.5)				

** Percentage in the parenthesis*

Table 31 reveals that 22.5 percent mother of arsenicosis, 24.5 percent mother of nonarsenicosis and 18.5 percent mother in nonexposed group had received ante-natal-care. Chi-square test (λ^2 = 0.34, p>0.05) showed that ever visit ANC was not significantly associated with exposed arsenicosis and nonarsenicosis group. Similar association (λ^2=1.73, p>0.05) of ANC received with exposed arsenicosis and nonexposed group..

Table 32: Association of health problems during pregnancy with exposed and nonexposed groups:

Health problem	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	_Nonarsenicosis and Nonexposed_
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z- value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z- value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Yes	191 (47.7)	206 (51.5)	148 (37.0)	Z=4.21 p=0.000 S λ^2 =16.64 p=0.000 S OR = 1.68 1.30<OR<2.16 RR = 1.18 1.09<RR<1.28	Z=1.08 p=0.280 λ^2 = 0.98 p=0.322 OR = 0.86 0.65<OR<1.05 RR = 0.93 0.81<RR<1.07	Z=3.08 p=0.001 S λ^2 =9.03 p=0.002 S OR = 1.56 1.16<OR<2.08 RR = 1.24 1.08<RR<1.43	Z=4.17 p=0.000 S λ^2=16.46 p=0.000 S OR = 1.81 1.35<OR<2.42 RR = 1.34 1.17<RR<1.54
No	209 (52.3)	194 (48.5)	252 (63.0)				

Percentage in the parenthesis

Table 32 shows that health problem during pregnancy, 47.7 percent of arsenicosis group was significantly higher than that of 37.0 percent in nonexposed group (Z=4.21; p<0.001; λ^2=16.64; p<0.001; OR=1.68; 1.30<OR<2.16; RR=1.18 1.09<RR<1.28). On the other health problem during pregnancy was significantly associated with arsenicosis and nonexposed group (Z=3.08 p<0.001; λ^2=9.03 p<0.002; OR=1.56; 1.16<OR<2.08; RR=1.24; 1.08<RR<1.43), nonarsenicosis and nonexposed group (Z=4.17; p<0.001; λ^2=16.46 p<0.001; OR=1.81; 1.35<OR<2.42; RR=1.34; 1.17<RR<1.54). Odds Ratio (OR=1.56) showed that health problem was positively associated with arsenicosis. Relative risk (RR=1.24) showed that health problem had 1.24 times higher risk to form arsenicosis than nonexposed group.

Table 33: Association of nature of delivery with exposed and nonexposed groups:

Nature of delivery	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Instrumental delivery	20 (5.0)	23 (5.7)	15 (3.7)	λ^2 =1.20 p=0.273 OR = 1.46 0.77<OR<2.78 RR = 1.12 0.96<RR<1.31	λ^2 = 0.10 p=0.753 OR = 0.86 0.45<OR<1.66 RR = 0.93 0.67<RR<1.29	λ^2 =0.48 p=0.489 OR = 1.35 0.65<OR<2.82 RR = 1.15 0.86<RR<1.55	λ^2 = 1.35 p=0.244 OR = 1.57 0.77<OR<3.21 RR = 1.22 0.94<RR<1.60
Normal delivery	380 (95.0)	377 (94.3)	385 (96.3)				

** Percentage in the parenthesis*

Table 33 shows that 5.0 percent mother of arsenicosis, 5.7 percent mother of nonarsenicosis in exposed group and 3.7 percent mother of nonexposed group had instrumental delivery. Based on Chi-square test (λ^2=0.10; p>0.05) it was found that nature of delivery was not significantly associated with arsenicosis and nonarsenocosis group and in exposed and nonexposed group.

Table 34: Association of time of recent delivery with exposed and nonexposed groups:

Time of delivery	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Not in fulltime	42 (10.5)	54 (13.5)	19 (4.7)	Z=5.32 p=0.000 S λ^2=15.35 p=0.000 S OR = 2.73 1.61<OR<4.70 RR = 1.29 1.17<RR<1.41	Z=1.30 p=0.194 λ^2 = 1.43 p=0.231 OR = 0.75 0.48<OR<1.18 RR = 0.86 0.68<RR<1.09	Z=3.11 p=0.002 S λ^2 =8.59 p=0.003 S OR = 2.53 1.30<OR<4.28 RR = 1.42 1.18<RR<1.71	Z=4.37 p=0.000 S λ^2= 17.43 p=0.000 S OR = 3.13 1.77<OR<5.59 RR = 1.55 1.33<RR<1.82
During fulltime	358 (89.5)	346 (86.5)	381 (95.3)				

** Percentage in the parenthesis*

Table 34 shows that delivery not in fulltime 10.5 percent of arsenicosis was significantly higher ($p<0.001$) than that of 4.7 percent in nonexposed group ($p<0.001$. On the other hand delivery not in full time was significantly associated ($\lambda^2=8.59$, $p<0.001$) with arsenicosis and nonexposed group ($p<0.001$) and in nonarsenicosis and nonexposed group ($p<0.001$). Odds ratio (OR=2.53) showed that exposure (not in fulltime) was positively associated with arsenicosis. Relative risk (RR=1.42) showed that delivery not in full time had 1.42 times higher risk to form arsenicosis than nonexposed group ($p<0.001$).

Table 35: Compare reproductive outcome in arsenic exposed and nonexposed group:

Reproductive Outcome	Exposed		Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Nonarsenicosis N (%)	Control group N (%)			
Alive child	283 (70.8) z-score=2.26 S p=0.024	311 (77.8) z-score=2.26 S p=0.024	361 (90.3) z-core=2.27S p=0.023	OR=0.69, 0.50<OR<0.96 RR =0.84, 0.72<RR<0.97	OR=0.26, 0.17<OR<0.39 RR =0.59, 0.52<RR<0.66	OR=0.38, 0.25<OR<0.58 RR =0.67, 0.58<RR<0.77
Neonatal death	16 (4.0) z-score=0.41 p=0.682	14 (3.5) z-score=0.39 p=0.697	8 (2.0) z-score=0.36 p=0.719	OR=1.15, 0.52<OR<2.53 RR =1.07, 0.76<RR<1.51	OR=2.04, 0.81<OR<5.27 RR =1.35, 1.01<RR<1.80	OR=01.78, 0.69<OR<4.68 RR =1.28, 0.93<RR<1.77
Stillbirth	17 (4.3) z-score=0.40 p=0.689	15 (3.8) z-score=0.38 p=0.704	9 (2.3) z-score=0.36 p=0.719	OR=1.14, 0.53<OR<2.44 RR =1.07, 0.76<RR<1.49	OR=1.93, 0.80<OR<4.74 RR =1.32, 0.99<RR<1.76	OR=1.69, 0.69<OR<4.24 RR =1.26, 0.92<RR<1`.73
Premature	26 (6.5) z-score=0.31 p=0.757	19 (4.8) z-score=0.34 p=0.734	7 (1.8) z-score=0.37 p=0.711	OR=1.39, 0.73<OR<2.67 RR =1.17, 0.90<RR<1.51	OR=3.90, 1.54<OR<10* RR =1.62, 1.33<RR<1.96	OR=2.80, 1.10<OR<7.42* RR =1.48, 1.16<RR<1.89
Handicapd	5 (1.3) z-score=0.52 p=0.603	3 (0.8) z-score=0.48 p=0.704	1 (0.3) z-score=0.42 p=0.675	OR=1.68, 0.35<OR<0.88 RR =1.25, 0.73<RR<2.15	OR=5.05, 0.57<OR<114* RR =1.68, 1.16<RR<2.41	OR=3.02, 0.28<OR<75.5* RR =1.50, 0.85<RR<2.66
Miscarriage	31 (7.8) z-score=0.26 p=0.795	21 (5.3) z-score=0.32 p=0.749	8 (2.0) z-score=0.37 p=0.711	OR=1.52, 0.83<OR<2.79 RR =1.21, 0.96<RR<1.53	OR=4.12, 1.78<OR<9.85 RR =1.64, 1.38<RR<1.95	OR=2.72, 1.13<OR<6.75 RR =1.47, 1.16<RR<1.86
Abortion	22 (5.5) z-score=0.35 p=0.726	17 (4.3) z-score=0.36 p=0.719	6 (1.5) z-score=0.38 p=0.704	OR=1.31, 0.66<OR<2.63 RR =1.14, 0.85<RR<1.51	OR=3.82, 1.45<OR<10* RR =1.60, 1.31<RR<1.97	OR=2.91, 1.07<OR<8.36* RR =1.50, 1.16<RR<1.93

** S= Z-score is significant at the .05 level*

Table 35 reveals that 70.8 percent mother of arsenicosis, 77.8 percent mother of nonarsenicosis in exposed group and 90.3 percent mother in nonexposed group delivered alive child. Their z-score were found to be significant ($p<0.05$). Neonatal death 4.0 percent, 3.5 percent and 2.0 percent; Stillbirth 4.3 percent, 3.8 percent and 2.3 percent; Premature 6.5 percent, 4.8 percent and 1.8 percent; Handicapped 1.3 percent, 0.8 percent and 0.3 percent; Miscarriage 7.8 percent, 5.3 percent and 2.0 percent; Abortion 5.5 percent, 4.3 percent and 1.5 percent were in different groups respectively. From the results of Odds ratio and relative risk it was also found that neonatal death, stillbirth, premature, handicapped, miscarriage and abortion were positively associated with arsenicosis. Degree of positive association and risk of exposure in arsenicosis and nonexposed group were higher than that of arsenicosis & nonarsenicosis and nonarsenicosis & nonexposed group respectively.

Table 36: Comparison of reproductive outcome in arsenic exposed and nonexposed group:

Reproductive outcome	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk(RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Not alive	117 (29.2)	89 (22.2)	39 (9.7)	Z=16.05 p=0.000S λ^2 =41.04p=0.000S OR = 3.21 2.19<OR<4.71 RR = 1.35 1.26<RR<1.46	Z=2.27 p=0.023 S λ^2=4.77 P=0.029S OR = 1.44 1.04<OR<2.01 RR = 1.19 1.03<RR<1.38	Z=2.71 p=0.007 S λ^2=47.2 p=0.000 S OR = 3.83 2.54<OR<5.79 RR = 1.71 1.51<RR<1.94	Z=4.90 p=0.000 S λ^2=22.33p=0.000S OR = 2.65 1.73<OR<4.06 RR = 1.50 1.31<RR<1.73
Alive	283 (70.8)	311 (77.8)	361(90.3)				

** Percentage in the parenthesis*

Table 36 shows that adverse reproductive outcome were significantly higher in exposed group than nonexposed groups (Z=16.05 p<0.001; λ^2 =41.04; p<0.001) (Z=4.90, p<0.001), arsenicosis and nonarsenicosis group were (Z=2.27 p<=0.05, λ^2=4.77; p<=0.05), arsenicosis and nonexposed (Z=2.71 p<0.005, λ^2=47.2; p<0.005), and nonarsenicosis and nonexposed (Z=4.90; p<0.001, λ^2=22.33p<0.001) Adverse pregnancy outcome was 3.21 times higher in exposed group than nonexposed group (OR=3.21; 2.19<OR<4.71, RR=1.35; 1.26<RR<1.46) and in arsenicosis 1.44 times higher than nonarsenicosis group (OR=1.44; 1.04<OR<2.01, RR=1.19; 1.03<RR<1.38). It was also found that strength of positive association and degree of risk of exposure higher in exposed than nonexposed group.

Table 37: Association of ever received PNC with exposed and nonexposed groups:

Ever received PNC	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis And Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
No	318 (79.5)	298 (74.5)	359 (89.7)	Z=5.79 p=0.000 S λ^2=39.25p=0.000 S OR = 0.32 0.22<OR<0.47 RR = 0.72 0.66<RR<0.78	Z=1.68 p=0.093 λ^2 = 2.55 p=0.100 OR = 1.35 0.94<OR<1.87 RR = 1.16 0.97<RR<1.38	Z=4.04, p=0.000 S λ^2=15.37 p=0.000 S OR = 0.46 0.29<OR<0.68 RR = 0.70 0.61<RR<0.82	Z=5.72, p=0.000 S λ^2 =30.65 p=0.000 S OR = 0.33 0.22<OR<0.50 RR = 0.64 0.56<RR<0.73
Yes	82 (20.5)	102 (25.5)	41 (10.3)				

** Percentage in the parenthesis*

Table 37 reveals that 20.5 percent mother of arsenicosis, 25.5 percent mother of nonarsenicosis in exposed group and 10.3 percent mother in nonexposed group had ever received post-natal-care. Ever received PNC in nonexposed group was significantly higher ($p<0.000$) than that of arsenicosis group. Chi-square test ($\lambda^2=2.55$, $p>005$) showed that ever received PNC was not significantly associated with arsenicosis and nonarsenicosis. On the other hand received PNC was significantly associated with exposed arsenicosis and nonexposed group ($\lambda^2=15.37$, $p<0.000$).

Table 38: Association of health problems during post-natal period with exposed and nonexposed groups:

Health problems	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR), Relative Risk (RR)
Yes	249 (62.3)	279 (69.7)	157 (39.3)	Z=8.98 p=0.000 S λ^2=76.80p=0.000S OR = 3.0 2.33<OR<3.88 RR = 1.46 1.33<RR<1.60	Z=2.09 P=0.036 S λ^2 = 4.68 P=0.030 S OR = 0.72 1.04<OR<1.37 RR = 0.85 1.02<RR<1.16	Z=6.72 p=0.000 S λ^2=41.41 p=0.000 S OR = 2.25 1.90<OR<3.43 RR = 1.60 1.38<RR<1.85	Z=8.96 p=0.000 S λ^2= 73.80 p=0.000 S OR = 3.57 2.63<OR<4.84 RR = 1.93 1.64<RR<2.26
No	151 (37.7)	121 (30.3)	243 (60.7)				

** Percentage in the parenthesis*

Table 38 shows that health problem of arsenicosis 62.5 percent mother were significantly higher than that of 69.5 percent of nonarsenicosis and 39.4 percent in nonexposed group respectively ($p<0.001$). Based on Chi-square test it was found that health problem during post natal period were significantly associated with exposed and nonexposed group respectively ($p<0.05$). Odds ratio (OR=2.25) showed that exposure (health problem) was positively associated with arsenicosis. Relative risk (RR=1.60) showed that exposure had 1.60 times higher risk to form arsenicosis than nonexposure (no health problem).

Table 39: Association with problems for never received PNC in exposed and nonexposed groups:

Problem for never received PNC	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Problem	69 (42.3)	180 (45.0)	105 (26.3)	Z=6.16 p=0.000 S λ^2 =41.81p=0.000S OR = 2.36 1.80<OR<3.09 RR = 1.30 1.20<RR<1.40	Z=0.77 p=0.441 λ^2 = 0.51 p=0.475 OR = 0.89 0.67<OR<1.19 RR = 0.95 0.63<RR<1.13	Z=4.83 p=0.000 S λ^2=22.03 p=0.000S OR = 2.06 1.51<OR<2.80 RR = 1.40 1.23<RR<1.61	Z=5.63 p=0.000 S λ^2=29.85p=0.000 S OR = 2.30 1.69<OR<3.13 RR = 1.48 1.29<RR<1.69
No Problem	231 (57.7)	220 (55.0)	295 (73.7)				

* ***Percentage in the parenthesis***

Table 39 shows that health problem for never received PNC 42.3 percent of arsenicosis was significantly higher than that of 26.3 percent of nonexposed group ($p<0.001$). It was also found that exposure (health problem for never received PNC) was not significantly associated ($\lambda^2=0.51$, $p>0.05$) with arsenicosis and nonarsenicosis group. It was found that exposure was significantly associated ($\lambda^2=22.03$, $p<0.001$) with arsenicosis and nonexposed group. Odds ratio (OR=2.06) showed that exposure was positively associated with arsenicosis.

Table 40: Association of duration of breast feeding with exposed and nonexposed groups:

Duration of breast feeding	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
< 6 months	380 (95.0)	386 (96.5)	372 (93.0)	λ^2 =3.57 p=0.058 OR = 1.70 0.98<OR<2.92	λ^2 = 0.77 p=0.380 OR = 0.69 0.32<OR<1.45	λ^2 =1.09 p=0.297 OR = 1.43 0.76<OR<2.64	λ^2=4.25 p=0.039 S OR = 2.08 1.03<OR<4.22
≥ 6 moths	20 (5.0)	14 (3.5)	28 (7.0)	RR = 1.23 0.98<RR<1.54	RR = 0.84 0.63<RR<1.13	RR = 1.21 0.86<RR<1.71	RR = 1.53 0.99<RR<2.36

• ***Percentage in the parenthesis***

Table 40 reveals that 5.0 percent mother of arsenicosis, 3.5 percent mother of nonarsenicosis in exposed group and 7.0 percent mother in nonexposed group had exclusive breast feeding. It was also found that most of the mothers fed their breast milk less than 5 months were 95.0 percent, 96.5 percent and 93.0 percent in different groups respectively. Based on Chi-square test it was found that duration of breast feeding were not significantly associated with exposed and nonexposed group respectively (p>0.05).

Table 41: Association of ever suffered STIs with exposed and nonexposed groups:

Ever suffered STIs	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Yes	53 (13.3)	43 (10.7)	24 (6.0)	λ^2 =12.67p=0.000S OR = 2.34 1.44<OR<3.82 RR = 1.27 1.15<RR<1.40	λ^2 = 0.796 p=0.327 OR = 1.27 0.81<OR<1.99 RR = 1.12 0.92<RR<1.36	λ^2 =11.27 p=0.000 S OR = 2.39 1.41<OR<4.09 RR = 1.43 1.21<RR<1.70	λ^2 =5.28 p=0.0221 S OR = 1.89 1.09<OR<3.28 RR = 1.32 1.09<RR<1.60
No	287 (71.7)	357 (89.3)	376 (94.0)				

** Percentage in the parenthesis*

Table 41 reveals that 13.3 percent mother of arsenicosis, 10.7 percent mother of nonarsenicosis in exposed group while 6.0 percent mother of nonexposed group had ever suffer sexually transmitted diseases STIs. Chi-square test showed that ever suffered STIs was significantly associated with arsenicosis and nonexposed group, and in nonarsenicosis and nonexposed group ($p<0.001$). Odds ratio (OR=2.39) showed that exposure (ever suffered STIs) was positively associated with arsenicosis. Relative risk (RR=1.43) showed that exposure had 1.43 times higher risk to form arsenicosis than non exposure (not suffered STIs).

Table 42: Association of ever received reproductive health care with exposed and nonexposed group:

Ever received RHC	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Traditional care	267 (66.7)	139 (34.7)	254 (63.5)	λ^2 =17.0 p=0.000 S OR = 0.59 0.46<OR<0.76 RR = 0.84 0.78<RR<0.91	λ^2 = 80.66 p=0.000S OR = 3.77 2.78<OR<5.11 RR = 1.95 1.67<RR<2.28	λ^2 =0.179 p=0.373 OR = 1.15 0.85<OR<1.56 RR = 1.08 0.93<RR<1.25	λ^2 =65.0 p=0.000S OR = 0.31 0.23<OR<0.41 RR = 0.55 0.47<RR<0.64
Modern care	133 (33.3)	261 (65.3)	146 (36.5)				

** Percentage in the parenthesis*

Table 42 shows that 33.3 percent mother of arsenicosis, 65.3 percent mother of nonarsenicosis in exposed group and 36.5 percent mother in nonexposed group had received modern reproductive health care. Chi-square test showed that received RHC was significantly associated with exposed and nonexposed group and with nonarsenicosis and nonexposed group($p<0.001$). Odds ratio (OR=3.77) showed that traditional care was positively associated with arsenicosis. Relative risk (RR=1.95) showed that exposure had 1.95 times higher risk to form arsenicosis than nonarsenicosis (modern care).

Table 43: Association of age of last child with exposed and nonexposed group:

Age of last child	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
< 2 Years	113 (28.3)	162 (40.5)	157 (39.3)	λ^2 =2.54 p=0.110 OR = 0.81 0.63<OR<1.05	λ^2 = 12.77 p=0.000 S OR = 0.58 0.43<OR<0.79	λ^2 =10.34 P=0.001 S OR = 0.61 0.45<OR<0.83	λ^2 = 0.08 p=0.777 OR = 1.05 0.79<OR<1.41
≥ 2 years	287 (71.7)	238 (59.5)	243 (60.7)	RR = 0.93 0.85<RR<1.01	RR = 0.75 0.64<RR<0.88	RR = 0.77 0.66<RR<0.91	RR = 1.03 0.89<RR<1.18

** Percentage in the parenthesis*

Table 43 reveals that 28.3 percent mother of arsenicosis, 40.5 percent mother of nonarsenicosis in exposed group and 39.3 percent mother in nonexposed group had their last child less than 2 years of age. On the other hand, 71.7 percent, 59.5 percent and 60.7 percent mother had their last child ≥ 2 years of age. The mean age were 4.38 (SD±4.13), 4.22 (SD± 3.70) and 3.33 (SD±2.28) years in different groups respectively. Chi-square test showed that age of last child of mother was significantly associated with arsenicosis and nonarsenicosis, and arsenicosis and nonexposed group respectively ($p<0.01$).

Table 44: Association of desire more children with exposed and nonexposed group:

Want more children	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Yes	130 (32.5)	127 (31.7)	204 (51.0)	λ^2 =39.36 p=0.000 S OR =0.45 0.35<OR<0.59 RR = 0.76 0.69<RR<0.83	λ^2 = 0.02 p=0.879 OR = 1.03 0.76<OR<1.41 RR = 0.02 0.88<RR<1.18	λ^2 =27.39 p=0.000 S OR =0.46 0.34<OR<0.62 RR = 0.67 0.58<RR<0.78	λ^2=29.77p=0.000S OR = 0.45 0.33<OR<0.60 RR = 0.66 0.56<RR<0.77
No	270 (67.5)	273 (68.3)	196 (49.0)				

** Percentage in the parenthesis*

Table 44 shows that 32.5 percent mother of arsenicosis, 31.7 percent mother of nonarsenicosis in exposed group and 51.0 percent mother in nonexposed group wanted more children. It was found that wanted more child was significantly associated with exposed and nonexposed group (p<.001), arsenicosis and nonexposed group (p<0.001) and nonarsenicos and nonexposed group (p<0.001).

Table-45: Association of health problems with exposed and nonexposed group:

Health problem	Exposed		Non Exposed	Exposed and Nonexposed	Arsenicosis and Nonarsenicosis	Arsenicosis and Nonexposed	Nonarsenicosis and Nonexposed
	Arsenicosis N (%)	Non Arsenicosis N (%)	Control group N (%)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)	Z-value Chi-square (λ^2) Odds Ratio (OR) Relative Risk (RR)
Problems	199 (49.7)	154 (38.5)	87 (21.7)	Z=8.99 p=0.000 S λ^2 = 56.53 p=0.000 S OR = 2.84 2.14<OR<3.78 RR = 1.36 1.26<RR<1.47	Z=3.21 p=0.001 S λ^2 = 9.82 p=0.001 S OR = 1.58 0.56<OR<1.26 RR = 1.25 0.77<RR<1.37	Z=8.64 p=0.000 S λ^2 = 67.05 p=0.000S OR = 3.56 0.61<OR<2.19 RR = 1.78 0.81<RR<1.42	Z=4.32 p=0.000 S λ^2 = 25.87 p=0.000S OR = 2.25 1.63<OR<3.11 RR = 1.45 1.27<RR<1.66
No problems	201 (50.3)	246 (61.5)	313(78.3)				

** Percentage in the parenthesis*

Table 45 shows that 49.7 percent various health problems of arsenicosis were significantly higher than that of 38.5 percent of nonarsenicosis and 21.7 percent in nonexposed group respectively ($p<0.001$). It was also found that health problem was significantly associated with arsenicosis and nonarsenicosis group($p<0.001$). Odds ratio (OR=1.58) showed that various health problem was positively associated with arsenicosis. Highly significant association of health problem with arsenicosis and nonexposed group was found (λ^2=67.05; $p<0.001$). Odds ratio (OR=3.56) showed that exposure (health problem) was positively associated with arsenicosis. Relative risk (RR=1.78) showed that exposure had 1.78 times higher risk to form arsenicosis than nonexposure (no health problem).

Figure14: Curvilinear relationship of arsenic level of arsenicosis group with classification of blood glucose level:

Figure 14 Curvilinear relationship of arsenic level in tube well water of exposed arsenicosis group by classification of blood glucose level

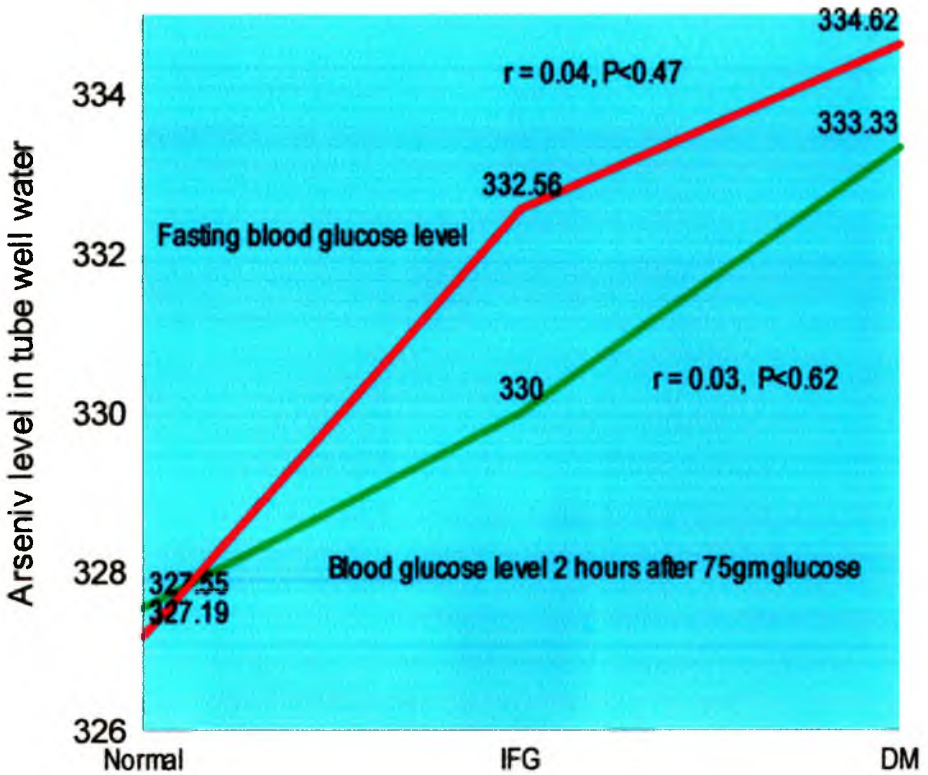

Figure 14 Curvilinear relationship shows that arsenic level in tubewell water of arsenicosis were positively correlated with the classification of blood glucose level. It was also found that strength of relationship of fasting blood glucose level with classification of blood glucose level was higher than the strength of relationship of blood glucose level 2 hours after 75gm glucose with classification of blood glucose level ($r=0.04$; $p<0.05$).

Figure 15: Curvilinear relationship of arsenic level of nonarsenicosis group with classification of blood glucose level:

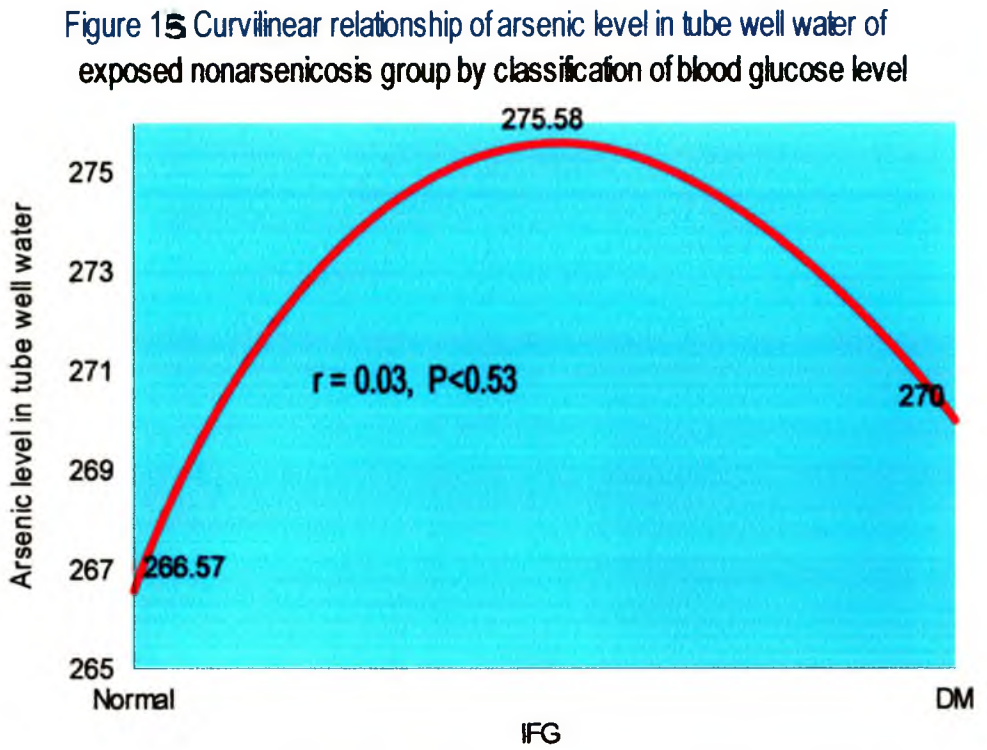

Figure 15: shows that arsenic level in tube well water of exposed nonarsenicosis was not significantly correlated (r=0.03, p>0.05) with the classification of blood glucose level.

Table 46: Comparison of age, birth order, fasting blood glucose level and blood glucose after 75gm glucose intake by reproductive outcome:

Variables	Groups	Reproductive outcome	Mean ± SD	Z-value	P-value
Age	Arsenicosis	Alive	33.23±7.73	- 1.29	0.199
		Not alive	34.26±7.07		
	Nonarsenicosis	Alive	29.55±6.55	- 2.59	0.011*
		Not alive	31.74±7.17		
	Nonexposed	Alive	29.39±6.10	- 0.55	0.58
		Not alive	30.03±6.86		
Birth order	Arsenicosis	Alive	3.45±1.67	- 3.84	0.000*
		Not alive	4.17±1.73		
	Nonarsenicosis	Alive	2.87±1.35	- 4.44	0.000*
		Not alive	3.62±1.53		
	Nonexposed	Alive	3.15±1.70	- 1.96	0.05*
		Not alive	3.79±1.98		
Fasting blood glucose level	Arsenicosis	Alive	5.29±1.36	- 0.77	0.444
		Not alive	5.42±1.53		
	Nonarsenicosis	alive	5.07±1.04	- 0.36	0.713
		Not alive	5.12±1.16		
	Nonexposed	alive	5.13±1.11	- 0.12	0.903
		Not alive	5.16±1.69		
Blood glucose after 75gm glucose intake	Nrsenicosis	Alive	6.38±2.04	- 0.35	0.726
		Not alive	6.46±2.09		
	Nonarsenicosis	alive	6.18±1.83	- 1.17	0.242
		Not alive	6.51±2.47		
	Nonexposed	alive	6.51±1.60	- 0.56	0.572
		Not alive	6.76±2.71		

**** The mean difference is significant at the0 .05 level.***

Table 46 shows that average age 31.74±7.17 of the respondent in nonarsenicosis group whose pregnancy outcome was not alive was significantly higher ($p<0.05$) than the average age 29.55±6.55 whose pregnancy outcome was alive. All in the three groups, average birth order whose pregnancy outcome was not alive was significantly higher ($p<0.05$) than whose pregnancy outcome was alive respectively.

Table 47: Relationship of arsenic level with others variable:

Variable	Exposed arsenicosis		Exposed nonarsenicosis	
	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value
Age group	0.110*	0.029	0.010	0.849
Income	- 0.142**	0.004	- 010	0.835
BMI	- 0.068	0.172	- 0.067	0.181
Age of marriage	- 0.152**	0.002	0.139**	0.005
Age of menarche	- 0.069	0.166	0.129**	0.010
Education	- 0.118*	0.019	0.030	0.471
Occupation	- 0.105*	0.035	- 0.016	0.745
Duration of drinking water	0.023	0.649	- 0.003	0.95
Fasting blood glucose level	0.036	0.475	0.037	0.445
Glucose after 75mg glucose	0.024	0.626	0.025	0.612
Birth order	0.136**	0.006	- 0.013	0.792
Reproductive outcome	0.017	0.741	0.039	0.435

***** Correlation is significant at the 0.01 level (2-tailed).***
**** Correlation is significant at the 0.05 level (2-tailed).***
+ ve correlation implies one variable increase as the other increase
- ve correlation implies one variable increase as the other decrease

Table 47 shows that age, income, age of marriage, education, occupation of the respondent and birth order of exposed arsenicosis group were significantly correlated with arsenic level of water ($p<0.05$). On the other hand age of marriage and age of menarche of the respondent of nonarsenicosis group were significantly correlated with arsenic level of water ($p<0.05$).

Table 48: Relationship of blood glucose level after 75gm glucose intake with other variables:

Variables	Arsenicosis		Nonarsenicosis		Nonexposed	
	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value	Correlation coefficient (r)	P-value
Age	0.136**	0.006	0.040	0.422	0.284**	0.000
Income	0.041	0.411	- 0.021	0.675	0.037	0.458
BMI	0.044	0.379	- 0.005	0.921	0.031	0.539
MAC	0.013	0.801	0.082	0.101	0.045	0.365
Age of marriage	- 0.108*	0.031	- 0.078	0.143	0.014	0.787
Age of menarche	0.068	0.177	- 0.068	0.178	- 0.051	0.307
Education	- 0.023	0.650	- 0.082	0.100	- 0.019	0.712
Occupation	- 0.026	0.601	0.089	0.075	- 0.027	0.595
Use contraceptive	0.055	0.269	- 0.023	0.643	0.037	0.455
Birth order	0.110*	0.028	0.101*	0.043	0.223**	0.000
Received of ANC	0.030	0.551	- 0.098	0.050	- 0.160**	0.001
Received of PNC	- 0.086	0.085	- 0.028	0.573	- 0.077	0.124
Pregnancy outcome	0.018	0.724	0.069	0.167	0.043	0.392
Duration of the source of drinking water	0.130*	0.010	0.051	0.306	-	-

***** Correlation is significant at the 0.01 level (2-tailed).***
**** Correlation is significant at the 0.05 level (2-tailed).***
+ve correlation implies one variable increase as the other increase
-ve correlation implies one variable increase as the other decrease

Table 48 shows that age, birth order and duration of the source of drinking water of arsenicosis were positively correlated with blood glucose level after 75gm glucose intake ($p<0.05$). Age of marriage was found to be negatively correlated ($p<0.05$) with blood glucose level after 75gm glucose intake ($p<0.05$). Only birth order in the nonarsenicosis group was positive and significantly correlated with blood glucose level after 75gm glucose intake ($p<0.05$). In the nonexposed group, age and birth order were positively correlated with blood glucose level after 75gm glucose intake ($p<0.05$). Received of ANC was negatively correlated with blood glucose level after 75gm glucose intake ($p<0.05$).

Table 49: Results of regression analysis using blood glucose after 75gm glucose intake as dependent variable:

Variables	Arsenicosis		Nonarsenicosis		Nonexposed	
	Regression coefficient (B)	P-value	Regression coefficient (B)	P-value	Regression coefficient (B)	P-value
(Constant)	1.398	0.019*	1.828	0.000**	1.592	0.005**
Age of Respondent	1.017E-02	0.036*	-8.122E-04	0.758	1.853E-02	0.001**
Income	8.143E-06	0.607	-3.263E-06	0.639	6.801E-06	0.197
BMI	1.146E-02	0.260	-4.413E-03	0.399	-4.218E-03	0.593
MAC	3.877E-03	0.752	-8.323E-03	0.156	5.362E-03	0.546
Age of marriage	-3.355E-02	0.039*	-1.494E-02	0.075	7.901E-03	0.466
Age of menarche	1.979E-02	0.521	-2.117E-02	0.112	-6.493E-02	0.038*
Education	-4.856E-02	0.429	3.637E-03	0.894	3.652E-02	0.466
Occupation	- 0.177	0.174	-1.016E-03	0.981	-6.355E-03	0.970
Use of contraceptive	8.770E-02	0.102	1.347E-02	0.587	-2.282E-02	0.667
Birth order	5.417E-03	0.800	2.031E-03	0.873	8.950E-03	0.654
Received ANC	-1.384E-02	0.856	-5.063E-02	0.108	- 0.148	0.016*
Ever received PNC	- 0.170	0.024*	7.392E-02	0.074	-6.359E-02	0.425
Pregnancy outcome	-6.658E-02	0.300	8.212E-03	0.792	2.137E-02	0.786

***** Regression Coefficient is significant at the 0.01 level (2-tailed).***
**** Regression Coefficient is significant at the 0.05 level (2-tailed).***

Table 49 presents the results of regression analysis using blood glucose after 75gm glucose intake as dependent variable. Age of the respondent, age of marriage and Post Natal Care (PNC) were found as significant determinants of blood glucose level after 75gm glucose intake in arsenicosis group. The results indicated that blood glucose level after 75gm glucose intake increased with increase in age. The coefficient indicated that as age increased blood glucose after 75gm glucose intake increases by 0.010 points. For age of marriage blood glucose level after 75gm glucose intake decrease by 0.034 point. Ever received PNC, blood glucose level after 75gm glucose intake decreased by 0.170 point. In the nonexposed group, age of the respondent, age of menarche and received ANC had significant influence on the dependent variable. The coefficient indicated that as age increases, blood glucose level after 75gm glucose intake increased by 0.758 points. For age of menarche, blood glucose level after 75gm glucose intake increased by 0.112 point. Ever received ANC, blood glucose level after 75gm glucose intake decreased by 0.108 point.

Table 50: Results of MLR using reproductive outcome of arsenicosis as dependent variable (1=alive birth, 2=not alive birth):

Independent variables	B	S.E.	Sig.	Exp(B)
Age of the respondent	.256	.281	.363	1.291
Income category (lower, medium and higher class)	.074	.297	.804	1.077
MAC	-.009	.050	.855	.991
BMI	-.013	.043	.758	.987
Age of marriage (1=age <18 year, 2= age ≥ 18 years)	-.017	.068	.807	.984
Age of menarche (1= age>12 year, 2=age ≤ 12 year)	.032	.127	.798	1.033
Education (1 = Illiterate, 2 = Literate)	.073	.287	.800	1.076
Education of husband (1 = Illiterate, 2 = Literate)	-.188	.154	.223	.828
Occupation (1=housewife 2=service holder and others)	.111	.522	.831	1.118
Occupation of husband (1=service 2=unemployed and others)	.057	.055	.299	1.058
Arsenic level in tube well water	.000	.002	.873	1.000
Use of contraceptive (1=used, 2=notused)	.435*	.217	.045	1.546
Birth order	.230**	.080	.004	1.258
Received of ANC	-.754*	.305	.013	.470
Received of PNC	-.342	.303	.259	.710
Fasting blood glucose level (1=normal, 2 = DM+IGT)	.575	.371	.121	1.777
Blood glucose after 75mg glucose intake (1=normal, 2=DM+IGT)	-.691*	.379	.050	.501
Constant	-.793	2.669	.766	.452

***** Regression Coefficient is significant at the 0.01 level (2-tailed).***
**** Regression Coefficient is significant at the 0.05 level (2-tailed).***

Table 50 presents the results of logistic regression analysis using reproductive outcome among arsenicosis as the dependent variable. Use of contraceptive, birth order, ANC and blood glucose after 75gm glucose intake were found as significant determinants of reproductive outcome. The coefficients of all these variables were significant at less than 5% level of significance. The coefficients of all the other variables were significantly different from zero at grater than 5% level of significance.

Table-51: Results of MLR analysis using reproductive outcome of nonarsenicosis as dependent variable (1=live birth, 2=not live birth):

Independent variables	B	S.E.	Sig.	Exp(B)
Age of the respondent	-.056	.316	.860	.946
Income category (low, medium, high class)	-.438	.319	.170	.645
MAC	-.030	.060	.615	.970
BMI	-.044	.053	.403	.957
Age of marriage (1=age <18 year, 2= age ≥ 18 years)	.017	.085	.842	1.017
Age of menarche (1= age>12 year, 2=age ≤ 12 year)	.053	.134	.692	1.055
Education (1 = Illiterate, 2 = Literate)	.165	.311	.596	1.179
Education of husband (1 = Illiterate, 2 = Literate)	.042	.168	.802	1.043
Occupation (1=housewife 2=service holder and others)	.016	.424	.971	1.016
Occupation of husband (1=service 2=unemployed and others)	-.026	.068	.703	.975
Arsenic level in tube well water	.001	.002	.575	1.001
Use of contraceptive (1=used 2=not used)	.398	.243	.101	1.489
Birth order	.377**	.116	.001	1.458
Received of ANC	-.125	.316	.691	.882
Received of PNC	-.218	.403	.588	.804
Fasting blood glucose level (1=normal, 2=DM+IGT)	-.037	.340	.913	.964
Blood glucose after 75mg glucose intake (1=normal, 2=DM+IGT)	.106	.493	.830	1.112
Constant	-1.722	3.286	.600	.179

** *Regression Coefficient is significant at the 0.01 level (2-tailed).*
* *Regression Coefficient is significant at the 0.05 level (2-tailed).*

Table 51 presents the results of logistic regression analysis using reproductiveoutcome among nonarsenicosis as the dependent variable. Only birth order was found as significant determinants of reproductive outcome. The coefficient of this variable was significant at less than 5% level of significance. The coefficients of all the other variables were significantly different from zero at grater than 5% level of significance.

Table 52: Results of MLR analysis using reproductive outcome of nonexposed as dependent variable (1=live birth, 2=not live birth):

Independent variables	B	S.E.	Sig.	Exp(B)
Age of the respondent	-.335	.410	.413	.715
Income category (low, medium, high class)	-.155	.462	.737	.856
MAC	-.047	.071	.511	.954
BMI	.034	.061	.574	1.035
Age of marriage (1=age <18 year, 2= age ≥ 18 years)	-.095	.088	.276	.909
Age of menarche (1= age>12 year, 2=age ≤ 12 year)	.289	.239	.227	1.335
Education (1 = Illiterate, 2 = Literate)	.474	.404	.242	1.606
Education of husband (1 = Illiterate, 2 = Literate)	-.205	.209	.326	.815
Occupation (1=housewife 2=service holder and others)	.944	1.169	.419	2.571
Occupation of husband (1=service 2=unemployed and others)	.030	.089	.735	1.031
Use of contraceptive (1=used 2=not used)	-.402	.440	.360	.669
Birth order	.265*	.117	.023	1.304
Received of ANC	.132	.469	.778	1.142
Received of PNC	-.770	.549	.161	.463
Fasting blood glucose level (1=normal, 2=DM+IGT)	.070	.803	.931	1.072
Blood glucose after 75mg glucose intake (1=normal, 2=DM+IGT)	-.220	.872	.801	.802
Constant	-3.526	4.294	.412	.029

** *Regression Coefficient is significant at the 0.01 level (2-tailed).*
* *Regression Coefficient is significant at the 0.05 level (2-tailed).*

Table 52 presents the results of logistic regression analysis using reproductiveoutcome of nonexposed group as the dependent variable. Only birth order was found as significant determinants of reproductive outcome. The coefficient of this variable was significant at less than 5% level of significance. The coefficients of all the other variables were significantly different from zero at grater than 5% level of significance.

4.3 Conclusions:

Maternal complications increased with high glucose level and increased concentration increased the risk of adverse pregnancy outcome. There is strong evidence of an association

between maternal nutritional status and adverse pregnancy outcome. Study findings suggested that the risk of stillbirth in pregnancies that occur after the onset of diabetes has been diminished. The risk of stillbirth was increased in both pre-diabetic and post-diabetic pregnancy.

The study findings reveals that there is an association between ingested arsenic and diabetes mellitus but causal relationship has not yet established. The strength of the study findings in terms of the high prevalence ratios, along with the plausibility of finding corresponding from other studies that diabetes mellitus are the effects that may indeed result from ingestion of inorganic arsenic. However, the mechanism underlying the ability of inorganic arsenic to induce these disorders is still unclear. The study assessed arsenic exposure is a risk factor for diabetes mellitus as indicated in a few earlier studies. The study findings reveals that there is an evidence for adverse pregnancy outcomes and increased neonatal death. Adverse pregnancy outcomes in terms of spontaneous abortion, stillbirth, and preterm birth, miscarriage and abortion rates were significantly higher in the exposed group than those in the nonexposed group as revealed in this study, arsenic contamination is also a threat to healthy and safe reproductive outcomes. The findings concerning adverse reproductive outcome need to be confirmed, ideally in a prospective cohort study.

CHAPTER-5

DISCUSSION AND CONCLUSION

Chapter-5

Discussion & Conclusion

5.1 Discussion:

Characteristics of the mother:

Meternal age influences the outcome of pregnancy and labour.[118] [119] The mean age of mother with arsenicosis was 33.58 (SD ± 7.63), nonarsenicosis was 30.08 (SD ± 6.82) in the exposed group while 29.45 (SD ± 6.17) in nonexposed group. The educational status of the mother in the exposed group, 59.3 percent in arsenicosis, 59.7 percent in nonarsenicosis while 54.0 percent in nonexposed group were literate. It was also found that 94.5 percent mother with arsenicosis, 89.8 percent mother with nonarsenicosis in the exposed group while 98.0 percent mother in nonexposed group were housewives. In the exposed group, 73.8 percent mother with arsenicosis, 74.3 percent mother with nonarsenicosis in the exposed group while 82.3 percent in nonexposed group were poor. The mean income was Tk. 3592.75 (SD±1935), 3566.75 (SD±1877) and 3636.06 (SD±4555) in different groups respectively. Most of the mothers 94.0 percent, 94.0 percent 93.3 percent in exposed and nonexposed group respectively were Muslims. In the exposed group, 50.3 percent mother with arsenicosis, 41.0 percent mother with nonarsenicosis while 62.3 percent mother in nonexposed group had no exposure to any media. The groups were comparable and consistent in terms of age, level of education, occupation, income and other socio-economic status, as these variables did not differ statistically. [115] [116] [117] [188]

Study findings reveals that 26.3 percent mother of arsenicosis and 25.7 percent mother of nonarsenicosis from exposed group still drinking arsenic contaminated water from the same tubewell. The finding is consistent with other studies. In Bangladesh, many persons

have been exposed to a wide range of doses of arsenic from drinking water over a significant period of time. [168] Women had significantly higher cumulative exposure to arsenic, while men had significantly higher prevalence of skin lesions On average, those people had been using tubewell water for about 20 years.[169] [171]

It was observed that 85.0 percent mother of arsenicosis, 85.0 percent mother of nonarsenicosis in exposed group and 91.5 percent mother in nonexposed group got married before they reach 18 years of age. The mean age of marriage was 16.7 (SD±1.86), 17.2 (SD±1.61) and 16.0 (SD±2.30) years in different groups respectively. Most of the respondents 65.7 percent mother of arsenicosis, 51.7 percent mother of nonarsenicosis in exposed group and 71.3 percent mother in nonexposed group had started their menstruation on or before 12 years of age. The mean age of menarche were 12.9 (SD±0.98), 12.7 (SD±0.98) and 12.9 (SD±0.82) years in different groups respectively. Early marriage is a prevailing custom, as a result it has been found that about 30 percent of adolescent girls are already mothers and another 6 percent is pregnant with their 1st child. Every year, 66 percent girls give birth before the age of 20 in Bangladesh.[196] Bangladesh has the highest proportion of girls under 20 years giving birth. A pregnant adolescent "A child in a child" has to meet the growing demands of her foetus in addition to her own demand, thus putting her in a stressful situation. She is at high risk and more vulnerable for complications. [118] [119]

Arsenicosis and diabetes mellitus (type-2):

It was observed that 7.0 percent, 4.3 percent and 4 percent were DM in arsenicosis, nonarsenicosis and nonexposed group respectively and 81.3 percent arsenicosis, 85.4 percent of nonarsenicosis in exposed group and 86.3 percent in nonexposed group had normal blood glucose level 2 hours after 75gm glucose. The rest 11.7 percent, 10.3 percent and 9.8 percent were IFG. This study finding is consistent with other national and international findings. The recent WHO report on diabetes prevalence of all ages worldwide was estimated to be 2.8 percent in 2000 and 4.4 percent in 2030. The number of diabetic population was estimated to rise from 171 million in 2000 to 366 million in 2030. According to the recent report, the highest relative increase will occur in the Middle East, Sub-Saharan Africa, India and Bangladesh. As estimated on the basis of

present prevalence rates of diabetes (NIDDM~5.2 percent and IGT~12.5 percent. [23] [25] [37] [229]

The relationship between ingested arsenic and diabetes mellitus has so far only been reported in a limited number of studies from Taiwan, Sweden and now in Bangladesh (Lai et al., 1994; Chen et al., 1995; Rahman and Axelson, 1995; Rahman et al., 1996a,b), it appears likely that there is a causal relationship.[175] Diabetes prevalence in arseniasis-hyperendemic villages in Taiwan has been reported to be significantly higher than in the general population. The findings are consistent with their previous cross-sectional observation that ingested inorganic arsenic is diabetogenic in human beings.[176] [177]

According to the Environmental Protection Agency (EPA), exposure to low concentrations of arsenic over many years can leads to diabetes, reproductive disorders. This information is particularly timely in light of recent research into the correlation between arsenic intake and the development of diabetes in populations in Argentina, Bangladesh, India, Mexico, Thailand, and Taiwan. [178] In Bangladesh, study assessed whether arsenic exposure is a risk factor for diabetes mellitus as indicated in a few earlier studies. The result corroborates earlier studies and suggests that arsenic exposure is a risk factor for diabetes mellitus. [179]

Two major forms of maternal diabetes may occur during pregnancy: preexisting or pregestational diabetes and gestational-onset or gestational diabetes mellitus (GDM. These pregnancies are at risk for both maternal and fetal complications. Stillbirths are now uncommon in diabetic pregnancies; congenital malformations and complications of maternal hypertensive disorders account for most of the 1.5-to 2-fold increase in perinatal mortality compared with non diabetic pregnancies.[63] [64]

Reproductive outcome of diabetic mother, 78.5 percent mother with arsenicosis and 70.5 percent mother with nonarsenicosis in the exposed group, while 81.3 percent mother in the nonexposed group delivered alive child. Neonatal death 3.6 percent, 11.8 percent and 6.3 percent; Stillbirth 0.0 percent 0.0 percent and 6.3 percent; Premature 3.6 percent, 5.9 percent and 0.0 percent; Handicapped 3.6 percent 0.0 percent 0.0 percent; Miscarriage 7.1 percent. 11.8 percent and 6.3 percent; Abortion 3.6 percent, 0.0 percent and 0.0 percent in different groups respectively.

Cundy et al. showed a threefold increased perinatal mortality in women with type 2 diabetes, mainly due to late stillbirths. The perinatal mortality rate was 2.5-fold greater than regional or national figures. The miscarriage rate in type 2 diabetes in the UK case series was 8.8 percent, almost doubling to 15.7 percent and half of the miscarriage occurred in the first trimester, in those with poor glycaemic control. Maternal morbidity in type-2 diabetes the risk of a maternal complication developing is high compared to general background figures. Delivery by caesarean section is common in women with type 2 diabetes, with a rate of 53% reported. Omori and colleagues identified a high rate of retinopathy (32%) and overt nephropathy (1.4%) in their series. Retinopathy is an independent predictor of poor fetal outcome. [65] [66]

Maternal nutrition and reproductive outcome:

Measurement of height showed that 75.5 percent mother of arsenicosis, 70.0 percent mother of nonarsenicosis in exposed group while 63.7 percent mother in nonexposed group had ≤150cm Weight measurement showed that 84.5 percent mother of arsenicosis, 87.7 percent mother of nonarsenicosis in exposed group and 89.5 percent mother in nonexposed group had weight less than 50 kg. Calculated BMI showed that 28.5 percent mother of arsenicosis, 44.5 percent of nonarsenicosis in exposed group and 59.0 percent in nonexposed group had BMI <18.5. A large number of epidemiological studies have demonstrated a direct relationship between adverse reproductive outcome and height, weight and BMI. [139] [140] [141] [142] [143] [169]

Diabetic mothers, who had LGA babies, had significantly higher pre-pregnancy body weight and BMI [121] [122] [1123] There is strong epidemiological evidence of an association between maternal nutritional status and birth weight and intrauterine growth retardation. Mothers with high parity are often more affected by malnutrition as too many pregnancies or pregnancies too close together deplete the mother's stores and result in low birth weight babies.[124] [1125] Low birth weight babies have high morbidity and mortality rates especially in the first year of life.[126] [127] [1288] [129] [130] [135]

Maternal overweight condition increased the risk of antepartum stillbirth, especially weight gain during pregnancy was not associated with risk.[131] [132] [133] There is significant controversy as to whether or not stillbirth is increased in pregnancies prior to the onset of diabetes. The risk of stillbirth was increased in both pre-diabetic and post-diabetic pregnancy.[35] [134] Although maternal weight gain is strongly associated with size, the indicated nutritional associations with weight gain are not reflected in similar associations with birth-size parameters. [143] [144] [145] [146] [147] Birth weight has now been accepted as an indirect indicator of nutritional status.[148] Birth weight is influenced by many factors, the most important of which is maternal nutrition during pregnancy. During pregnancy it is the mother who provides to the fetus with the nutrients necessary for its survival and development. Poor weight gain during gestation has been co-related to low birth weight.[149] [150] [151]

Vahter and Marafante found that a low amount of methionine or protein in diet decreased methylation of inorganic arsenic in rabbits. Deficiency of certain other trace elements, including zinc and selenium, associated with malnutrition, may also contribute to the toxic effects of accumulated levels of arsenic in the body. Their study confirmed previous reports of the relationship between malnutrition and increased arsenic toxicity. They can not, however, draw a causal inference from the association between the nutritional status and the duration of disease. [7] [[151] [171]

Diabetes mellitus and reproductive outcome:

In this study 78.5 percent mother with arsenicosis and 70.5 percent mother with nonarsenicosis in the exposed group, while 81.3 percent mother in the nonexposed group delivered alive child. Neonatal death 3.6 percent, 11.8 percent and 6.3 percent; Stillbirth 0.0 percent 0.0 percent and 6.3 percent; Premature 3.6 percent, 5.9 percent and 0.0 percent; Handicapped 3.6 percent 0.0 percent 0.0 percent; Miscarriage 7.1 percent. 11.8 percent and 6.3 percent; Abortion 3.6 percent, 0.0 percent and 0.0 percent in different groups respectively. The adverse reproductive outcome is consistent and comparable with other international studies. Pregnancy complicated by type 2 diabetes is a high-risk pregnancy. Associated with birth defects and high perinatal mortality. Pre-eclampsia is 2

to 3 times more common in women with type 2 diabetes than in non diabetic women. [74] [75] Dunne has recently reported that women with type 2 diabetes have up to a 11 times greater risk of a congenital malformation compared with the general population. Perinatal mortality is substantially higher than in the general population.[14] [76] [77] [78]

Maternal factors are more important than feto-placental factors in determining glucose-insulin metabolism in the offspring. [79] [80] Both spontaneous and preterm deliveries are increased in pregestational diabetes. Type 2 diabetes was associated with a 3.4% congenital malformations..[81] In a Japanese study of women with pregestational diabetes in pregnancy, 5.8% of infants born to women with type 2 diabetes had major congenital anomalies In another study of women in the UK, women with type 2 diabetes, most of whom were from the Indian subcontinent, also had twice the frequency of congenital malformations compared with women with type 1 diabetes (12.2% *vs* 6.1%).[82] [83] [84]

Women with pregestational diabetes or gestational diabetes plus fasting hyperglycemia have a three-to four-fold increased risk of infant malformations. It is also generally believed that women with gestational diabetes are not at risk for infant malformations, whereas those with pregestational diabetes have a three-to five-fold increased risk compared with the general obstetric population. [89] [90] [91] The association between blood level glucose and gestation was inversed and significantly shortened when glucose concentrations were higher.[92] [93] [94]

Pregnancy in diabetic women is associated with an increased perinatal mortality, stillbirths and neonatal deaths within the first week of life, low birth weight and congenital malformation. [26] Uncontrolled diabetes leads to more birth defects. Women who had diabetes before they got pregnant or who developed gestational diabetes with elevated fasting blood-glucose levels were three to four times more likely to have babies with birth defects than women who either did not have diabetes before pregnancy. [51] [52] [53] The prevalence and risk of complication of a population of Spanish pregnant women with GDM diagnosed complicated only with impaired glucose intolerance (IGT) (0.94%) showed a worst outcome. [54] Women with GDM who failed to achieve established levels of glycemic control had significantly higher adverse pregnancy outcomes.[55] The

neonatal macrosomia is influenced by variables that are largely independent of plasma glucose concentrations.[56]

Maternal and fetal complications are increased when pregnancy is complicated by diabetes, and this may be further influenced by racial and cultural differences. Pregnancies complicated by type 2 diabetes in Indo-Asian and Caucasian women pose the greatest threat to successful pregnancy outcome. [57] [58] [59] Women with IGT were at increased risk of premature rupture of membranes, preterm birth breech presentation, and high birth weight.[60] Some placental hormones in association with gestational diseases may reflect an abnormal differentiation of adverse conditions: Down's syndrome, fetal growth restriction, preeclampsia, preterm delivery, and diabetes mellitus.[61] [62]

Marital age, parity and reproductive outcome:

The study has been observed that 85.0 percent mother of arsenicosis, 85.0 percent mother of nonarsenicosis in exposed group and 91.5 percent mother in nonexposed group got married before they reach 18 years of age. The mean age was 16.7±1.86, 17.2±1.61 and 16.0±2.30 years in different groups respectively. It was found that adverse outcome of pregnancy increases when number of pregnancy increases. Age of marriage influences the outcome of pregnancy and labour. The study findings is consistent with other national and international study findings. Ten to fifteen percent of deliveries all over the world are from adolescent mothers. It has been found that abou.30 percent of adolescent girls are already mothers and another 6 percent is pregnant with their 1st child. Every year, 66 percent girls give birth before the age of 20 in Bangladesh. Bangladesh has the highest proportion of girls under 20 years giving birth. A pregnant adolescent ''A child in a child'' [118] [119]

Arsenicosis and reproductive outcome:

The findings from this investigation provide evidence for a potential role for arsenic exposure through drinking water increases the risk of adverse reproductive outcome. It reveals that, 70.8 percent mother with arsenicosis and 77.8 percent mother with nonarsenicosis in the exposed group, while 90.3 percent mother in the nonexposed group

delivered alive child. Neonatal death 4.0 percent, 3.5 percent and 2.1 percent; Stillbirth 4.3 percent 3.8 percent and 2.3 percent; Premature 6.5 percent, 4.8 percent and 1.8 percent; Handicapped 1.3 percent, 0.8 percent and 0.3 percent; Miscarriage 7.8 percent, 5.3 percent and 2.0 percent; Abortion 5 percent, 4.3 percent and 1.5 percent in different groups respectively. However, limited research has been directed at the association of arsenic exposure and human reproductive health outcomes. The data indicate an elevation of the late fetal, neonatal, and post-neonatal mortality rates for specific time periods, which generally coincide with the period of highest arsenic concentration in the drinking water. The findings from this investigation may support a role for arsenic exposure in increasing the risk of late fetal and infant mortality. [187]

The study suggests that arsenic exposure through well water contributes to excess risk of low birth weight. [111] Adverse pregnancy outcomes in terms of spontaneous abortion, stillbirth, and preterm birth rates were significantly higher in the exposed group than those in the nonexposed group.[188] Clear correlation between reproductive outcome and arsenic exposure and mortality could be of some biological significance.[189] Epidemiological studies have pointed out to the existence of other non-cancer health effects are noted as well, such as spontaneous abortions and stillbirths. [190]

Several associations were found between the reproductive outcomes of interest and selected covariates. These findings were consistent with what has been reported in the literature, lending support to negative findings that arsenic exposure is not spurious. For instance, maternal under nutrition, as reflected by low BMI, is a risk factor for low birth weight infants, preterm birth, and other delivery complications for mothers. Improved maternal nutrition, as reflected by weight gained during pregnancy, reduces the risk of adverse reproductive health outcomes, such as low birth weight infants, stillbirth, and premature birth. The findings of this study concurred with earlier findings in that elevated BMI and increased weight gain during pregnancy reduced the odds of having a low birth weight infant.[225]

The present study suggests that arsenic exposure through tube-well water contributes to excess risk of low birth weight, although the effects of other unmeasured risk factors can

not be excluded with certainty. Due to inherent methodological limitations, future investigation should consider using defined populations with individual level data of exposure assessment for arsenic and collection of data for confounding variables. [11] Also in an Andean village in northern Argentina, the water arsenic concentration remained about the same over the period of about 10 years. Thus we believe that the estimated historical exposure represent the true (or actual) exposure. We are presently following up the water arsenic concentrations in a subset of the tube-wells for assessment of seasonal and temporal variations. [169]

However, there was a poor correlation between maternal and developmental toxicity in an extensive literature analysis. Therefore, arsenic is likely to have direct toxic effects on adverse reproductive outcomes. [13] The risk estimates for fetal loss in relation to arsenic exposure was lower than those reported in previous studies in Bangladesh and West Bengal, India. However, those studies were either ecologic or cross sectional in design and included only a few hundred women, and reproductive outcomes were collected by recall. After clinical recognition of pregnancy, the rate of early fetal loss reported varies between 10-15 percent although much lower rates have also been observed. The rates vary with data collection methods and are usually low if based on regular vital statistics data. In the recent study in West Bengal, India, the association between arsenic exposure and infant mortality had a size that that corresponds well with the result of our study. [226]

Recently a study conducted in Bangladesh showed an increased risk of stillbirth for women with current arsenic levels greater than 100µg/l. Neonatal death risks were investigated only in recent study by Milton et al. who found risks similar to those observed in their study. In an ecologic study carried out in Chile, and neonatal and post neonatal infant mortality were found to be increased in the high arsenic exposure city compared with low exposure city. In rural West Bengal, no medical records on adverse pregnancy outcomes and infant deaths are available. Therefore, self reported reproductive histories are the only source of information.[148]

It should be noted that there were some limitations in their data set. It was difficult to find whether the significant associations shown in the paper were causal or not due to cross

sectional data analysis. Information biases may also have occurred for cross sectional study (Guo et al. 2003). In spite of these limitations, they have found some important findings. On the basis of their study, they may infer the associations, the outcome of ground water arsenic poisoning in Bangladesh, has been increasing in an alarming way since its declaration (Khan et al. 1993). For its gravity and magnitude it has appeared as the most important issue in public health at present. [184]

In that study, a significantly increased prevalence of diabetes mellitus was found among subjects with keratosis compared with subjects who did not have keratosis. A significant trend in risk between an approximate time weighted arsenic exposure and the prevalence of diabetes mellitus strengthens the possibility of causal association. However the lack of comprehensive, systematic, long term sampling in the study area is a limitation of the study because directly measured individual exposure data over time would have been desirable.[227]

A few of recent reports suggests that chronic ingestion of arsenic may lead to adverse reproductive outcomes. In Chile, a 10 fold deviation of arsenic water changed from approximately 100-900μg/l for 13 years coincided with the rise of late fetal and early infant mortality. In Bangladesh, a group of arsenic exposed women experienced significantly higher rate of spontaneous abortion, stillbirth, and preterm birth than the control groups matched for age, socio-economic status, education and married age. In central Bulgaria, residents leaving a near copper smelter area experienced 3 fold increase of fatal defects among the fetus. It was found that the placenta of delivered women in the smelter area contained arsenic 3 times higher than that in the control area. Quantitative comparison of the existing results including their preliminary analysis is difficult due to the different indices chosen and varying degree of the consideration to the confounding factors. [228]

The evidence from animal studies clearly shows that arsenic is teratogenic and the findings of limited human studies that inorganic arsenic may be associated with several reproductive and developmental outcomes, including increased rates of spontaneous abortion, stillbirth, perinatal death, low birth weight, congenital malformations, pre-

eclampsia and infant mortality. Recent studies found that arsenic readily crosses the human placenta, giving to arsenic concentrations that are about as high in cord blood as in maternal blood (Concha et al. 1998). However, more than 90 percent of the arsenic in plasma and urine was in the form of DMAA, a percentage that was significantly higher in pregnant women than in non-pregnant women. That finding indicated an increased methylation of arsenic in pregnancy.[230]

Characteristics skin lesions (keratosis, hyper-pigmentation and hypo-pigmentation) are the hallmarks of high exposure to arsenic. At very high levels of arsenic in drinking water, acute symptoms may occur long before the appearance of skin lesions. However, arsenic is a probable contributor to diabetes mellitus and is usually accompanied by hyper-pigmentation and/or keratosis. Furthermore, there is suggestive evidence for arsenic to be related to human developmental toxicity and low birth weight, increased infant and neonatal mortality and spontaneous abortion.[231]

5.2 Conclusion:

Arsenic toxicity and its impact on health has been increasing in an alarming way since its declaration. For its gravity and magnitude it has appeared as the most important public health threat in Bangladesh. So it should take preventive measures immediately. It is clear that there is an urgent need to assess the severity of all patients in all stages of arsenicosis. To prevent the disease supervising programs and strict management of regular cutaneous and systemic examinations of patients of arsenic symptoms should be performed. Intervention must be used effectively for some targeted factors that are significantly associated with arsenic symptoms. Finally, our findings may help to understand about the severity of complications of the patients and the policy makers may take appropriate strategies in this regard.

The study reveals that females are more susceptible to toxic effects of chronic arsenic exposure and as such their reproductive outcomes are likely to be adversely affected. This added stress on women in the arsenic affected areas call for special attention to this vulnerable group of population. Therefore, the issue of arsenic contamination in Bangladesh is a potential threat to pregnancies and thus may have serious implications on

reproductive health. This is the first population based study considering the relation of skin lesions and risk for glucosuria and thereby also diabetes mellitus. On the basis of our findings, we conclude that the appearance of dermatological signs of chronic arsenic toxicity is a poor marker for a risk of glucosuria and diabetes, as these conditions may well occur also in the absence of skin lesions.

The adverse reproductive outcomes in terms of live birth, stillbirth, spontaneous abortion, and pre-term birth, neonatal death, and miscarriage were significantly higher among exposed women than those who were not exposed. Thus, conclusion regarding the possible effect of chronic arsenic exposure on the reproductive performance awaits further epidemiological researches that should be either large scale (prospective cohort) and/or taking major confounding factors as much as possible.

5.3 Lessons learn from the study:

5.3.1 Measures to intensify mass awareness campaigns:

About arsenic toxicity, health hazards and adverse consequences of reproductive health problems, strengthening early diagnosis and treatment and improve nutritional status of the mother. It may be necessary to go door to door to build women awareness and to make women specially detoxify arsenic contaminated water.

5.3.2 Screening of all the tube-wells:

Both hand pumps and irrigation wells should be screened for the arsenic content in the water and unsafe ones marked. Those wells found to have higher arsenic content 0.05mg/l should be sealed and those with less than 0.05mg/l should be monitored regularly at least once in a year. Reference laboratories should be set up at regional level to validate analysis.

5.3.3 Alternative water supply options:

Safe water supply in arsenic contaminated areas is a priority to avoid arsenic poisoning. Uncontaminated shallow tube-wells will continue to be the sources of safe water supply even in arsenic affected areas for years until these tube-wells are found contaminated.

5.3.4 Regular water quality monitoring and surveillance program:

It is also required to observe the possible change in arsenic content of these shallow tube-wells. Alternate water supply systems would replace the contaminated tube-wells and those turn out to be subsequently contaminated during monitoring to maintain quality of water supply.

5.3.5 Emergency Intervention:

Contamination of ground water by arsenic as a public health emergency would facilitate the prompt expansion of intervention. The core activity of an emergency action plan for this threat to women health should be rapid case ascertainment and to monitor arsenicosis mothers progress and compliance in treatment and continuation of care of the patients.

5.3.6 Quick establishment of arsenic mitigation project:

To prevent arsenicosis women should be given priority in arsenic mitigation project. To working in the particular social context of Bangladesh, easy access of women must be ensured and they must be incorporated in mitigation activities.

5.3.7 Ensure reproductive health care:

Provide reproductive health care including family planning counseling, ANC, INC and PNC for every mother and treatment of diabetes and control glycemic status during pre-gestational and gestational period to prevent adverse pregnancy outcome.

Summary

Background:

Chronic arsenic poisoning has become a worldwide public health issue. The World Health Organization (WHO) calls the arsenic poisoning in Bangladesh the largest mass poisoning of a population in history. The association between arsenic exposure and diabetes mellitus is a relatively new finding. WHO predicts that by 2030, the number of type 2 diabetes cases world-wide will be double to 350 million. Such predictions indicate that over the next several decades, more and more women of reproductive age will have type-2 diabetes. Conclusion on the causality of the relationship between arsenicosis, diabetes mellitus and reproductive outcomes are suggestive and less clear. The current available evidence is inadequate to establish a causal role of arsenic in diabetes should be a research priority. Quantitative information about the scale of the arsenic contamination has been author limited until recently Further research is urgently needed to address arsenic poisoning in Bangladesh since the situation can be described as a "crisis" due to devastating effects of arsenic on human health and reproductive lives.

Aims and Objectives of the study:

The aim of this study is to investigate diabetes mellitus (type-2) among arsenicosis affected mothers of child bearing ages (15-49 years) and their reproductive outcome in two rural areas which has a well documented history of arsenic exposed and non-exposed from naturally contaminated ground water.

Materials and Methods:

The cross sectional comparative study was carried out to compare the prevalence of diabetes mellitus among mother of reproductive ages (15-49 years) having arsenicosis and non-arsenicosis living in areas with and those without exposure to arsenic in drinking

water. Mother of reproductive age who previously had at least one outcome of pregnancy and who had lived in the study places and who had used the same tube-well water for more than 2 years as long as it had been existed were considered as study population. The prevalence of diabetes mellitus and their reproductive outcome of these groups were compared along with their socio-demographic characteristics. The study population was divided into two groups-exposed and nonexposed. The exposed group was further categorized into arsenicosis and non-arsenicosis subgroups. Selection of sample was purposive and the total sample size 1200 mother were investigated.

Pre-tested structured interview questionnaire were used to collect relevant information regarding demographics, socio-economic status, reproductive events, drinking water sources and pattern of well water used. Every mother underwent a thorough physical examination by one of the study physician and clinical data including the presence of melanosis, keratosis, rain drop pigmentation were collected. The study obtained interview data and drinking water samples from the study participants. Water samples were collected directly from the tube-wells (one tube-well covered each cluster) and collected information on the respondents lifetime reproductive history which included the number of pregnancies, live births, pre-term births, stillbirths, neonatal deaths, spontaneous and induced abortion, miscarriage and congenital abnormality. Standing height and body weight were measured. Individual body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Data analysis was done by using SPSS and Epi-Info soft ware package. The presence of differences in the mean and median values was assessed using a one way analysis of variance (ANOVA) for continuous variables, general association (Chi-square) statistic for categorical variables. Bivariate analysis were performed to determine if reproductive outcomes and select covariates varied across arsenic exposure categories. Prevalence ratio with 95% confidence interval was calculated and Logistic regression models were used for assessing whether any associations existed between arsenic exposure and selected outcome of interest reproductive outcome and diabetes mellitus.

Results and Findings:

The mean age of mother with arsenicosis was 33.58 (SD±7.63), nonarsenicosis was 30.08 (SD±6.82) in the exposed group while 29.45 (SD±6.17) in the mother of nonexposed group. The educational status of the mother in the exposed group, 59.3 percent mother with arsenicosis, 59.7 percent mother with nonarsenicosis while 54.0 percent mother in the nonexposed group were literate. It was also found that 94.5 percent mother with arsenicosis, 89.8 percent mother with nonarsenicosis in exposed group while 98.0 percent mother in nonexposed group were housewives. The mean income was Tk. 3592.75 (SD±1935), 3566.75 (SD±1877) and 3636.06 (SD±4555) in different groups respectively. In the exposed group, 50.3 percent mother with arsenicosis, 41.0 percent mother with nonarsenicosis while 62.3 percent mother in nonexposed group had no exposure to any media.

It has been observed that 87.0 percent mother of arsenicosis, 69.7 percent mother of nonarsenicosis and 66.5 percent mother of nonexposed group had a long duration (more than 2 years) of drinking arsenic contaminated water. Mean duration of drinking water were 12.98±5.91 years, 9.93±2.85 years and 9.92±2.85 years respectively. We also found that 23.3 percent had raindrop pigmentation, 21.56 percent melanosis and 20 percent keratosis respectively of arsenicosis mother. On the other hand 10.8 percent melanosis+keratosis, 10.0 percent had keratosis+raindrop pigmentation and 3.5 percent melanosis+raindrop pigmentation.

In the exposed group, 95.0 percent mother of arsenicosis, 92.7 percent mother of nonarsenicosis while 96.0 percent mother in nonexposed group delivered their baby at home. Normal blood glucose level 2 hours after 75gm glucose was 81.3 percent in arsenicosis, 85.4 percent in nonarsenicosis in exposed and 86.3 percent in nonexposed group. The rest 11.7 percent, 10.3 percent and 9.8 percent were IFG and 7.0 percent, 4.3 percent and 4 percent were DM respectively in arsenicosis, nonarsenicosis and nonexposed groups respectively. IFG and DM were 18.7 percent mother with arsenicosis, 14.6 percent mother with nonarsenicosis in exposed group while 13.7 percent in nonexposed group. Blood glucose level 2 hours after 75gm glucose was significantly associated with arsenicosis and nonexposed group. Odds ratio and relative risk showed

that impaired fasting glucose (IFG) and diabetes mellitus (DM) was positively associated with arsenic exposure ($p<0.05$; OR=1.45; RR=1.19).

The average fasting blood glucose level 5.33±1.41 of arsenicosis group were significantly higher when compared with that of 5.08±1.07 and 5.13±1.17 of nonarsenicosis and nonexposed group respectively ($p<0.05$). Average blood glucose level after 75gm glucose intake 6.40±2.05 of arsenicosis, 6.25±1.99 of nonarsenicosis in exposed group was significantly higher when compared with 6.23±1.74 of nonexposed group ($p<0.05$).

The reproductive outcome indicates that, 70.8 percent mother with arsenicosis and 77.8 percent mother with nonarsenicosis in the exposed group, while 90.3 percent mother in the nonexposed group delivered alive child. Neonatal death 4.0 percent, 3.5 percent and 2.1 percent; Stillbirth 4.3 percent 3.8 percent and 2.3 percent; Premature 6.5 percent, 4.8 percent and 1.8 percent; Handicapped 1.3 percent 0.8 percent 0.3 percent; Miscarriage 7.8 percent. 5.3 percent and 2.0 percent; Abortion 5.5 percent, 4.3 percent and 1.5 percent in different groups respectively. . From the results of Odds ratio and relative risk it was also found that dead after birth, stillbirth, premature, handicapped, miscarriage and abortion were positively associated with arsenicosis. Degree of positive association and risk of exposure in arsenicosis and nonexposed group were higher than that of arsenicosis & nonarsenicosis and nonarsenicosis & nonexposed group respectively.

The adverse pregnancy outcome were significantly higher in exposed group than nonexposed groups ($Z=16.05$ $p<0.001$; $\lambda^2=41.04$; $p<0.001$) ($Z=4.90$, $p<0.001$), arsenicosis and nonarsenicosis group were ($Z=2.27$ $p<=0.05$, $\lambda^2=4.77$; $p<=0.05$), arsenicosis and nonexposed ($Z=2.71$ $p<0.005$, $\lambda^2=47.2$; $p<0.005$), and nonarsenicosis and nonexposed ($Z=4.90$; $p<0.001$, $\lambda^2=22.33 p<0.001$) Adverse pregnancy outcome was 3.21 times higher than nonexposed group (OR=3.21; 2.19<OR<4.71, RR=1.35; 1.26<RR<1.46) and in arsenicosis 1.44 times higher than nonarsenicosis group (OR=1.44; 1.04<OR<2.01, RR=1.19; 1.03<RR<1.38). It was also found that strength of positive association and degree of risk of exposure higher in exposed than nonexposed groups. The adverse outcome of pregnancy increases when number of pregnancy

increases. Degree of relationship of exposed group was higher than that of nonexposed group ($p<0.001$).

The mean age of marriage was 16.7±1.86, 17.2±1.61 and 16.0±2.30 years in different groups respectively. It reveals that 85.0 percent mother of arsenicosis, 85.0 percent mother of nonarsenicosis in exposed and 91.5 percent mother in nonexposed group got married before they reach 18 years of age. Marriage age was significantly associated with exposed and nonexposd groups, arsenicosis and nonexposed ($p<0.005$). Birth order more than two 73.3 percent of exposed arsenicosis were significantly higher ($Z=3.35$, $p<0.0009$) than that of 62.8 percent of exposed nonarsenicosis and 58.0 percent of nonexposed group ($Z=4.62$, $p<0.001$) respectively. Based on Chi-square test ($\lambda^2 = 10.58$, $p<0.001$) it was found that birth order was significantly associated with exposed arsenicosis and nonexposed group. Odds ratio (OR=1.66) showed that exposure (birth order >2) was positively associated with arsenicosis. Relative risk (RR=1.30) showed that exposure had 1.30 times higher risk to form arsenicosis than nonexposure (birth order ≤2). It was also found that birth order was significantly associated ($\lambda^2 =19.95$, $p<0.000$). with arsenicosis and nonexposed (control) group. Odds ratio showed that exposure (birth order >2) was positively associated with arsenicosis. Relative risk (RR=1.43) showed that exposure had 1.43 times higher risk form arsenicosis than nonexposure.

The average age 31.74±7.17 of the respondent in nonarsenicosis group whose pregnancy outcome was not alive was significantly higher ($p<0.05$) than the average age 29.55±6.55 whose pregnancy outcome was alive. All in the three groups, average birth order whose pregnancy outcome was not alive was significantly higher ($p<0.05$) than whose pregnancy outcome was alive respectively. The age, income, age of marriage, education, occupation of the respondent and birth order of exposed arsenicosis group were significantly correlated with arsenic level of water ($p<0.05$).

On the other hand age of marriage and age of menarche of the respondent of nonarsenicosis group were significantly correlated with arsenic level of water ($p<0.05$). Results of logistic regression analysis using pregnancy outcome among arsenicosis as the dependent variable. Use of contraceptive, birth order, ANC and blood glucose after 75gm glucose intake were found as significant determinants of pregnancy outcome. The

coefficients of all these variables were significant at less than 5% level of significance. The coefficients of all the other variables were significantly different from zero at grater than 5% level of significance.

Conclusions:

Arsenic toxicity and its impact on health has been increasing in an alarming way since its declaration. For its gravity and magnitude it has appeared as the most important public health threat n Bangladesh. So it should take preventive measures immediately. It is clear that there is an urgent need to assess the severity of all patients in all stages of arsenicosis. The pregnancy outcomes in terms of live birth, stillbirth, spontaneous abortion, and pre-term birth among the arsenic exposed women of reproductive age (15-49 years). Adverse pregnancy outcomes were significantly higher among exposed women than those who were not exposed. Thus, conclusion regarding the possible effect of chronic arsenic exposure on the reproductive performance awaits further epidemiological researches that should be either large scale (prospective cohort) and/or taking major confounding factors as much as possible.

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APPENDICES

QUESTIONNAIRE

Appendix-1

Interview Questionnaire

A- Address:

Name of District :----------

Name of Upazila :----------

Name of Union :----------

Name of Village : ----------

House Hold No : | | | | |

Respondent's name :----------

ID. No. : | | | | |

B-Socio-demographic information:

Sl.No	Questions	Please circle the right answer	Skip	Code	Variable
1	How old are you?	_____ (in complete years)			Age
2	What is your educational qualification?	1-Illiterate 2. Primary level 3-Secondary 4-College 5-University 9-Others (specify)			Educat
3	What is your husband's qualification?	1-Illiterate 2. Primary level 3-Secondary 4-College 5-University 9-Others (specify)			HEducat
4	What is your main occupation?	1-Housewives 2-Agriculturc 3-Govt. Job 4. Privte Job 5-NGO 6-Business 9-Others (specify)			Occupa
5	What is your religion?	1-Islam 2-Hinduism 3-Christian 4-Buddhist 9-Others			Religion
6	What is your husband's main Occupation?	1-Agriculture 2-Govt. Job 3. Privte Job 4-NGO worker 5-Businessman 9-Others (specify)			HOccupa
7	How much your monthly family income?	_____ Taka			Income
8	How many members in your family?	_____ person			FMember

9	What Type of house you live in?	1-Kacha house 2-Bamboo's house 3-Tin made house 4-Semi-Pakka 5-Pakka 9-Others Others (specify)			House
10	Do you have following things in your house?	1-Nothing 2-Radio 3-Television 4-Cassete player 5-VCR 6-Newspaper 9-Others (specify)			Media
11	How much have your weight? Measure	---------- kg			Weight
12	What is your height? measure	---------- m^2			Height

C-Information of source of drinking water:

13	From where you are getting drinking water?	1-Tube well 2-Deep Tube well 3-Ponds,Canal & River 4-Dug well 5-Rain water 9-Others (specify)			WSource
14	How long have you been drinking water from this source?	_____Years _____Months			Duration
15	Was examined this tube-well water for arsenic?	1-Yes 2-No			ArsExam
16	Was arsenic found in this tube-well water?	1-Yes 2-No			ArsPrest
17	Was this tube-well water colored?	1-Yes (Red, Green) 2-No			Colour
18	Was this tube-well for main source of drinking water?	1-Yes 2-No			MSource
19	Present arsenic level in this tube-well water.	_____ mg/Liter			PrsLevel
20	Past arsenic level in this tube-well water.	_____ mg/Liter			PastLevel
21	Do you know arsenic toxicity?	1-Yes 2-No			Toxicity
22	Have you been found any symptom in your body?	1-None of any symptom → 28 1-Black or brown spot (Melanosis) 2- Rough or dry skin (Keratosis) 3-Rain drop pigmentation 4-All of the above 9-Others (specify)			Symptom
23	How long have you been found these symptom in your body?	_____ Years _____ Months			SymDurat
24	Have you been found	1-Yes			

	thick/hard nodule in your body?	2-No →	28		Nodule
25	If so, how long have beenfound?	_____ Years _____ Months			NodDura
26	What are the source of water for cooking?	1-Same tube-well 2-Deep Tube well 3-Ponds,Canal & River 4-Dug well 5-Rain water 6-Boil water 9-Others (specify)			CookWat
27	At present, from what source are you getting drinking water?	1-Same tube-well 2-Deep Tube well 3-Ponds,Canal River 4-Dug well 5-Rain water 6-Boil water 9-Others (specify)			PrSource

D-Reproductive Health Information:

28	When you have got married?	_____(in completed years)			MarryAge
29	Have you ever used contraceptive method?	1-Yes 2-No 3-No response → 34 4-Widow → 39			ContrUse
30	Which method have you been used?	1-Oral pill 2-Copper T 3-Condom 4-Injection 5-Norplant 6-Safe period 9-Others (specify)			ContMeth
31	How to make decision regarding Family Planning?	1-Self 2-Husband 3- Both 9-Others (specify)			Involve
32	Have you got pregnant now?	1-Yes 2-No → 40			Pregnant
33	Please tell me your Last Menstrual Period (LMP)	1-LMP ☐☐ ☐☐ ☐☐ Day Month Year 2-Not remember			LMP
34	Have you ever visit for ANC ?	1-Yes 2-No			ANC
35	How many times did you visit for ANC?	_____ Times			ANCTime
36	Have you ever faced any problem during pregnancy?	1-Faced no problem 2-Abortion → 35 3-High BP 4-Headache-Vomitting 5-Diabetes 6-Convulsion 7-Unconscious 8-Oedema leg 9- Others (specify)			PregProb
37	How have you became aborted?	1-Unwillingly (complete/incomplete) → 38 2-Willingly 3-Illness of mother 4-Ectopic pregnancy 5-Septic abortion 6-Illness of fetus 9- Others (specify)			Abortion

38	Where have you planned to deliver or delivered	1-Mother's home 2-Husband's home 3-Relative's home 4-Govt. Hospital 5-Private Hospital 6-NGO Clinic 7-Maternity Clinic 9-Others (specify)			PlacDelv
39	When have you delivered?	1-Before full time 2-During full time 3-After full time			DelvTime
40	Would you please tell me about your recently delivered child?	1-Living 2-Dead after birth 3-Still birth 4-Low birth weight 5-Handicapped 9-Others (specify)			RecDeliv
41	Please tell me the birth order of your present child?	[ ][ ]			BirthOrd
42	How long have you ever fed Exclusive Breast Feeding?	1-Less than one month 2-1 to 2 months 3-3 to 4 months 4-5 to 6 months 5-More than 6 months 6-Not Exclusive Breast Feeding (EBF) 9-Others (specify)			EBF
43	Have you ever received Post Natal Care within 6 weeks of delivery?	1-Yes 2-No			PNC
44	Have you ever faced any reproductive health problem?	1-Face no problem 2-Lower abdominal pain (PID) 3-Excessive menstrual bleeding 4-Scanty menstruation 5-Irregular menstruation 6-Infertility 7-Habitual abortion 9-Others (specify)			RHProb
45	Have you ever suffered any Sexually Transmitted Diseases (STD)?	1-Yes 2-No 3. Do not know			STD
46	From where do you receive reproductive health care (RHC)?	1-Satellite clinic (Green Umbrella) 2-Union Health & Family welfare center 3-UpazilaHealth Family welfare complex 4-Maternity clinic 5-District Sadar Hospital 6-Health & Family welfare worker 7-Village doctor 8-Traditional system 9-Others (specify)			RHC
47	Why you never used Reproductive health care (RHC)	1-Not necessary 2-Familial barrier 3-No helper to accompany 4-Service center is not near 5-Too expensive 6-Do not know where to get service 7-Medicine is not available 8-Nobody to look after my children 9-Others (specify)			RHCNorec

48	What is the age of your youngest child?	---------- Month ---------- Year			YonChild
49	Do you want more children?	1-Yes 2-No 3-Do not know 4-Depends on husband 5-Depends on God 6-Not sure 9-Others (specify)			MoreChild
50	Would you please tell me regarding your previous pregnancy?	1 Living : Number 2 Dead after birth : 3 Handicapped : 4 Low birth weight : 5 Premature : 6 Still birth : 7 Miscarriage : 8 MR/Abortion : 9 Others (specify) :			PrevPreg
51	If you will become pregnant what will you do?	1-Nothing to do 2-Try to stop (success) 3-If not success, try again to stop 4-If failed, continue pregnancy 5-Do not know 9-Others (specify)			Decision

52. Would you please provide your suggestion how to stop the toxicity of arsenic?

Thank you very much for answering these questions.

Name and signature of Interviewer: ----------

Name and signature of Supervisor: ----------

Appendix-2

INFORMED CONSENT FORM (ICF)

ID No. _____

Name of the mother _____

Address of the mother _____

_____

I would like to ask you some questions for the study entitled ***"Diabetes mellitus among arsenicosis affected mother and their reproductive outcome"*** Would you please answer the following questions the best describe closest to your opinion that would be most useful to conduct this research. You are free to participate in this study and you have freedom to refrain from the study without any hesitation. You are allowed to abstain from answering any questions during interviewing. We are promised not to disclose your name and any information. You face no physical, mental and social problem if you will participate in this study and will continue services even you will not participate in this study. Confidentiality and anonymity is our responsibility. Would you please agree to participate in this study? If you decide to participate in this study, please put your signature/thumb impression in the space provided below.

Participants Signature/Thumb impression ----------

Date ----------

Women's verbal consent

The mother has read the information or mother has been informed by the interviewer the nature and purpose of the study and consent of her participation in this study. She is willing to take part in this study.

Investigator's Signature

Date :----------

Appendix-3

Personal Data Sheet (PDS)

Name : **Dr. Md. Nazrul Islam**
Gender : Male
Date of birth : 1st January, 1956

Present Position and Department: Assistant Professor, Department of Maternal and Child Health, NIPSOM, Mohakhali, Dhaka-1212.

Educational Qualification (Graduate and above):

Degree	University	Year	Result
i. M. Sc. in Health Development (BMRDC recognized as MPhil degree)	Chulalongkorn University Bangkok, Thailand	2000	Passed
ii DPH (renamed as Master of Public Health (MPH)	University of Dhaka	1987	**Stood first**
iii. MBBS	University of Dhaka	1982	Passed

Field of Specialization: Reproductive and Child Health
Health service Management

Teaching Experience:

No	Program/Subject	Sponsored by	Venue	Duration/Yea
i	Short Course in Environmental Health Sciences	Columbia University, Mailman School of Public Health, USA	Dhaka, Bangladesh	20-21 October 2 days, 2003
ii	Training Course on Data Analysis	WHO and NIPSOM	NIPSOM	21-28th November, 2002. 8 days
iii	Training Course on Teaching Methodology	WHO and NIPSOM	NIPSOM	9-13th November, 2002. 5 days
iv	Workshop on Teaching Methodology for Post Graduate Medical Institutes	Center for Medical Education (CME) and DGHS	Center for Medical Education (CME)	18-20th Augus 2002. 3 days
v	Operation Research on Reproductive Health	Institute of Health Economics, Population Council, Bangladesh	Dhaka University	21st January to 1st February, 2001. 10 days.

Research article published in the journal:

1. Socio-demographic characteristics of the patient's suffering from Rheumatic fever and Rheumatic heart diseases: JOPSOM 2000; 19 (1): 47-51.

2. Medico-legal injury cases attended in a private medical college hospital in Bangladesh: JOPSOM 2000; 19 (1): 81-85.

3. Assessment of effectiveness of different drug regimen according to the nature of malaria cases in some selected areas of Bangladesh: JOPSOM 2000; 19 (1): 86-92

4. Secondary level health related sector's mid level manager's awareness about ongoing primary health care program in Bangladesh: BMJ 2001; 30 (2): 28-30.

5. Prevailing Health Problems and Disease Profiles in a selected rural area of Bangladesh. JOPSOM, December 2001; vol. 20: no (2): 35-40.

6. Waste Management Situation in Secondary and Tertiary Level Hospital in Bangladesh. JOPSOM, December 2001; vol. 20: no (2): 51-57.

7. Parental child preference and fertility pattern in the slum area of Bangladesh. Journal of Medicine, July 2002; vol. 3: no. (2); p80-88.

8. Pregnant adolescent perception on their needs of Pregnancy Counseling and Services provided trough District Maternal and Child Welfare center. Journal of Medicine, July 2002; vol. 3: no. (1); p11-20.

9. Fertility pattern of contraceptive practice among the married female tea garden workers of reproductive age. Journal of Medicine, July2002; vol.3:no.(1); p25-33.

10. Acceptance of injectable contraceptives among contraceptive users in a selected family planning clinic. JOPSOM, June 2002; vol. 21: no (1): p31-36.

11. Adolescent pregnancy: Is it a planned affair? JOPSOM, June 2002; vol. 21: no (1): p67-74.

12. Maternal factors related to foetal outcome at Dhaka Medical College Hospital, Dhaka. Bangladesh. JOPSOM, December 2003; vol. 22: no (2): p33-39.

13. Assessment of knowledge on HIV/AIDS among Madrassa Teachers. JOPSOM, December 2005; vol. 24: no (2): p64-72.

14. Pregnancy planning among married pregnant adolescents. JOPSOM, June 2006; vol. 25: no (1): p85-92.

Unpublished & ongoing Research:

Research ongoing:

1. Adolescent pregnancy and child birth is an emerging research focus in Bangladesh (BMRC Project)

Research Protocol submitted:

1. Uncontrolled pregnancy and uncontrolled fertility: challenges of current decade of Bangladesh (BMRC Project)

Research completed:

1. Review of health and rehabilitation activities of Bangladesh Protibondhi Foundation in respect of handicapped children.
2. Perception of pregnant adolescent on their needs of pregnancy counseling and services provided through District Maternal and Child Welfare Center (MCWC) in Bangladesh.
3. Client satisfaction for continuation of Norplant use among the rural women of Bangladesh.
4. Practices during menstrual period among the urban and rural adolescent girls of Bangladesh.
5. Awareness of the slum adults about condom use in preventing RTI, STDs HIV/AIDS.
6. Health facilities utilization by low income maternal and child health and family planning users.
7. Pre-lacteal feeding practice among mother's within 24 hours of delivery in a Baby Friendly Hospital.
8. Knowledge about breast cancer and examination of breast among the female university students.
9. Laparoscopic sterilization approach: Silicon rubber band technique in context of Bangladesh.
10. Chronic exposure of arsenic in drinking water and women's reproductive health outcome under the financial assistance of WHO and administrative support of NIPSOM

11. Complication of pregnancy among arsenicosis women.

12. Acid violence and adolescent girls

13. Male involvement in family planning in rural-urban perspective

14. Client's satisfaction and provider's perception on syndromic management of reproductive tract infections.

15. Knowledge on sexually transmitted infections of health and family planning providers of government and non government organization (NGO).

16. Arsenicosis: Maternal BMI and their Reproductive Health Outcome (BMRC Project)

17.. Diabetes Mellitus among arsenicosis affected mother and their Reproductive Health Outcome under Ph.D. program.

11. Computer & Language efficiency: Excellent in Computer literacy: Microsoft Word, Power Point, Microsoft Excel, Epi-Info an SPSS
Excellent in reading writing and speaking in English and Bengali.

12. Address of correspondence: Assistant Professor, Department of Maternal and Child Health, National Institute of Preventive and Social Medicine (NIPSOM), Mohakhali, Dhaka-1212, Bangladesh.
Phone: 9898569, Mobile 01711671540.

25/10/2007

Signature