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Pregnancy Outcome of Diabetic Mothers Attending a Tertiary Hospital in Rajshahi

Hossain, Shamima Akhter

University of Rajshahi

PREGNANCY OUTCOME OF DIABETIC MOTHERS ATTENDING A TERTIARY HOSPITAL IN RAJSHAHI

**THESIS SUBMITTED FOR THE DEGREE
OF
DOCTOR OF PHILOSOPHY
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BY

SHAMIMA AKHTER HOSSAIN (MBBS)

JUNE, 2013

**INSTITUTE OF BIOLOGICAL SCIENCES
UNIVERSITY OF RAJSHAHI
RAJSHAHI-6205, BANGLADESH**

DECLARATION

I, hereby, declare that, the research work submitted as a dissertation entitled "**PREGNANCY OUTCOME OF DIABETIC MOTHERS ATTENDING A TERTIARY HOSPITAL IN RAJSHAHI**" to the Institute of Biological Sciences, University of Rajshahi, Rajshahi, Bangladesh for the degree of Doctor of Philosophy (Ph. D) is the outcome of the original research work carried out by me under the supervision of **Dr. Md Anwar Ul Islam**, Professor, Department of Pharmacy and Dean Faculty of Science, University of Rajshahi, Rajshahi, Bangladesh and **Dr. A R M Saifuddin Ekram**, Professor, Dept of Medicine, Rajshahi Medical College Hospital, Rajshahi, Bangladesh.

I, further, declare that, this dissertation or part thereof has not been the basis for the award of any degree, diploma or associate ship of any other similar title.

Signature of the candidate

(Shamima Akhter Hossain)

CERTIFICATE

This is to certify that **Shamima Akhter Hossain** is the sole author of the dissertation entitled "**PREGNANCY OUTCOME OF DIABETIC MOTHERS ATTENDING A TERTIARY HOSPITAL IN RAJSHAHI**". This dissertation has not been previously submitted for the award of any degree or diploma of any other similar title.

We are forwarding this dissertation to be examined for the degree of Doctor of Philosophy (Ph.D) to the Institute of Biological Sciences, University of Rajshahi, Bangladesh. **Shamima Akhter Hossain** has fulfilled all the requirements according to the rules of the University for Submission of a dissertation for the degree of Doctor of Philosophy (Ph.D).

The research work of **Shamima Akhter Hossain** is authentic and up to our full satisfaction.

Principal supervisor :   **Co-supervisor:**

(Dr. Md Anwar Ul Islam)   **(Dr. A RM Saifuddin Ekram)**
Professor,   Professor,
Department of Pharmacy   Dept. of Medicine
University of Rajshahi, Rajshahi   Rajshahi Medical College Hospital
Bangladesh.   Rajshahi, Bangladesh.

(Already printed do not print)

DEDICATED
TO THE MEMORY OF
MY
DEPARTED BELOVED
HUSBAND

ACKNOWLEDGEMENT

ABBREVIATIONS

ADA- American Diabetic Association

AIDS- Acquired Immune deficiency syndrome

BIRDEM-Bangladesh Institute of Research on Diabetes, Endocrinology and Metabolic disorder

BMI-Body Mass Index

DAB –Diabetic Association of Bangladesh

DM- Diabetes mellitus

FBG-Fasting Blood glucose

CS- Cesarean section

GCT-Glucose Tolerance Test

GDM-Gestational Diabetes Mellitus

GDP–Gross Domestic Product

HNPSP-Health Nutrition and Population Sector Program

IFG-Impaired Fasting Glucose

IGT-Impaired Glucose Tolerance

IUD-Intra Uterine Death

IUGR- Intrauterine growth restriction

LGA-Large for Gestational Age

MCHTI-Maternal and Child Health Training Institute

MDG–Millennium Development Goal

MMR-Maternal Mortality Rate

ABBREVIATIONS (contd.)

MOHFW-Ministry of Health and Family Welfare

MPS-Making Pregnancy Safer

NCD-Non Communicable Disease

NGO–Non Governmental Organization

NHN–National Healthcare Network

OGSB-Obstetric and Gynecological Society Bangladesh

OGTT-Oral Glucose Tolerance Test

PDM- Pregestational Diabetes Mellitus

PE- Pre-eclamsia

PGDM- Pregestational Diabetes Mellitus

PIH- Pregnancy induced hypertension

PROM- Preterm rupture of membrane

RBG-Random Blood Glucose

RDS- Respiratory distress syndrome

UNICEF–United Nations Children's Fund

UTI- Urinary tract infection

WHO- World Health Organization

2hBG-Blood Glucose 2 Hours after 75gm Glucose Intake

ABSTRACT

Background and objectives: Diabetes is often detected in women during their childbearing years and can affect the health of both the mother and her baby. Poor control of diabetes in a pregnant woman increases the chances for birth defects and other problems for the baby. It might also cause serious complications for the woman. Proper health care, before and during pregnancy, will help prevent birth defects and other poor outcomes, such as miscarriage and stillbirth.

Though prevalence of diabetes is alarmingly high among Bangladeshi's there have been very few studies assessing the effect of diabetes on pregnancy outcomes, particularly comparing pre-gestational diabetes mellitus (PDM) and gestational diabetes (GDM). Studies on pregnancy outcomes of Bangladeshi mothers with diabetes mellitus are very limited.

To fill this information gap, the present study was undertaken, with the view to determine the prevalence of antepartum and intrapartum maternal and perinatal complications of diabetic pregnancy, particularly comparing pregnancy outcomes in pre-gestational diabetes mellitus (PDM) and gestational diabetes (GDM) among pregnant diabetics in a tertiary level Hospital in Rajshahi, Bangladesh.

Methods:

Pregnant diabetic (both PDM and GDM) women who attended, got admitted, treated and delivered at Rajshahi Medical College Hospital (RMCH), Rajshahi, Bangladesh a tertiary level Government owned public hospital in Rajshahi, a divisional city in the Northern part of Bangladesh from August, 2008 to September, 2011 were selected for this observational retrospective study. Of the total 187 diabetic pregnant women in the study, 113 (60.43%) women were diagnosed as having gestational diabetes (GDM) and the rest 74 (39.57%) women had pre-gestational diabetes (PDM).

Research instruments of the study were a structured questionnaire and sources for data were answers from the participants in interview, antenatal checkup cards, diabetic book of the women and hospital files for delivery and birth records. Selection of cases of this study was performed on random (continuous) sampling basis and was based upon some preset inclusion and exclusion criteria. Screening of patients as GDM and PDM was performed on the method adopted by Rajshahi Medical College Hospital following the guideline for diagnosis and screening of DM proposed by the clinical research division BIRDEM, Dhaka, Bangladesh to set a cut off value for screening DM women.

GDM and PDM were the only dependent variables of the study. All others were independent Socio demographic variables like, maternal age, level of education of the women, monthly expenditure of the family. Family history of diabetes, first and second degree relatives. Details of pregnancy outcome variables included maternal complications like Pre-eclamsia (PE), Eclamsia, PROM, Caesarean section rate, delivery per vagina, polyhydramnios, the incidence of vulva and vaginal candidiasis and UTI weight were documented. Fetal and Neonetal outcome of diabetes variables were live birth, fetal abortions, congenital malformations, intrauterine death (IUD, and incidence of large babies (macrosomia).

Results: Majority (54.54 %) of the diabetic pregnant women were within the 30-39 years age group. Nearly fifty-eight percent (58.22%) women progressed to term pregnancy where as in 41.78 % diabetic pregnant women it ended before 37 weeks of gestation. Average gestational age was 36.75 ± 0.9 (28-41) weeks. The mean maternal age was 28.9 (18-45) years.

Among maternal complications of diabetic pregnancy, pre-eclampsia (PE) developed among 12.9% women; while Eclampsia developed among 2.2% women. Incidence of Pre-eclamsia (PE) was comparatively higher in pre-gestational diabetic (PDM) mothers than in GDM mothers (15 vs 9) and the difference found to be statistically significant ($p> 0.014$). Similarly, the incidence of Eclampsia was also higher among women having PDM than GDM (3 vs 1) but this differences found to be statistically insignificant ($p=0.172$).

Preterm rupture of membrane (PROM) was higher (15.0%) in pregnant women with GDM as compared to 8.1% women of PDM. but their differences were statistically insignificant (p= 0.158). Ante-partum fetal distress developed in (23.9%) women having GDM and 21.6% women with PDM; but the differences between them was statistically insignificant (p= 0.718).

Incidence of polyhydramnios was higher (59.5%) in pregnant women with PDM as compared to 29.2% having GDM and the differences between them found statistically very highly significant (p < 0.001). The rate of delivery by cesarean section (CS) was very high (72.1%) and only 10.7% babies were by vaginal delivery. Nearly seventy eight (77.8%) women of GDM and 47(63.5%) women of PDM delivered babies by cesarean section and the difference is not statistically significant (p>0.634). The results of statistical analyses also revealed that rate of vaginal delivery was significantly higher in GDM mothers than the PDM mothers (p=0.048). The incidence of abortion was higher (18.91%) in the PGDM women as compared to (5.03%) in GDM women and statistical analysis reveled that abortion rate was significantly higher in pregnant women having PDM (p= 0.003).

The incidence of vulva and vaginal candidiasis was found to be almost very similar in pregnant women having GDM and PDM. It was 41.6% and 40.5%, respectively and the difference was statistically insignificant (p>0.886). Similarly, the incidence of urinary tract infection (UTI) was found to be almost same in pregnant women having GDM and PDM; 41.6% and 40.5%, respectively and the difference was also found to be statistically insignificant (p>0.771).

Regarding Fetal and Neonetal outcome of diabetes; there were 155 (82.88%) normal live birth, 05 (2.67%) live birth with congenital malformations and 12 (6.4 %) intrauterine death (IUD). Among 12 intrauterine deaths, 11 had developed preeclampsia and in one woman the cause was unknown. Regarding congenital malformation, the prevalence was almost the same in pregnant women with PDM and GDM and were 3(4.1%) and 2(1.7%), respectively. The above differences were found to be statistically insignificant (p >0.308).

In the present study, the prevalence of 'large babies' i.e. Macrosomic babies was much higher (70.3%) in pregnant women having PDM as compared to that of GDM (26.5%) groups. PDM group therefore gave birth to large baby more frequently than the GDM group did. The above difference was found to be statistically highly significant (p <0.001).

Regarding socio-economic statuses of the participants, highest numbers of patients (60%) were from the lower middle class group while the lowest number of patients (08%) belonged to the poor class. Educational level of majority (about 44%) of the diabetic patients was less than S.S.C and the least number of patients (only 4.81%) were graduates.

Results of study of relation between diabetes incidences in relation to familial history of diabetes showed that 72.92% of PDM patients had first degree relatives, 18.97% second degree relatives and 8.11% had no family history. And of those who had GDM, 76.99% had first degree relatives, 8.85% second degree relatives, and 14.15% had no family history.

Results on the frequency of diabetes mellitus (depending upon their type) and their possible relation to location of resident areas demonstrated that 51.35% of those who had PDM had lived in the city, and 36.49% lived in villages, and 12.16% had lived in slums. As gestational diabetes is concerned, 57.52% had lived in the city, 37.18% had lived in villages, and 5.3% had lived in slums.

Conclusion: Women with diabetes in our study population have worse pregnancy outcomes as compared to other South Asian countries of the world and even worse than other parts of Bangladesh. And those with pre-gestational diabetes had far worse pregnancy outcome than those with gestational diabetes. The study emphasizes the fact that strict glycemic control is extremely important during diabetic pregnancy for achieving better pregnancy outcome.

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CHAPTER-1

INTRODUCTION

1. INTRODUCTION

The term "diabetes mellitus" describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus (DM) is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both (Gojka Roglick WHO 1999, Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997, Beverley and Eschwège 2003).

Chronic hyperglycemia, from whatever cause, leads to a number of complications such as cardiovascular diseases, renal, neurological, ocular and intercurrent infections. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs (Diabetes program: About Diabetes WHO 1999). Diabetic patients develop multiple chronic complications leading to irreversible disability and death if undiagnosed of inadequately treated. Coronary heart disease and stroke are more common in diabetics than in the general population.

Diabetes is an "iceberg" disease. According to the recent estimates, the prevalence of diabetes mellitus in adults was around 4% worldwide which indicates over 150 million persons is affected. It is projected that the disease prevalence will be 5.4% by the year 2025, with global diabetic population reaching 300 million. Of this, around 77% of the global burden of disease is projected to occur in the developing countries (Wild *et al.* 2004).

There has been an exponential rise in the prevalence of diabetes throughout the world, with South Asia being its focal point. Its incidence has increased in South Asia by 111% in the past 15 years, when compared to other continents such as North America, Australia and Europe which have less than a 50% rise (Zimmet 2000).

In most Western societies, the overall prevalence has reached 4-6%, and is as high as 10-12% among 60-70-year-old people. The annual health costs caused by diabetes and its complications account for around 6-12% of all health-care expenditure.

Diabetes mellitus is the second most common medical problem complicating pregnancy (Marquette *et al*. 1995, Drexel *et al,* Langer and Mazzea 1988). The World Health Organization defines diabetes in pregnancy as a fasting glucose $\geq$ 7.9 mmol/l, or a value > 11 mmol/12 hours after a 75 g glucose load (oral meal).

Diabetes mellitus (DM) complicates 3–5% of all pregnancies and is a major cause of perinatal morbidity and mortality, as well as maternal morbidity (Gabbe and Graves 2003). Gestational Diabetes Mellitus (GDM), a glucose tolerance disorder of variable severity which occurs or is diagnosed for the first time during pregnancy, constitutes a public health problem because of its frequency (1 to 6% of all pregnancies) and its short and long term consequences for the fetus and/or the mother (Vambergue *et al.* 2002).

GDM has emerged as a common medical complication of pregnancy (Wijeyaratn *et al.* 2006) with a parallel increase to the pandemic of type 2 diabetes mellitus. Currently GDM affects approximately 7% of all pregnancies and up to 14% of pregnancies in high-risk populations while pregestational diabetes mellitus (PGDM) is estimated to affect about 1.3% (American Diabetes Association 2004). The incidence of GDM in South India is reported to be 16.55% (Seshiah *et al.* 2006).

Metabolic disorders in pregnant diabetic women as well as those caused by gestational diabetes poses a high health risk, to both the mother and fetus. Diabetes in pregnancy, either GDM or pre-gestational diabetes mellitus (PGDM), is linked to several maternal and fetal/neonatal complications. Maternal complications

include pregnancy-induced hypertension, pre-eclampsia, postpartum haemorrhage, abortion, still birth, congenital anomalies, polyhydramnios, increased incidence of caesarian section, traumatic delivery and later development of type 2 diabetes (Ben-Haroush *et al.* 2004). An increased frequency of urinary tract infections, candidiasis of the vagina and vulva is also noticed.

Foetal complications are even more serious. Poorly controlled diabetes greatly increases the risk of congenital malformations (Sacral dysgenesis). Fetal macrosomia is one of the main perinatal complications in all types of diabetic pregnancy, especially in women with GDM having poor glycemic control and has been associated with a higher rate of Cesarean delivery (Gabbe and Graves 2003). Fetal macrosomias commonly leads to obstructed labour and shoulder dystocia. It is also associated with sudden intrauterine foetal death late in pregnancy. After birth the new born may suffer from respiratory distress.

Pregnancy and preconception period are of particular importance to people with diabetes as pregnancy challenges to the metabolic management in diabetes and, at the same time it increase risk of diabetes related complications in mother. The above maternal and fetal/neonatal complications can be prevented by tight control of maternal glycemia before gestation and during the early weeks of pregnancy.

Statement of the problem

Diabetes mellitus is prevalent among 4.8% people of Bangladesh and prevalence of IGT is 8.5% (Khan *et al.* 2007). Among them a significant number are female. Gestational diabetes mellitus (GDM) develops among 6.7% of all pregnancies in our population (Tofail *et al.* 1997). In view of the increasing prevalence of type 2 diabetes in Bangladesh, it is reasonable to postulate that there is a growing prevalence of gestational diabetes. Bangladeshi women have been seen to have higher IGT than their male counterpart (Abu *et al.* 1997). Compared to the other

South Asian population Bangladesh has higher birth rate (BBS 2000) and has the prevalence of multiparty. Perinatal mortality and infant mortality is also high in Bangladesh (Low Birth Weight of a Meeting, Dhaka). Though there is no published report on the prevalence of preeclampsia in Bangladesh the Obstetric and Gynaecological society (OGSB) in Bangladesh estimates 16% of maternal death from eclampsia (Begum *et al.* 2004). In addition, according to OGSB obstructed labour accounts for 8% of maternal death. Frequency of congenital malformations and low birth weight also appears to be higher in Bangladesh.

Increased morbidity and mortality among mothers and newborns in Bangladesh may in part be due to the effect of GDM (Sayeed *et al.* 2005). Data on the subject is scarce resulting in a lack of guideline for clinical investigation for pregnant mother which is likely to bear grave consequence. Risk factors predisposed to GDM need to be identified in this region in order to initiate a selective screening during pregnancy period to ensure safe mother hood and identify women with risk of diabetes later in life.

Studies addressing the relationship of gestational age at GDM diagnosis and pregnancy outcomes are scarce in Bangladesh. Evidences report that gestational diabetes affects pregnancy and fetus adversely if mother's glycaemia is uncontrolled and has been high. Therefore the aim of treatment during the pregnancy is to keep mothers' blood glucose level under normal range either by diet or by insulin. Information on the risk of these complications would have helped to continue or readjust the treatment protocol of GDM in Bangladesh.

Careful search of literature provided very little data on prevalence of GDM or PDM based on the time of diagnosis in Bangladesh perspectives. Inspite of reports that claim 40-66% of gestational diabetes can be detected in early pregnancy there have been conflicting studies on the usefulness of glucose screening at early

pregnancy (Meyer *et al.* 1996). Nevertheless one could reasonably suggest that women with gestational diabetes in early pregnancy could benefit from earlier metabolic control as well as prediction of pregnancy and fetal complication in this group.

A study conducted in India found different types of fetal complication at different level of glycaemic control. With improved glycaemic control and advanced neonatal care perinatal adversities in GDM have approached that of non diabetic mothers (Banerjee *et al.* 2004). Thus intervention either by diet or by insulin in GDM may predict risk or possible outcome of the index pregnancy. Information on this would help to take preventive measures and make a birth planning in order to ensure a safer pregnancy for Bangladeshi women.

Very little data is available from Rajshahi, the Northern region of Bangladesh with regard to the prevalence of gestational diabetes mellitus (GDM) and PDM. This is quite unbecoming considering the fact that a lot of research focus today is on the well being of mother and the newborn child in general and in the situation of GDM or diabetes mellitus in particular.

The present study, therefore, attempts to elicit valuable inputs to fill this void and was based in Governmental Rajshahi Medical College Hospital, which is one of the largest public sector hospitals in Northern Bangladesh catering to patients from different parts of the Northern region.

Abnormal metabolic environment due to hyperglycemia has a profound impact on maternal and fetal outcome. Indians and South Asians belong to higher risk for developing diabetes due to their ethnicity (Naylor *et al.* 1997). The present study was conducted to determine the maternal and fetal outcomes of pregnancies in women with diabetes mellitus in a tertiary level Hospital in the Northern region of Bangladesh.

Justification of the study

• Pregestational diabetes mellitus (PDM) and gestational diabetes mellitus (GDM) has been seen to be associated with growing pregnancy complication by hospital observation in Bangladesh. Urban prevalence of GDM is predicted even much more while the rural prevalence was found 6.8% and 8.2% according to FBG and 2hBG respectively (Sayeed *et al.* 2005).

• According to Millennium development goals complicated pregnancies need to be identified beforehand so that pregnant women can make a safer birth planning and be attended by skilled health personnel at their delivery.

• Neonatal mortality and morbidity would have also to be reduced in line with the targets of MDG.

• Most of the GDM cases progress to diabetes type 2 later in life. In Bangladesh diabetes has become highly prevalent and is growing at a faster rate. Identification of high risk group like GDM helps to initiate preventive measures for them so that the onset of diabetes can be delayed or prevented. Thereby the huge health expenditure for diabetes can be minimized.

CHAPTER-2

RATIONALE, HYPOTHESIS, AIMS AND OBJECTIVES

2 RATIONAL, HYPOTHESIS, AIM AND OBJECTIVES

2.1. Rationale of the study:

Inadequate awareness about the real dimension of the problem among the general population particularly the diabetes women during pregnancy compel them to face number of poor outcome of the conditions. Poor management of primary health care system fails to detect diabetic cases early, suboptimal treatment and insufficient follow up leading to unnecessary disabilities and severe complications, often resulting in early death of fetus.

Diabetes is a major cause of disability through its complications such as blindness, kidney failure and coronary thrombosis. Diabetic mothers are at high risk of developing complication. Incidences of larges baby, congenital malformations, IUD are more frequent than normal pregnant women. There is a need to organized specialized clinics at tertiary level hospital to provide diagnostic and management skills of high order. The tertiary level should also be involved in basic, clinical and epidemiological research.

The proposed study is unique in the concerned area. No such in-depth study has been carried out so far by any scholar in this related field. So, the present study was undertaken and it is believed to be an innovative work on the outcome of pregnancy among the diabetic women.

It is expected that the proposed study will be able to show the effect of diabetes on pregnant women. The end result of the pregnancy, usual complications of mothers and foetus could be explored through this study. The findings of the study will be useful for the diabetic women at the time of pregnancy. The study will be able to add new knowledge in the discipline of Obstetric, gynecology and pediatrics.

The findings of the present study would certainly enrich the existing knowledge on diabetic mellitus during pregnancy. The physicians particularly the obstetricians will get information regarding pregnancy outcome in diabetic women. This will sensitize them to develop skills in proper management of diabetic mothers at the time of delivery.

2.2. Research hypothesis:

1. Large baby is more frequent out come of pregnancy among the irregular and late reported diabetic mothers.

2. The incidence of IUD is higher among the elderly diabetic mothers than that of other normal pregnant mothers. Incidence of abortion is higher among the diabetic women than non-diabetics.

2.3. Research objectives:

General Objectives

- To investigate the outcome of pregnancy among the diabetic mothers attending Rajshahi Medical College Hospital.

Specific Objectives

- To calculate the proportion of diabetics giving birth to normal baby.
- To examine the physical condition of the new born in order to determine the outcome of pregnancy.
- To identify the complications of pregnancy among the diabetic mothers.
- To estimate the proportion of outcome of fetus in terms of intrauterine death (IUD), abortion, still birth, large baby and deformed baby.
- To determine the socio-demographic and economical status of the diabetic mothers.

2.4. Variables of the Study:

Independent Variables

> Socio-demographic variable
>
> Age of participant,
>
> Educational status of the subject,
>
> Occupation of the respondent,
>
> Monthly income of the family

Obstetrical variable

> Parity
>
> Past obstetrical history
>
> Number of live birth,
>
> Still birth,
>
> Abortion,
>
> IUD,
>
> Macrosomia (large baby)
>
> Duration of current pregnancy
>
> Diabetic variables
>
> Length of diabetes mellitus of the respondent.
>
> Receive treatment for diabetes.

Dependent variables

> Fetal Outcome
>
> Normal live baby
>
> Large baby
>
> IUD
>
> Still birth/abortion
>
> Congenital malformation
>
> Respiratory distress

CHAPTER-3

REVIEW OF LITERATURE

3. REVIEW OF THE LITERATURE

A detail literature search was conducted in order to elicit known and unknown facts on pre-gestational (PDM) and gestational diabetes (GDM) relevant to the present study. Specific search was also conducted on risk factors, ethnic distribution and fetal and maternal complication of PDM and GDM.

As the subject of the present study, is on the pregnancy outcome of diabetic pregnant women in Bangladesh firstly literature review related to Bangladesh has been provided followed by global ones.

3.1.0. Country Profile – Bangladesh

Bangladesh though has made great strides in improving the lives of its people, yet remains as one of the poorest countries in the world (The World Bank 2005). An overview of the country is given below:

Location: Southern Asia (Table1.1a)

Population density: 819/Sq. Km

GDP-per capita: 2100$ (PPP)

Literacy rate: 43.1%

Female literacy rate: 31.8%

Local currency: Taka (1USD eq. 65 Taka)

Total Fertility rate: 3.13 children per woman

Crude Birth rate: 30.1 births/1000 population

Infant mortality: 62.6 per 1000 live births

Source: World Fact book, 2005

Bangladesh Demographics Profile 2012

Population: 161,083,804 (July 2011 est.)

Age Structure
0-14 years: 34.3% (male 27,551,594/female 26,776,647)
15-64 years: 61.1% (male 45,956,431/female 50,891,519)
65 years and over: 4.7% (male 3,616,225/female 3,778,119) (2011 est.)

Median age

Total: 23.3 years

Male: 22.7 years

Female: 23.7 years (2011 est.)

Population growth rate: 1.579% (2011 est.)

Birth rate: 22.53 births/1,000 population (2011 est.)

Death rate: 5.71 deaths/1,000 population (July 2011 est.)

Net migration rate: -1.04 migrant(s)/1,000 populations (2011 est.)

Urbanization

Urban population: 28% of total population (2010)

Rate of urbanization: 3.1% annual rate of change (2010-15 est.)

Major cities - population

DHAKA (capital) 14.251 million; **Chittagong** 4.816 million;

      Khulna 1.636 million;   **Rajshahi** 853,000 (2009)

Sex ratio

At birth: 1.04 male(s)/female

Under 15 years: 1.03 male(s)/female

15-64 years: 0.9 male(s)/female

65 years and over: 0.96 male(s)/female

Total population: 0.95 male(s)/female (2011 est.)

Infant mortality rate

Total: 48.99 deaths/1,000 live births

Male: 51.48 deaths/1,000 live births

Female: 46.39 deaths/1,000 live births (2011 est.)

Life expectancy at birth

Total population: 70.06 years

Male: 68.21 years

Female: 71.98 years (2011 est.)

Total fertility rate: 2.55 children born/woman (2011 est.)

HIV/AIDS - adult prevalence rate: less than 0.1% (2009 est.)

HIV/AIDS - people living with HIV/AIDS: 6,300 (2009 est.)

HIV/AIDS - deaths

Fewer than 200 (2009 est.)

Major infectious diseases

Degree of risk: high

Food or waterborne diseases: bacterial and protozoal diarrhea, hepatitis A and E, and typhoid fever

Vectorborne diseases: dengue fever and malaria are high risks in some locations

Water contact disease: leptospirosis

Animal contact disease: rabies

Note: highly pathogenic H5N1 avian influenza has been identified in this country; it poses a negligible risk with extremely rare cases possible among US citizens who have close contact with birds (2009)

Nationality

Noun: Bangladeshi(s)

Adjective: Bangladeshi

Ethnic groups

Bengali 98%, other 2% (includes tribal groups, non-Bengali Muslims) (1998)

Religions

Muslim 89.5%, Hindu 9.6%, other 0.9% (2004)

Languages

Bangla (official, also known as Bengali), English

Literacy

Definition: age 15 and over can read and write

Total population: 47.9%

Male: 54%

Female: 41.4% (2001 Census)

School life expectancy (primary to tertiary education)

Total: 8 years   Male: 8 years   Female: 8 years (2007)

Education expenditures: 2.4% of GDP (2008)

Maternal mortality rate: 340 deaths/100,000 live births (2008)

Children under the age of 5 years underweight: 41.3% (2007)

Health expenditures: 3.4% of GDP (2009)

Physicians density: 0.295 physicians/1,000 population (2007)

Hospital bed density: 0.4 beds/1,000 population (2005)

http://www.indexmundi.com/bangladesh/demographics_profile.html.

Accessed on: 12/10/2012

3.1.1. Geography

With an area of about 144,000 sq km, Bangladesh is situated between latitudes 20°34' and 26°38' North and longitudes 88°01' and 92°41' East. The country is bordered by India on the east, west and north and by the Bay of Bengal on the south. There is also a small strip of frontier with Burma on the southeastern edge (Fig. 1.b).
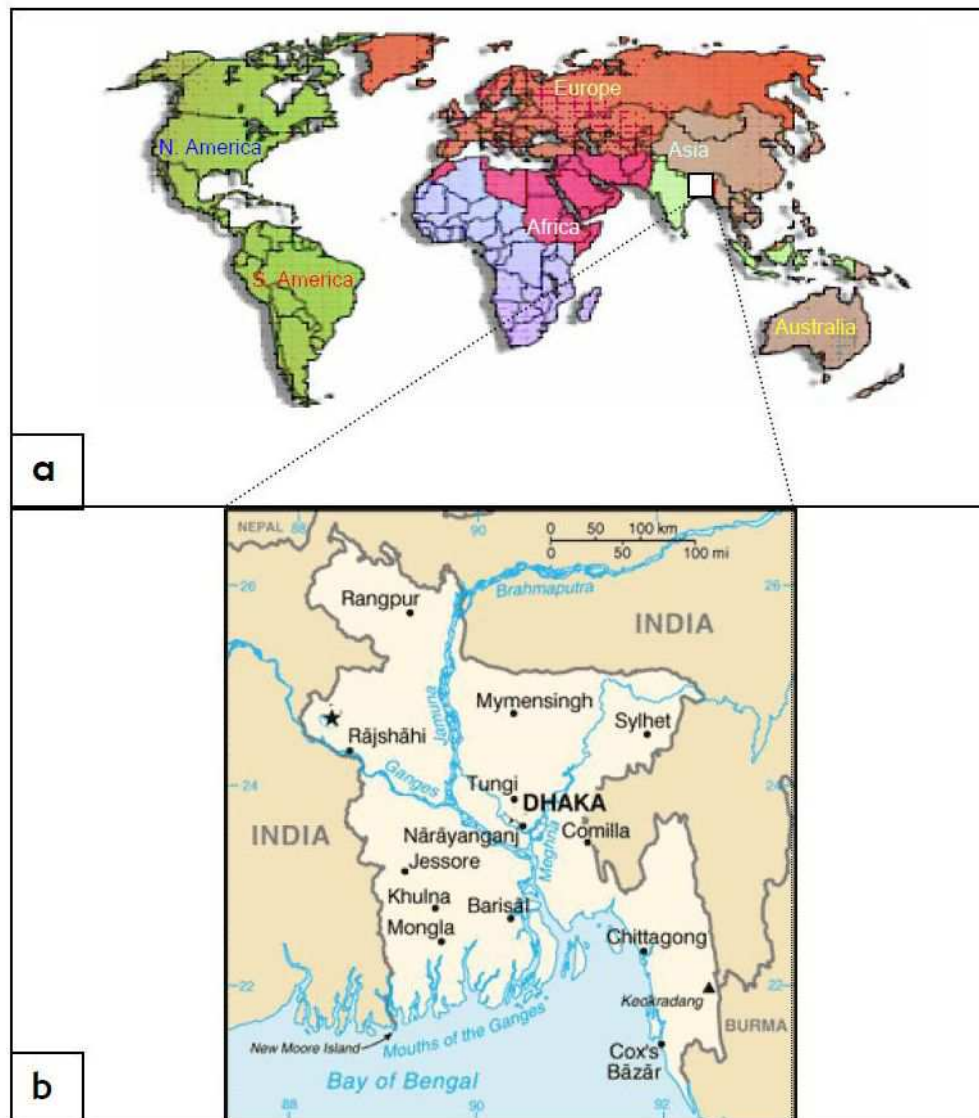
Fig.1. a) Location of Bangladesh within the world map (marked by the white square). b). Map of Bangladesh and its surrounding area. The area of study hospital is marked by the black star.

Bangladesh has mostly tropical monsoon type climate with sweltering temperature and high humidity. It is a low-lying country situated in the middle of the Ganges delta. This delta landmass comprises mainly of three mighty rivers the Ganges, the Brahmaputra and the Meghna. Though the alluvial deposits from flood makes the soil very fertile, the devastation and loss from this type of catastrophe causes huge loss of life, different health problems and affects economy massively.

3.1.2. Economy

Bangladesh's economy depends heavily on agriculture. Textile industry and remittance from people abroad are also the potential sources of GDP in Bangladesh. Bangladesh suffers from economic difficulties and relies on foreign aid. The country's total health expenditure per capita is 3.1% of GDP. A greater part of the health expenditure comes from out of pocket due to insufficient capacity in public sector even for basic health needs.

3.1.3. People and culture

According to the world health report 2005 total population of Bangladesh is assumed to be 147,360000 and population density more than 819 per sq.km. Despite better progress in growth rate (2.23%) it has remained as one of the most densely populated countries in the world. About 25% of the population lives in urban areas.

Over 97.5% of its people are Bengalis; the remainders are Biharis and indigenous tribal peoples. Bangladeshis identify themselves closely with Bangla, their state language. Family and kinship was the core of social life in Bangladesh. Although the age at marriage appeared to be rising since the 1980s, still 80% of girls are married by adolescent period (Versi *et al.* 1995).

3.1.4. Socio cultural history

Bengal was probably the wealthiest part of the subcontinent until the 16th century. Bangladesh came to today's shape through a long history of political and cultural evolution. This nation was ruled by the British regime for about 200 years until 1947. Initially a part of Pakistan, following partition from India in 1947, Bangladesh achieved full independence in 1971.

The present and main ethnic identity of Bangladeshi people is represented by Bengali. Ethnicity refers to a complex concept which has both socio-cultural and biological components. Ethnic groups change through time in complex ways. Thus ethnicity bears a historical construct. Like Hindi, Urdu or Punjabi speaking people Bengalis are also the modern decedents who might be belonged to ancient Indo Aryan and Dravidian arising out of central and Middle East Asia. That's why a closed ethnic similarity is found among them.

3.1.5. Education

Education in Bangladesh is mostly subsidized by the Government, which operates many schools and colleges in the primary, secondary and higher secondary level as well as many public universities and university colleges. The current literacy rate of Bangladesh is about 41% while female literacy rate is 30%. To promote literacy among women, education is now free up to the higher secondary level for female students. There are also government funded programs which gives incentives like stipends and food for continuing education to girls in the secondary level. But this has also been heavily criticized for nonfunctioning of the system due to hugely practiced corruption in the country. In contrast the role of UNICEF and some NGOs working for development of women in Bangladesh has been greatly recognized.

In Bangladesh, educational system is categorized in the following steps depending upon duration

Primary Level .... 1-5 years

Secondary Level .... 6-10 years

Higher Secondary level .... 11-12 years

Higher study

Graduation (Pass course) ....13-14 year

Graduation (Honours) ....13-15 year or more

Post graduation.................................... 15/16 year or more

3.1.6. Life style and physical activity

The life style of people of Bangladesh differs markedly according to rural and urban dwellings. Women in the rural area have to do various kinds of manual works during their daily activities even inside the house which includes cleaning of house, cooking, washing, taking care of children, gardening etc. all those requires good physical activities in the rural place. On the other hand, city people are exposed to rather easy way of daily life. But economic condition of the people and social status do also control the way of life of the people. Like the other Asians, Bangladeshi people do not have the tradition of doing extra physical exercise apart from the requirement for their occupation in daily life.

Most of the women put lots of their efforts in house hold activities being a housewife after marriage. However there prevails a marked difference in amount of work in household activities between rural and urban set up and socioeconomic status.

3.1.7. Food habit

The Bengali food is very similar to that of the rest of the Indian subcontinent. There are more fish recipes in the standard diet because of the availability of fish from the rivers and sea. But it has been seen to be insufficient as well as expensive

to meet increasing population load and people of varying economic status. As rice has been the main staple food, available in sufficient quantity and relatively cheap, people developed a kind of dependency on rice in almost every meal. People of this region have a tendency to satisfy hunger by taking bulks of rice with very minimum spicy fish or meat or vegetable curry. Their inherent taste for a spicy, sweet or salty food often restrains them to take less cooked vegetables and salad. Similar to other countries of south Asia sleeping after lunch and immediately after late dinner is also a very common tradition in Bangladesh.

3.1.8. Trend of urbanization in Bangladesh

Bangladesh is still an agrarian society though nearly one quarter of the population lives in the urban areas. A total of 50.1 million of people are involved in institutional work. Due to gradual urbanization relatively educated and rich people had moved in to the urban area. Poor people also moved towards urban area in search of work. Population burden and political instability pushed the country towards severe poverty tarnishing the history of glorious past which is once used to have food surplus.

Dhaka with a total population of 9.4 million is one of the densest cities of the world. It is expanding very rapidly. Population of Dhaka, the capital city of Bangladesh, is 3 times greater than the next largest city. According to the 2001 population census, the urban population in Bangladesh is 29 million, and has increased at the rate of 38% during the last 10 years, which is about 4 times the rural rate (MOHFW 2001). This shift may have a large impact on the urban health care system. Compared to demand of this huge population, health care facilities in Dhaka are quite inadequate.

Source: MOHFW-Ministry of Health and Family Welfare, Bangladesh (2001).

3.1.9.   Overall health status in Bangladesh

Though there has been a significant decline of infant and child morality the maternal death ratio is still high at over 380 per 100,000 live births (WHO statistics 2005). Apart from new and old infectious diseases, such as malaria, tuberculosis and acquired immune deficiency syndrome (AIDS) non communicable diseases such as diabetes, hypertensions are important threats to health for the years ahead. The nutritional status of adolescent girls and women is a key factor in the persistence of malnutrition in Bangladesh. Low birth weight is estimated to affect 30-50 percent of infants (UNICEF, Bangladesh). About 70% of the women suffer from nutritionally deficient anemia (National policy on Maternal Health, Ministry of Health, Bangladesh).

Bangladesh has been experiencing an epidemiological transition from communicable diseases to non-communicable diseases (NCD). Tertiary level hospital data indicates that cardiovascular diseases have already appeared as one of the leading causes of mortality. NCDs are important cause of disease burden, morbidity and mortality. At least 25% of the deaths in primary and secondary government health facilities are caused by these diseases. Presently, Bangladesh does not have a community based public health program for NCDs. Only hospital based service, although poor, is available (Health Profile of Bangladesh, WHO Health Organization, Bangladesh).

The Health, Nutrition, Population Sector Programme (HNPSP) has identified three NCDs-cancer, cardiovascular diseases and diabetes mellitus-as major public health problems. Looking at the surveillance finding worldwide WHO has recommended to list prevalence of diabetes as one of the basic health indicator for its member states (King *et al.* 1998).

3.1.10. Health care system in Bangladesh

Government of Bangladesh provides health care service under a health system infrastructure which follows local government system. Six divisions of local government are broken down into 64 districts, subdivided into 460 thanas, thence into unions and villages (Table 1). Besides the public sector, private, citizen organizations and NGOs (Non Governmental Organizations) also play large roles in the Bangladesh health sector.

Table 1. Health care service in public sector in Bangladesh.

Level of care	Administrative Unit (Number)	Health facility (Number)
Tertiary level	Division (6)	Teaching hospital /Institute (16)
Secondary level	District (64)	District hospital (59)
Primary level	Upazilla (460)	Upazilla health complex (397)
	Union	Union Health and Family Welfare centers (3275)
Out reach service	Village (68000)	Satellite or mobile clinic

Source: Bangladesh National Health Accounts, 1996-97

3.2. Diabetes Mellitus – Background

Diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced (Alberti and Zimmet 1998). An acquired deficiency may be triggered by life style factors. However a deficiency of insulin results in increased

concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves.

There are two principle forms of diabetes:

• Type 1 diabetes (formerly known as insulin dependent) in which the pancreas fails to produce the insulin which is essential for survival. This form develops most frequently in children and adolescents, but is being increasingly noted later in life.

• Type 2 diabetes (formerly named non-insulin dependent) which results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is much more common and accounts for around 90% of all diabetes cases worldwide. It occurs most frequently in adults, but is being noted increasingly in younger people as well.

Certain genetic markers have been shown to increase the risk of developing Type 1 diabetes. Type 2 diabetes is strongly familial, but it is only recently that some genes have been consistently associated with increased risk for Type 2 diabetes in certain populations. Both types of diabetes are complex diseases caused by mutations in more than one gene, as well as by environmental factors.

3.2.1. The global burden of diabetes

As per estimates of WHO in 2004 at least 171 million people worldwide had diabetes; this figure is likely to be more than double by 2030. WHO predicts 170% increase in the number of people with diabetes for the developing countries (UNICEF Bangladesh).The greatest increase (195%) is projected in India (Global Burden of diabetes 1998). An increasing trend of prevalence of diabetes has been found in the urban areas in comparison to rural areas in developing countries and in female population in Indian continent (UNICEF Bangladesh 2005).

3.2.2. Diabetes in Bangladesh

Diabetes mellitus particularly type 2 diabetes is now recognized as a major chronic public health problem in Bangladesh. The magnitude of diabetes remains unknown due to lack of countrywide survey. Some studies showed that the prevalence is higher in urban areas (Hussain *et al.* 2005; Abu *et al.* 1997). In a recent study in Bangladesh a higher prevalence of diabetes was found in urban (8.1%) compared with rural populations (2.3%) (Hussain *et al.* 2005).

3.2.3. Existing diabetes health care services in Bangladesh

The comprehensive diabetic health care delivery in Bangladesh is a unique program of Diabetes Association of Bangladesh (DAB). The Association executes its program primarily through its central institute called the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), and through the Satellite Diagnostic Clinic at different peripheral region to provide services at doorsteps. Now days, BIRDEM is recognized as the center of excellence and reference center in diabetes care. To improve the diabetic care and enlarge the service for a wide range of population, diabetic association has established National Healthcare Network (NHN) throughout the country. In addition to diagnosis, the NHN centers provide out patients service free of cost.

3.3.0. Gestational Diabetes Mellitus (GDM)

GDM as mentioned is any form of diabetes mellitus or impaired glucose tolerance (IGT) or impaired fasting glucose with first onset or first recognition during the index pregnancy. Thus the diagnosis of GDM is independent of possibility that diabetes or glucose intolerance may have antedated the pregnancy. As diabetes or glucose intolerance in women is more frequently discovered during pregnancy WHO has recommended including such cases under the definition of GDM. Such a broad definition has a great practical value and has boosted research on GDM.

3.3.1. Glucose tolerance in Normal and GDM pregnancy

Pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester. The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. Moreover pancreatic β cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy. As a result, changes in circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity (Buchanan & Xiang 2005).

From a pathophysiological point of view, GDM pregnancies are characterized by increased insulin resistance compared with normal pregnancies. The insulin resistance affects carbohydrate and lipid metabolism and presumably protein metabolism as well (Ben Haroush *et al.* 2004). Though in most of the cases it disappears once the pregnancy is over, it may persist as diabetes, impaired fasting plasma glucose or impaired glucose tolerance- after delivery or recur as such in the following pregnancy or any time after delivery.

3.3.2. Clinical importance of GDM

i)   Maternal hyperglycemia causes fetal outcome i.e. macrosomia, large for gestational age, baby, intrauterine death, preterm birth, birth defects etc.

ii). Association of GDM with preeclampsia, which very often threats mother's life and pregnancy outcome, has been evident in many studies.

iii). GDM predicts subsequent development of diabetes later in life. The incidence of subsequent type 2 diabetes following gestational diabetes has been reported to be between 3 and 60 % in various studies.

Fig. 2. Effect of Gestational diabetes on child health (Macrosomic baby).

3.3.3. Effects of GDM on Maternal and child health

The millennium development Goals have placed maternal and newborn's health firmly on international agenda. Though gestational diabetes has not yet brought up directly in developing countries in maternal and newborn health; it is the fact that it threats pregnancy and the newborn if maternal glucose level is not controlled during the pregnancy. Certainly it has potential role on reducing risk of maternal health and infant mortality. In GDM risk of macrosomia, intrauterine death of the fetus and preeclampsia make the pregnancy unsafe. WHO is working on supportive funding for the interventions necessary to ensure the health of pregnant women and newborn babies.

3.3.4. Maternal and child health situation in Bangladesh

WHO launched the Making Pregnancy Safer (MPS) initiative in Bangladesh in 1999 to respond to global challenges of maternal and newborn health (Making Pregnancy Safer).Their strategy is to focus on evidence based intervention that

target the major causes of maternal and newborn morbidity and mortality. The five major causes of maternal death are haemorrage, eclampsia, unsafe abortion, sepsis and obstructed labor (Ahmed *et al.* 1998).

The goal is to reduce maternal and newborn mortality and morbidity. Maternal mortality ratio is aimed to be reduced by 75 percent from 1990 levels by 2015 and infant mortality ratio to below 35 per1000 live birth. The MPS initiative aims to save the lives of more than 500,000 women who die world wide every year, as a result of causes related to pregnancy and child birth.

The key indicators related to maternal and child health in Bangladesh is presented in the Table 2.

Table 2.   Maternal and child health in Bangladesh: Key Indicators.

Average age of first marriage, 2003	16[1]
Average age at first Birth, 2003	18[1]
Total fertility rate (TFR), 2000-2005	3.3[1]
Maternal mortality ratio (MMR), 2000	320[1]
Infant mortality rate (IMR), 2000-2005	66[1]
Anemia in pregnant women (<11mg %)	49%[2]
Home Delivery	90%[3]
Attended by trained health personnel	11.8[3]
% of low birth weight	50%[4]
Woman avail one or more antenatal care check	47.5%[3]

Source:
1. The Department of Family and Community health, WHO South East Asian Regional Office.
2. HNPSP (PIP)
3. Making Pregnancy Safer, Family and Community Health, World Health Organization, Bangladesh.
4. United Nation Administrative Committee on Coordination, Sub Committee on Nutrition, Nutrition Policy. Paper No.18, February' 2000.

3.3.5. Maternal and child health service in Bangladesh

There has been a significant increase in use of antenatal care among pregnant women, from 33% in 2000 to 49% in 2004. Now, almost half of pregnant women receive at least one antenatal care visit from a trained health provider. Despite the rise in antenatal care, only one in four women receive three or more antenatal visits during her pregnancy, and a vast majority of women give birth without a trained birth attendant.

Component of antenatal care in public health facility in Bangladesh

- Measurement of Height of pregnant women.

- Measurement of Weight of pregnant women.

- Physical examination for anemia and edema.

- Blood test for Hb%.

- Urine examination for glucose and albumin.

- Blood Pressure measurement of the women.

- Fundal height.

- Fetal sound in late pregnancy.

- Health education on pregnancy care.

- Tetanus toxoid vaccination

- Birth planning

- Knowledge on danger sign of the pregnancy and what to do if situation arises like these.

- In referral (secondary and tertiary hospital)

- Random blood sugar ±

- Ultra sonogram for pregnancy profile ±

3.3.6. Screening of GDM in Bangladesh

WHO and BIRDEM jointly worked for formulation of standard treatment guideline for diabetes. Thereby they proposed screening of diabetes in non

pregnant women which is also applicable to pregnant women of Bangladesh. Screening for diabetes has not yet integrated in antenatal care component routinely in Bangladesh. Secondary and tertiary hospitals advise the pregnant women to do random blood glucose test. Based on the report they make further planning of respective pregnancies. A standard guideline for screening diabetic pregnancy is still non existent. Some of the private practitioners or specialists recommend diabetes screening routinely or if they find any risk factor to their patients. A guideline for screening diabetes proposed by BIRDEM is presented in the material and method chapter (Fig. 2.1) which can also be used for screening GDM.

3.4. Statement of problem of the present study

In view of the increasing prevalence of type 2 diabetes in Bangladesh, it is reasonable to postulate that there is a growing prevalence of gestational diabetes. A previous study conducted by Abu *et al.* (1997) reported that Bangladeshi women have been seen to have higher IGT than their male counterparts.

Compared to the other South Asian population Bangladesh has higher birth rate (BBS 2000) and has the prevalence of multiparty. Perinatal mortality and infant mortality is also high in Bangladesh (Low Birth Weight of a Meeting, Dhaka, Bangladesh, 14-17 June 1999). Though there is no published report on the prevalence of preeclampsia in Bangladesh the Obstetric and Gynaecological society (OGSB) in Bangladesh estimates 16% of maternal death from eclampsia (Begum *et al.* 2004). In addition, according to OGSB obstructed labour accounts for 8% of maternal death. Frequency of congenital malformations and low birth weight also appears to be higher in Bangladesh.

Sayeed *et al.* (2005) stated that increased morbidity and mortality among mothers and newborns in Bangladesh may in part be due to the effect of GDM. Data on the

subject is scarce resulting in a lack of guideline for clinical investigation for pregnant mother which is likely to bear grave consequence. Risk factors predisposed to GDM need to be identified in this region in order to initiate a selective screening during pregnancy period to ensure safe mother hood and identify women with risk of diabetes later in life.

Insufficient studies addressing the relationship of gestational age at GDM diagnosis and pregnancy outcomes have been conducted in Bangladesh. Evidences report that gestational diabetes affects pregnancy and fetus adversely if mother's glycaemia is uncontrolled and has been high. Therefore, the aim of treatment during the pregnancy is, to keep mothers' blood glucose level under normal range either by diet or by insulin. Information on the risk of these complications would have helped to continue or readjust the treatment protocol of GDM in Bangladesh.

Careful search of literature provided very little and incomplete data on prevalence of GDM based on the time of diagnosis in Bangladesh perspectives. In spite of reports that claim 40-66% of gestational diabetes can be detected in early pregnancy there have been conflicting studies on the usefulness of glucose screening at early pregnancy (Meyer *et al.* 1996)). Nevertheless one could reasonably suggest that women with gestational diabetes in early pregnancy could benefit from earlier metabolic control as well as prediction of pregnancy and fetal complication in this group.

A study conducted in India found different types of fetal complication at different level of glycaemic control. With improved glycaemic control and advanced neonatal care perinatal adversities in GDM have approached that of non diabetic mothers (Metzger & Coustan 1998, Banerjee *et al* 2004). Thus intervention either by diet or by insulin in GDM may predict risk or possible outcome of the index

pregnancy. Information on this would help to take preventive measures and make a birth planning in order to ensure a safer pregnancy for Bangladeshi women.

3.5.0. What is Diabetes Mellitus?

The definition of diabetes mellitus, according to The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002), is several metabolic diseases characterized by some degree of hyperglycemia. Hyperglycemia, or high levels of blood glucose, is caused by deficiencies in insulin secretion, insulin action, or both. These insulin deficiencies can be caused by a range of pathogenic processes from autoimmune destruction of the beta cells of the pancreas, which make and secrete insulin, to abnormalities that can result in insulin resistance.

Diabetes can lead to several chronic conditions such as cardiovascular complications, neuropathy (disease of the nerves), nephropathy (disease of the kidneys), and retinopathy (disorder of the retina) which is the leading cause of blindness in the United States. There are several non-modifiable risk factors for these problems such as duration of diabetes, age, genetics and race, as well as modifiable risk factors such as glycemic control and hypertension (Franz 2001).

Diabetes mellitus (DM) is categorized into three main types—type 1 DM, type 2 DM, and Gestational (GDM). In the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2002), up-to-date definitions for each type of diabetes were given. Type 1 DM is classified as a total deficiency in secretion of insulin. Type 2 DM, which is much more prevalent, is classified as a combination of resistance to insulin action and inadequate insulin secretion.

Type 1 and type 2 DM may be referred to as pregestational diabetes, because diagnosis occurred before pregnancy. GDM is defined as any degree of glucose intolerance with onset or first diagnosis during pregnancy.

3.5.1. Type 1 diabetes

Type 1 diabetes results from a destruction of the β-cells of the pancreas, usually leading to absolute insulin deficiency. Most often the reason is autoimmune mediated destruction. These patients require insulin for survival to prevent the development of ketoacidosis and coma (WHO Study group 1998).

In Type 1 diabetes mellitus, insulin secretion is either totally lacking or severely impaired. During pregnancy in Type 1 diabetics, the requirement of insulin to maintain the same glycemic level increases from the end of the first trimester until the end of pregnancy. On average, the insulin needs increases from 0.7 IU/kg body weight per day in the first trimester to 0.8 IU/kg per day in the second trimester and to 0.9 IU/kg per day in the third trimester until 36 weeks of pregnancy. At term the insulin requirement is 1.0 IU/kg per day (Jovanovic and Kitzmiller 2008).

However, individual variation in the increase of insulin requirement during pregnancy is relatively large. During the first weeks of pregnancy, insulin sensitivity is often increased, which at least partly explains the increase in hypoglycemic episodes in Type 1 diabetic mothers during the first trimester (Nielsen *et al.* 2008). Gabbe and Graves (2003) reported that insulin requirements increase throughout pregnancy, most markedly in the period between 28 and 32 weeks of gestation, after which it can actually decrease in some Type 1 diabetic mothers. After parturition, the daily insulin requirement decreases within a day or two to the pre-pregnancy level (Buchanan *et al.* 1986, Jovanovic and Kitzmiller 2008) and when lactation starts, even to a lower level.

3.5.2. Type 2 diabetes

Type 2 diabetes is characterized by disorders of insulin action and secretion, either of which may be a predominant feature (WHO Study group 1998). Though it is the

most common form of diabetes, it is seldom diagnosed in patients less than 40 years, and is therefore rare in women of childbearing age (WHO Study group 1998).

The risk of Type 2 diabetes increases with age, obesity and lack of physical activity, and it occurs more frequently in individuals with hypertension or dyslipidemia, or in women with previous GDM (WHO Study group 1998). Some degree of hyperglycaemia may be present for a long period before the detection of diabetes. While these patients often have an increased risk of developing vascular complications, it may be more important to identify and treat other risk factors such as dyslipidemia and hypertonia, instead of mild hyperglycaemia. Although Type 2 diabetes is associated with a strong genetic predisposition, its genetics have not been defined (WHO Study group 1998).

3.5.3. Gestational diabetes mellitus (GDM)

In 1952, Jackson reported the reversible state of impaired glucose tolerance related to pregnancy, called the "prediabetic state of pregnancy" (Jackson 1952). Today, gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or initial recognition during pregnancy (Metzger & Coustan 1998). It complicates 1 - 4% of all pregnancies (Naylor *et al.* 1997) depending on the population studied.

According to WHO recommendations, GDM is diagnosed by OGTT using a 75 g oral dose of glucose after over-night fasting for women with anamnestic or clinical risk factors. The present international cut-off levels are 5.3 mmol/l for fasting, 10.0 mmol/l after 1 h and 8.6 mmol/l after 2 h in venous plasma (Metzger and Coustan 1998). Glucose regulation will return to normal after delivery in the majority of cases. According to different studies, 40-60 % of women with previous GDM will

develop Type 2 diabetes during the next 10-15 years (Teramo *et al.* 2006). Metzger and Coutan (1998) found insulin resistance and impaired β-cell function in GDM women conveying a high risk (relative risk (RR) 8.0) for later diabetes development.

By giving dietary advice, stabilizing weight, exercise and periodic glucose monitoring it is possible to prevent or delay the progression of diabetes and the development of its complications in women with previous GDM (Gregory *et al.* 1998).

The prevalence of GDM differs considerably in different ethnic populations. In the United States the prevalence of GDM ranges from 1 to 14%, with 2–5% being the most common rate (Ben-Haroush *et al.* 2008). The adjusted relative risk of GDM in black women has been reported to be 1.81 and in Hispanic women 2.45 compared with Caucasian women (Dooley *et al.* 1991). In another study, in Australia Asian women were more likely to have GDM than Caucasian women (Gunton *et al.* 2001).

The main goal of treatment in GDM pregnancies is to achieve normoglycemia, i.e. to prevent both fasting and postprandial hyperglycemia from the diagnosis of GDM until labor and delivery. When women with GDM achieve normoglycemia, their weight gain during pregnancy is usually less than that of healthy pregnant women (Suhonen and Teramo 1993).

If normoglycemia cannot be maintained by diet alone, insulin therapy is started. Recently, it has been reported that treatment with glyburide alone (Langer *et al.* 2005a) or with metformin alone or with supplemental insulin (Rowan *et al.* 2008) is an effective and safe treatment option for women with GDM. Immediately after delivery, women with GDM rarely need to continue with insulin or oral

medication treatment in order to maintain euglycemia. However, they remain at an increased risk of Type 2 diabetes mellitus later in life and they should therefore have regular check-ups for blood glucose levels for the rest of their lives.

3.5.4.   Monitoring glycemic control

Optimal glycemic control during diabetic pregnancy is the basis for good outcome, both for the mother and her newborn infant (Pedersen 1977, Langer *et al.* 1989, Inkster *et al.* 2006). Monitoring of both preprandial and postprandial blood glucose values is important in order to achieve euglycemia (Crowther *et al.* 2005, Fadl *et al.* 2006, Jovanovic and Kitzmiller 2008).

Recently, subcutaneous continuous glucose monitoring has increasingly been used to achieve maternal normoglycemia in order to reduce the risk of fetal macrosomia and neonatal hypoglycemia in diabetic pregnancies (Kerssen *et al.* 2007, Stenninger *et al.* 2008).

Monitoring glycemic control has been greatly improved by the introduction of methods which reflect the mean blood glucose level over a prolonged period of time. The chemical reaction between glucose and proteins results in production of nonenzymatically glycated proteins in blood and tissues. The level of glycation of hemoglobins is proportional to the average glucose concentration during the previous 4 to 8 weeks (Bunn *et al.* 1978) and therefore it does not detect rapid changes in plasma glucose concentration. The glycation level also depends on the lifespan of red blood cells in the circulation. The turnover rate of red blood cells during pregnancy is about 90 days, compared with 120 days in non-pregnant adults (Albertson and Jovanovic 2008). The amount of glycated hemoglobin is expressed as a percentage of the total hemoglobin.

Early methods for fractionation of hemoglobin included cation exchange column chromatography. The procedures were elaborate and time-consuming, requiring several days of work. Subsequently, automated methods, such as high performance liquid chromatography (HPLC), were developed (Gruber and Koets 1979). Stenman *et al.* (1984) developed a fully automated rapid HPLC method for the measurement of hemoglobin A1c (HbA1c) levels. The method permits separation and quantification of HbA1c, even in the presence of elevated levels of fetal hemoglobin (HbF). It has been shown recently that a 1% unit increase in the HbA1c level equals a mean plasma glucose increase of 1.6 mmol/l in non-pregnant diabetic adults (Nathan *et al.* 2008).

Several recommendations exist for evaluating glycemic control in women with GDM. A relatively recent recommendation is that both pre- and postprandial glucose levels should be measured four times a day (Gabbe and Graves 2003). The optimal time for measuring the postprandial glucose level is one hour after the meal. Insulin- treated women with GDM should measure their blood glucose level 5-6 times each day (Jovanovic 2008). Subcutaneous continuous glucose monitoring is a new method for measuring glucose values continuously over several days. However, its advantage over self-monitoring of blood glucose still needs to be demonstrated (Yogev *et al.* 2008).

3.5.5. Glucose metabolism and pregnancy

3.5.5. 1. Normal pregnancy

Maternal glucose metabolism changes throughout pregnancy. Concentrations of fasting blood glucose decreases as early as in the first trimester and remain low throughout pregnancy compared with fasting levels before pregnancy (Pedersen 1977a, Mills *et al.* 1998). In contrast, postprandial glucose values increase from the 16th pregnancy week until the 36th pregnancy week (Siegmund *et al.* 2008).

During the first half of pregnancy, basal insulin levels are normal or slightly elevated, coinciding with a decrease of about 10% in fasting blood glucose values (Freinkel 1985, Hollingsworth 1985). Basal insulin levels increase by 50–80% in the third trimester. Normally the development of increasing insulin resistance during pregnancy is compensated for by a simultaneous increase in insulin secretion (Ryan *et al.* 1985, Buchanan *et al.* 1990, Sivan *et al.* 1997). Mild glucosuria in normoglycemic mothers is considered physiological, because glucose reabsorption from the renal tubules is decreased during pregnancy (Davison and Dunlop 1980).

Placental glucose transfer from mother to fetus takes place by facilitated diffusion (Leonce *et al.* 2006). The transport mechanism is controlled by blood glucose concentrations both in the fetus and in the mother. The primary transporter responsible for maternal-to-fetal glucose transport, placental glucose transporter 1 (GLUT1), was first described by Fukumoto *et al.* (1988) and Bell *et al.* (1990). Insulin-like growth factors IGF-1 and IGF-2 also stimulate glucose transport across the placenta (Kniss *et al.* 1994).

Fetal blood glucose levels are lower than maternal levels, but they correlate linearly (Hay and Sparks 1985). Fetal insulin production starts during the first trimester (Adesanya *et al.* 1966), but it responds to increased glucose levels only during the latter half of pregnancy (Adam *et al.* 1969). Free insulin does not cross the placenta (Adam *et al.* 1969).

3.5.5. 2. Diabetes-related complications to pregnancy

There are several complications that can occur for both mother and baby when a mother has diabetes during pregnancy. Congenital anomalies are common among infants born to diabetic mothers (American Diabetes Association 2002, Harvard

Health Publications 2002, Langer *et al.* 2000, Uvena-Celebrezze & Catalano, 2000). Fetal loss is another common outcome of diabetic pregnancies (Brydon *et al.* 2000, Dunne *et al.* 2003; Hawthorne *et. al* 2000; Langer *et al.* 2000; Lauenborg *et al.*2003 Uvena-Celebrezze & Catalano, 2000, Wylie *et al.* 2002). Types of fetal loss include spontaneous abortion, stillbirth, and perinatal mortality. Excessive fetal growth, referred to as fetal macrosomia or large for gestational age infants, is a common characteristic in infants born to diabetic mothers (American Diabetes Association 2003, Brown & Hare 1995; Brydon *et al.*2000; Casson *et al.*1997; Davey, 2003; Dunne *et al.*2003; Platt *et al.* 2002; Svare *et al.* 2001, Thoenen *et al.*2001, Wylie *et al.* (2002). Complications of labor and delivery, such as cesarean section and preterm delivery, occur more often in pregnancies complicated by diabetes compared to those that are not (Blatman and Barss 1995, Dunne *et al.* 2003, Harvard Health Publication 2002, Jensen *et al.* 2000; Svare *et al.*2001; Thoenen *et al.* 2001, Wylie *et al.* 2002).

Diabetes during pregnancy can also mean adverse outcomes for the mother. Pregnancy-induced hypertension occurs more frequently among diabetic mothers than non-diabetic mothers (American Diabetes Association 2003, Cundy *et al.* 2002, Dunne *et al.* 2003, Jensen *et al.* 2000, Sibai *et al.* 2000, Wylie *et al.* 2002). Increased severity of preexisting diabetes-related complications is also a maternal complication of a diabetic pregnancy (Brown and Hare 1995, Rosenn & Miodovnik, 2000, Thoenen *et al.* 2001).

The level of risk for and severity of these complications will depend on several factors, some of which include the previous health of the mother and her glycemic control during pregnancy. This review of literature will focus on the complications of maternal diabetes that occur most frequently.

3.5.5. 3. Maternal outcome

3.5.5. 3. 1. Maternal hypoglycemia

Maternal hypoglycemia is a well-recognized and potentially dangerous complication of intensive insulin therapy in pregnant women with Type 1 diabetes. Severe hypoglycemia is defined as impairment of consciousness of a diabetic, who needs help from another person to administer glucose orally or to give a glucagon injection or intravenous glucose infusion (ADA workgroup 2005).

Severe hypoglycemia during pregnancy occurs in 41–45% of Type 1 diabetic women (Evers *et al.* 2002a, Nielsen *et al.* 2008) The risk of severe hypoglycemia is greatest during the first trimester of pregnancy (Evers *et al.* 2002a, Nielsen *et al.* 2008). Subjective symptoms of low blood glucose levels are often diminished during pregnancy, which decreases the patient's awareness of hypoglycemia (Nielsen *et al.* 2008). Furthermore, pregnancy attenuates glucose counter-regulation mechanisms during hypoglycemia in Type 1 diabetic women (Rosenn *et al.* 1996). Therefore, intensive insulin therapy during pregnancy predisposes patients to severe hypoglycemia in cases of Type 1 diabetes.

Recurrent severe maternal hypoglycemic episodes during pregnancy can result in impairment of cognitive functions of the mother. Animal studies indicate that maternal hypoglycemia is teratogenic during organogenesis (ter Braak *et al.* 2002). However, studies in pregnant women with Type 1 diabetes have not revealed any association between maternal hypoglycemia and adverse fetal outcome (Rosenn and Miodovnik 2000) or diabetic embryopathy (ter Braak *et al.* 2002). Similarly, no abnormal changes in fetal behavior have been reported in women with Type 1 diabetes during induced moderate maternal hypoglycemia (Diamond *et al.* 1992, Rosenn *et al.* 1996).

3.5.5. 3. 2. Preeclampsia and pregnancy-induced hypertension

Preeclampsia is defined as hypertension with a diastolic blood pressure repeatedly above 90 mm Hg during the second half of pregnancy, in combination with proteinuria (Roberts and Redman 1993). However, the definition of preeclampsia varies in different publications (Harlow and Brown 2001). Pregnancy-induced hypertension (PIH) is defined as high blood pressure (diastolic blood pressure repeatedly over 90 mm Hg) during the second half of pregnancy without proteinuria.

Pre-eclampsia is a disease of unknown etiology (Redman and Sargent 2005). However, it is characterized by widespread endothelial cell dysfunction (Rodie *et al.* 2004, Sibai *et al.* 2000). Moreover, pre-eclampsia is also characterized by insulin resistance, immune maladaption, coagulation defects and increased systemic inflammatory response (Rodie *et al.* 2004, Sibai *et al.* 2000).

Pre-eclampsia complicates about 4% of pregnancies in nulliparous women and about 2% in multiparous women (Sibai *et al.* 2000), and it is one of the major pregnancy complications causing increased morbidity and mortality in both the mother and the newborn infant (Roberts and Cooper 2001). Pre-eclampsia and PIH increase the risk of iatrogenic preterm birth and intrauterine growth restriction and these women are at an increased risk to obtain cardiovascular disease later in life (Rodie *et al.* 2004, Sibai *et al.* 2000).

Pregnancy-induced hypertension, according to Reeder *et al.* (1997), is a syndrome in pregnant women characterized by hypertension, edema, and proteinuria (high levels of protein in the urine). Eclampsia and preeclampsia are categories of pregnancy-induced hypertension. Pregnancy-induced hypertension has been found to affect women with type 1 DM, type 2 DM and GDM more often than non-

diabetic women. 22.0% of women with type 1 diabetes had pregnancy-induced hypertension, while only 6.3% of the non-diabetic controls were affected.

In an analysis of pregnancies complicated by type 2 DM, Dunne *et al.* (2003) found that 19.7% of women with type 2 DM had pregnancy-induced hypertension and/or preeclampsia compared to 10% of women who were not diabetic. They also found that fetal loss was more common when the mother had pregnancy-induced hypertension/preeclampsia (8.7%) compared to infants of women who did not have pregnancy-induced hypertension/preeclampsia (2.7%).

In a comparison between hypertensive disorders of pregnancy between women with type 1 and type 2 DM, Cundy *et al.* (2002) found that the incidence of hypertension during pregnancy was similar between the two groups of women. For instance, women with type 2 DM had more chronic hypertension (diagnosed at < 20 weeks gestation) than did women with type 1 DM. The impact of hypertension of adverse outcomes of pregnancy was significantly more severe for women with type 1 DM compared to women with type 2 DM, though.

Sibai *et al.* (2000) did not specify between types of diabetes, but found that the frequency of preeclampsia rose with increasing severity of diabetes in women with pregestational diabetes. In this study of 462 women with pregestational diabetes, they also found that the women with preeclampsia in their study had a significantly higher rate of preterm delivery (56.5%) compared to those without preeclampsia (33.3%).

GDM is associated with an increased risk for maternal hypertensive disorders (American Diabetes Association, 2003; Jensen *et al.* 2000). Sendag *et al.* (2001) found that there was double the amount of women in the GDM group with hypertensive disorders (9.4%) compared to the non-diabetic controls (4.3%).

Pregnancy-induced hypertension is more common in women with type 1 DM, type 2 DM, or GDM compared to women without diabetes. The timing of onset and the impact on adverse outcomes of pregnancy may differ between women with different types of diabetes (Cundy *et al.* 2002).

3.5.5. 3.3. Cesarean section

Women with diabetes are more likely to suffer one or more complications of labor and/or delivery (such as cesarean section, preterm delivery or induction of labor) than are women who do not have diabetes (Thoenen *et al.* 2001). Complications of labor and delivery-namely cesarean section, induction of labor and/or preterm delivery (either spontaneous or medically induced) have been found to be more common in pregnancies complicated by type 1 DM, type 2 DM, or GDM (Blatman & Barss, 1995, Dunne *et al.* 2003, Harvard Health Pulication 2002, Jensen *et al.* 2000, Svare *et al.*2001; Thoenen *et al.* 2001; Wylie *et al.*2002).

Blatman and Barss (1995) stated that maternal diabetes by itself is not a certain indication for cesarean section, however, macrosomia and large for gestational infants along with the associated problem of shoulder dystocia are indications for cesarean section.

Women with GDM (Sermer *et al.* 1998, Langer *et al.* 2005) and Type 1 diabetes (El-Sayed and Lyell 2001) have an increased risk of cesarean section delivery. The majority of diabetic women with vascular complications are delivered by cesarean section. Fetuses of diabetic women are frequently macrosomic (Bradley *et al.* 1988, Schwartz and Teramo 2000), which increases the rate of cesarean section deliveries. In a study by Jolly *et al.* (2003), macrosomia, defined as birth-weight over the 90th percentile, was more likely in women with pre-gestational diabetes and GDM and this increased the risk of emergency cesarean sections.

Steer (2004) reported that women with GDM and overt diabetes had a greater likelihood of delivering an infant weighing over 4000 g than women with normal glucose tolerance and that macrosomic fetuses were more than twice as likely to be delivered by emergency cesarean section as fetuses weighing less than 4000 g.

The increased risk of maternal complications in diabetic women seems at least partly to be related to emergency cesarean section deliveries (Nasrallah *et al.* 2004). Although fetal macrosomia is the leading reason for cesarean delivery in diabetic women, chronic fetal hypoxia, particularly in women with poor glycemic control during the last weeks of pregnancy, also increases the risk of cesarean delivery (Teramo *et al.* 2004).

3.5.5. 3.4. Maternal childbirth trauma

Delivery of a macrosomic infant increases the risk of both maternal and neonatal injury. In a study by Stotland *et al.* (2004), diabetes was associated with macrosomia, fourth-degree perineal lacerations and postpartum hemorrhage. Both forceps and vacuum extraction deliveries are additional risk factors for trauma. In a study by Johnson *et al.* (1992) forceps delivery was associated with an increase in major perineal and vaginal tears. Jolly *et al.* (2003) analyzed data from 350 311 singleton pregnancies between 1988 and 1997 using logistic regression analysis and found that macrosomia, defined as birth weight over 4000 g, predicted increased risks of both third degree perineal lacerations and postpartum hemorrhage.

3.5.5. 3.5. Maternal mortality

Maternal mortality is defined by the World Health Organization (WHO) as pregnancy-related (accidents excluded) death rate per 100 000 during pregnancy or within 42 days after delivery. In a review including the English literature from

1975 to 2001 and covering publications evaluating maternal mortality in relation to the mode of delivery, Vadnais and Sachs (2006) reported that the overall maternal mortality rate ranged from 6 to 54 deaths per 100 000 live births.

Operative delivery clearly is associated with an increased risk of maternal mortality. Cesarean section for any reason is associated with a 3–13 times increased risk compared with vaginal delivery. In a study carried out in the Netherlands and covering 1983 to 1992, the risk of dying in connection with cesarean delivery was 13 per 100 000 operations (Schuitemaker *et al.* 1997), which was 3 times the risk of maternal mortality after vaginal delivery. The incidence of maternal mortality in women with Type 1 diabetes is about 0.5% (Gabbe *et al.* 1976, Cousins 1987). Severe hypoglycemia, massive bleeding, anesthetic complications and high maternal age are important contributing factors to maternal deaths in Type 1 diabetic pregnancies (Schuitemaker *et al.* 1997, Leinonen *et al.* 2001).

3.6.0. Fetal outcome

3.6.1. Malformations

The incidence of congenital malformations is two to six times higher in pregnancies of women with Type 1 diabetes mellitus than in healthy women (Garner 1995, Kitzmiller *et al.* 1996, Platt *et al.* 2002, Macintosh *et al.* 2006, Yang *et al.* 2006). The most common congenital malformations among women with Type 1 diabetes are cardiac, skeletal, CNS, uro-genital, gastro-intestinal, and facial malformations (Merlob and Hod 2008). The majority of the studies have demonstrated a relationship between maternal hyperglycemia in early pregnancy and the occurrence of malformations (Miller *et al.* 1981, Rose *et al.* 1988, Greene *et al.* 1989, Nielsen *et al.* 2008). Preconception counseling, pregnancy planning and improvement of glycemic control before conception are associated with a

decrease in the rate of malformations (Fuhrmann *et al.* 1983, Mills *et al.* 1988, Steel *et al.* 1990, Kitzmiller *et al.* 1991, Evers *et al.* 2004b, Inkster *et al.* 2006, Pearson *et al.* 2007).

Most fetal malformations start to develop already before the 7th week of pregnancy (Mills *et al.* 1979). Therefore, it is of utmost importance to achieve and maintain euglycemia already before pregnancy. Although a strong association exists between hyperglycemia and malformations, the exact mechanism or mechanisms responsible for abnormal fetal development have not been completely elucidated.

The prevalence of congenital malformations among the offspring of mothers with gestational diabetes mellitus is similar to or only slightly higher than that in the general non-diabetic obstetric population (Janssen *et al.* 1996, Aberg *et al.* 2001).

It has been suggested that a subgroup with an increased risk of malformations exists among women with GDM, perhaps as a result of pregestational but undetected Type 2 diabetes (Aberg *et al.* 2001).

3.6.2. Fetal growth

3.6.2.1. Normal growth

Fetal growth is primarily controlled by the capability of the placenta to transport nutrients and oxygen to the fetus (Carrera and Devesa 1998). Normal fetal growth is proportional and linear (Elejalde and de Elejalde 1986). Catecholamines, angiotensin II, aldosterone and prostaglandins play important roles in maintaining uteroplacental blood flow and are indirectly involved in fetal growth by ensuring adequate concentrations of oxygen**,** glucose and nutrients to the fetus (Carrera and Devesa 1998). Human chorionic somatomammotropin is an important placental hormone related to fetal growth (Carrera and Devesa 1998, Jovanovic and

Kitzmiller 2008). Only 10% of the fetal weight at term is reached during the first half of pregnancy and 2/3 is acquired during the last trimester. Fetal weight gain occurs mainly in the third trimester when fetal insulin acts as a strong growth-promoting hormone (Hill 1976). Locally produced peptide growth factors coordinate fetal growth (Hill *et al.* 1998). The insulin-like growth factors IGF-1 and IGF-2 in particular play an important regulatory roles in fetal growth (Forbes and Westwood 2008). In addition, fibroblast growth factor-2 (FGF-2) has been shown to be involved in the regulation of fetal growth (Hill *et al.* 1998). Maternal and fetal serum levels of FGF-2 both correlate directly with fetal and placental size (Hill *et al.* 1995).

Maternal pre-pregnancy weight has a strong association with fetal size (Love and Kinch 1965, Griffiths *et al.* 2007), whereas maternal height is only weakly associated with birth weight (Kirchengast *et al.* 1998, Griffiths *et al.* 2007). The quality of the diet and the maternal ability to nourish the fetus properly are important factors affecting fetal growth (Carrera *et al.* 1998). Fetal genotype accounts for about 15% of the variation in birth weight (Carrera *et al.* 1998).

3.6.3. Fetal macrosomia

Macrosomia and Large for Gestational Age

Reeder *et al.* (1997) define macrosomia as "excessive fetal growth" with a "birth weight in excess of 4,000 to 4,500 grams." These authors defined large for gestational age as "a neonate weighing above the 90th percentile for the gestational age. Large for gestational age infants are immature but overgrown and are typical of diabetic mothers. These conditions are related to several complications during labor of the infant.

According to Thoenen *et al. (*2001), excessive fetal growth can cause shoulder dystocia at birth (complication in oversized infants whose large shoulders catch at

the pelvic brim or outlet, (Reeder *et al.* 1997), traumatic birth injury, and/or asphyxia. Current literature consistently associates these conditions with pregnancies complicated by diabetes. Type 1 DM is associated with an increased risk of macrosomia.

Fetal macrosomia complicates 30–50% of pregnancies in women with pregestational diabetes (Evers *et al.* 2004, Yang *et al.* 2006). It has been suggested that all fetuses of Type 1 diabetic mothers are actually 'macrosomic' (Bradley *et al.* 1988).

Diabetes during pregnancy, whether it is type 1, type 2 or GDM is associated with an increased risk for excessive fetal growth (American Diabetes Association 2003, Brown & Hare 1995, Brydon *et al.*2000, Casson *et al.*1997, Dunne *et al.* 2003, Hsu-Hage & Yang 1999, Jensen *et al.* 2000, Jovanovic 2001, Platt *et al.* 2002, Svare *et al.* 2001, Thoenen, *et al* .2001, Wylie *et al.* 2002). *Maternal risk factors of fetal macrosomia-* Several complications of delivery such as shoulder dystocia, birth injury, and asphyxia are common when an infant is larger than normal for gestational age (Thoenen *et al.* 2001, Wylie *et al.* 2002). The causes for excessive fetal growth in diabetic pregnancies are still unknown, but possible explanations include maternal weight and maternal glycemic control (Brydon *et al.* 2000; Uvena-Celebrezze and Catalano, 2000).

3.6.3.1. Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is defined as a relative birth-weight below-2 SD of the mean birth-weight. An IUGR infant has, by definition, not reached his/her genetic growth potential *in utero* (Bamberg and Kalache 2004). Maternal pregestational diabetes mellitus may also be associated with IUGR, especially when retinopathy and nephropathy complicate diabetes (Reece *et al.* 1998). In

patients with retinopathy and nephropathy, vascular adaptation of the placental bed is often insufficient, resulting in IUGR. In women with diabetic nephropathy, IUGR is observed in 15–21% of cases (Reece *et al.* 1998) compared with 3–10% in the normal population (Haram and Gjelland 2007).

Erythropoietin (EPO) is an endogenous hormone which controls the production of erythrocytes. The main stimulus to EPO production is low tissue oxygen concentration (hypoxia) (Marsden 2006). Teramo *et al.* (2004) reported that levels of amniotic fluid EPO correlate in a U-shaped fashion with fetal birth-weight zscores in Type 1 diabetic pregnancies. Amniotic fluid EPO levels correlated inversely with the birth-weight z-score below -0.6 SD units, suggesting that these fetuses were actually growth restricted and that it was associated with chronic fetal hypoxia (Teramo *et al.* 2004).

3.7. Shoulder dystocia

3.7.1. Shoulder dystocia in General population

Shoulder dystocia can be defined as arrest of delivery after expulsion of the fetal head, although no general agreement has been reached (Gottlieb and Galan 2007). The incidence of shoulder dystocia varies widely, from 0.1 to 2.8% in unselected populations (Acker *et al.* 1985, Langer *et al.* 1991, Christoffersson and Rydhstr 2002, Dandolu *et al.* 2005). Dandolu *et al.* (2005) reported that there was an increase in the rate of shoulder dystocia from 0.2% in 1979 to 2.1% in 2003. Both excessive maternal weight before pregnancy and weight gain during pregnancy are associated with shoulder dystocia (Spellacy *et al.* 1985, Johnson *et al.* 1992).

The incidence of shoulder dystocia is 3–13% in newborn infants with a birth weight of 4000 g or more (Acker *et al.* 1985, Langer *et al.* 1991). In the study by Acker *et al.* (1985) the incidence of shoulder dystocia was 13% when the birth

weight exceeded 4000 g, but only 1% when the birth weight was under 4000 g. Shoulder dystocia has been reported to occur in 40% of cases (31/78) when the birth-weight of vaginally delivered infants was at least 5700 g (Rydhstrom and Ingemarsson 1989).

3.7. 2. Shoulder dystocia in Diabetic pregnancies

Large fetal size among women with GDM is a common risk factor for shoulder dystocia (Bennett 1999). Dystocia occurs more often in GDM pregnancies than in non-diabetic pregnancies, even when the birth weights are the same because of increased shoulder width. Any type of diabetes mellitus increases the risk of shoulder dystocia in vaginal deliveries (Acker 1985, Langer *et al.* 1991). Dandolu *et al.* (2005) observed an increased rate of shoulder dystocia both in GDM pregnancies and in pregnancies of women with pre-gestational diabetes. The risk of shoulder dystocia and trauma is further increased by the use of vacuum or forceps. In a study by Nesbitt *et al.* (1998) the risk of shoulder dystocia in cases of instrumentally assisted births among diabetic women was 12.2% for infants weighing 4000 to 4250 g, 16.7% for those weighing 4250 to 4500 g, 27.3% for those weighing 4500 to 4750 g and 34.8% for those weighing 4750 to 5000 g.

Insulin treatment in cases of GDM has been reported to decrease the rates of macrosomia and serious perinatal complications such as shoulder dystocia, bone fractures and brachial plexus nerve injury (Crowther *et al.* 2005). Langer *et al.* (2005) reported a 2- to 4-fold increase in neonatal morbidity in cases of untreated GDM. They found an increased rate of macrosomia in the untreated GDM group. On the other hand, non-diabetic subjects and diet-treated or diet- and insulin-treated GDM patients had the same rate of macrosomia. In another study, Langer *et al.* (2005c) reported that an adverse pregnancy outcome was found in all women

with GDM who had poor glucose control. On the other hand, obese women with GDM (BMI at least 30 kg/m2) had pregnancy outcomes comparable with those among women with GDM and BMI <25 kg/m2 when treated by means of diet and insulin but not by diet alone. They had a 2- to 3-fold risk of adverse outcome, despite acceptable glucose control with diet therapy. The outcome may thus be adverse even when glucose control is considered good. In a study among women with Type 1 diabetes, Evers *et al.* (2002b) showed that the incidence of fetal macrosomia was increased despite apparently good glycemic control throughout pregnancy.

Gestational diabetes mellitus has an unfavorable effect on fetal body composition (Neggers *et al.* 1995, Catalano 2007a). Newborn infants of women with GDM have increased fat mass compared with the infants of healthy women (Catalano 2007b). Fat deposition in the human fetus occurs mainly in the third trimester (Widdowson *et al.* 1972). Macrosomic infants of women with Type 1 diabetes (Pedersen 1977b) or GDM (Persson and Hanson 1998) also have organomegaly, e.g. enlargement of the liver and heart. The growth of these infants may be asymmetric, with larger shoulder/head and chest/head ratios than in the infants of non-diabetic women (Modanlou *et al.* 1982, Ballard *et al.* 1993).

3.7.3. Birth trauma

Shoulder dystocia and high birth-weight are the strongest risk factors as regards clavicular and other fractures and brachial plexus injury (Erb's palsy) (Levine *et al.* 1984, Mollberg *et al.* 2005). The incidence of brachial plexus injury is 0.15-0.3% (Gilbert *et al.* 1999, Mollberg *et al.* 2005, Backe *et al.* 2008). In an analysis of 66 086 births, Gregory *et al.* (1998) reported a brachial plexus injury rate of 0.1% among vaginally delivered infants weighing under 4000 g, but 0.9% when

the birth weight was at least 4000 g. Similarly, others have reported rates of 0.6–1.1% for brachial plexus injury in vaginally-born infants weighing at least 4000 g among mothers without diabetes (Ecker *et al.* 1997, Kolderup *et al.* 1997, Bryant *et al.* 1998). The frequency of plexus injury was increased in the infants of women with GDM and in cases of vacuum extraction or forceps delivery (Gilbert *et al.* 1999).

Diabetes increases the risk of brachial plexus injury by 2 to 5 times in infants weighing at least 4000 g at birth. In a Swedish study the overall perinatal mortality rate resulting from shoulder dystocia was 1.2%. It increased to 6.4% in mothers with diabetes mellitus (Christoffersson and Rydhstrom 2002). Fracture of the clavicle occurs particularly during a difficult vaginal delivery, and especially when shoulder dystocia is present, or when the arms are extended in breech delivery. Fractures of the humerus (greenstick or full-thickness fracture) at birth are seen mostly when the newborn infant is macrosomic or is delivered vaginally in breech presentation (Caviglia *et al.* 2005). Fracture of the skull bones is associated with instrumental vaginal delivery (vacuum or forceps) and it may result in intracranial hemorrhage (Doumouchtsis and Arulkumaran 2008).

3.7.4. Fetal hypoxia

The incidence of abnormal fetal heart rate pattern during delivery, cord blood acidosis and low Apgar scores at birth is increased in diabetic pregnancies, indicating an increased risk of fetal hypoxia (Mimouni *et al.* 1986, Salvesen *et al.* 1992, Casson *et al.*1997). The exact mechanisms of fetal hypoxia are not fully understood. It is likely that several factors, alone or in combination, can result in decreased oxygen delivery to the fetus in diabetic pregnancies.

Experimental and human studies have shown that both fetal hyperglycemia and hyperinsulinemia can independently cause fetal hypoxemia (Carson *et al.* 1980, Philipps *et al.* 1982, Milley *et al.* 1984). Elevated plasma and amniotic fluid EPO levels suggest that the fetuses of diabetic women can suffer from chronic hypoxia (Teramo *et al.* 2004).

The iron stores in the fetal liver and brain are totally depleted in most cases of stillbirth in diabetic pregnancies reflecting increased erythropoiesis, further suggesting that these fetuses die from chronic hypoxia. Concentrations of maternal HbA1c during the last weeks of pregnancy correlate directly with fetal cord plasma (Widness *et al.* 1985) and amniotic fluid EPO levels (Teramo *et al.* 2004), indicating that poor glycemic control during the last weeks of pregnancy increases the risk of intrauterine hypoxia. In a recent study of Type 1 diabetic pregnancies, the correlation between amniotic fluid EPO concentrations and birth-weight z-scores was U-shaped.

Below a z-score of -0.6 SD units the correlation was negative but above +1.0 SD unit it was positive (Teramo *et al.* 2004). This suggests that the optimal birthweight in Type 1 diabetic pregnancies is relatively narrow, and that fetal chronic hypoxia can occur when the birth-weight z-score is below -0.6 or above +1.0 SD unit.

3.7.5. Perinatal mortality

Perinatal mortality is defined according to WHO as a fetal death occurring at or after 22 weeks of gestation and/or 500 g birth-weight or a neonatal death occurring during the first 7 days of life. Perinatal mortality has decreased from 20–30% to fewer than 5% during the last 50 years in pregnancies complicated by Type 1 diabetes mellitus (Schwartz and Teramo 2000, Gabbe and Graves 2003). However,

it is still 3–5 times higher, even in centers specializing in the care of diabetic pregnancies, than the perinatal mortality rate in the general population (Jensen *et al.* 2003, Macintosh *et al.* 2006, Bell *et al.* 2008).

In Type 1 diabetic pregnancies the perinatal mortality rate ranges from 2.8 to 4.8% (Casson *et al.* 1997, Hawthorne *et al.* 2000, Platt *et al.* 2002, Evers *et al.* 2004b). About 30 to 40% of perinatal deaths in Type 1 diabetic pregnancies are caused by malformations and 20 to 30% by prematurity and intrauterine asphyxia, respectively (Schwartz and Teramo 2000). Stillbirths after 30 weeks of gestation form the majority of perinatal deaths in Type 1 diabetic pregnancies (Schwartz and Teramo 2000).

Before 30 weeks, prematurity is the main cause of perinatal death (Teramo *et al.* 2005). In the 1950s, the risk of fetal death in Type 1 diabetic pregnancies was 5% at 32 weeks of gestation, increasing gradually to 15% at term (Hagbard 1956). Chronic fetal hypoxia is postulated to be the most likely reason for the majority of 'unexplained' stillbirths in diabetic pregnancies after 35 weeks of gestation (Schwartz and Teramo 2000).

3.7.6. Neonatal complications

3.7.6. 1. Hypoglycemia

Neonatal hypoglycemia is defined as a plasma glucose level below 2.6 mmol/l in a full-term infant (Cornblath *et al.* 2000). The prevalence of neonatal hypoglycemia ranges between 0.5 and 4% in infants born at term (Uvena-Celebrezze and Catalano 2000, Shand *et al.* 2008). Among the infants of women with GDM, hypoglycemia occurs in 6–19% (Langer *et al.* 2005a, Shand *et al.* 2008) and in the pregnancies of pregestational diabetes (Type 1 or Type 2) the figure is 25–48% (Cordero *et al.* 1998, Evers *et al.* 2004b, Shand *et al.* 2008).

High amniotic fluid EPO levels obtained within 2 days before delivery can identify fetuses with an increased risk of neonatal hypoglycemia in Type 1 diabetic pregnancies (Teramo *et al.* 2004). Neonatal hypoglycemia during the first days of life is a consequence of fetal hyperinsulinemia (Pedersen 1977b). A decreased ability to use glycogen and diminished hepatic glucose production in the first days of life predisposes newborn infants to hypoglycemia (Merlob and Hod 2008).

Impaired counter-regulation by catecholamines may also have a role in the development of neonatal hypoglycemia (Schwartz and Teramo 2000). Most infants with neonatal hypoglycemia recover spontaneously, but symptomatic and prolonged hypoglycemia may result in permanent neurologic impairment or death (Armentrout and Caple 1999, Vannucci and Vannucci 2001).

3.7.6. 2. Respiratory distress syndrome

The risk of respiratory distress syndrome (RDS) in newborn infants of Type 1 diabetic mothers is increased compared with that in the general population when matched for gestational age (Robert *et al.* 1976). Poor glycemic control during the last week of pregnancy has been shown to delay fetal lung maturation (Ylinen 1987), whereas the risk of RDS in infants of women with diabetes in good glycemic control approaches that in the non-diabetic population (Kjos *et al.* 1990). Evaluation of fetal lung maturity by means of analysis of amniotic fluid has been recommended in insulin-treated diabetic pregnancies when an elective cesarean section is contemplated before the 38th gestational week (Hallman and Teramo 1979).

3.7.6. 3. Polycythemia

Fetal polycythemia is defined as cord blood hematocrit at or above 65% at birth. The occurrence of polycythemia is increased in infants of diabetic mothers

(Salvesen *et al.* 1992). These infants have polycythemia up to five times more often than infants of non-diabetic women (Mimouni *et al.* 1986). Fetal polycythemia is a result of accelerated erythropoietin-induced red blood cell production in response to chronic fetal hypoxia (Shannon *et al.* 1986, Widness *et al.* 1985, Teramo and Widness 2008). Polycythemia may lead to hyperviscosity syndrome and fetal renal vein thrombosis (Avery *et al.* 1957, Hibbert *et al.* 1997).

3.7.6. 4. Hyperbilirubinemia

The definition of neonatal hyperbilirubinemia is complicated. Both gestational age and the age of the newborn infant are related to serum bilirubin levels. A serum bilirubin concentration exceeding 205–222 µmol/l in term infants is considered abnormally high (Maisels 1992). Hyperbilirubinemia complicates up to 20% of the newborn infants of women with GDM compared with 10% in the general population (Uvena-Celebrezze and Catalano 2000). Hyperbilirubinemia has been reported in 24 to 45% of the newborn infants of Type 1 diabetic pregnancies (Cordero *et al.* 1998). The etiology of the increased frequency of hyperbilirubinemia in diabetic pregnancies is not fully understood. It may be due to delayed clearance of bilirubin in newborn infants of diabetic mothers (Stevenson 1987). In addition, polycythemia contributes to hyperbilirubinemia because of the increased amount of breakdown products (Merlob and Hod 2008).

3.7.6. 5. Hypocalcemia and hypomagnesemia

Hypocalcemia and hypomagnesemia in infants of diabetic mothers are clinically less important than other neonatal complications. Maternal magnesium and parathyroid hormone concentrations are decreased in diabetic women, who may result in fetal hypomagnesemia (Uvena-Celebrezze and Catalano 2000) and this in turn can lead to reduced concentrations of fetal parathyroid hormone and

hypocalcemia. Neonatal hypocalcemia is defined as an ionized serum calcium level below 1.05 mmol/l and hypomagnesemia as a plasma magnesium level of less than 0.5 mmol/l. Hypocalcemia affects 18–32% of infants born to Type 1 diabetic women (Demarini *et al.* 1994). The severity of hypocalcemia has been reported to correlate with the degree of glycemic control during pregnancy (Tsang *et al.* 1975, Demarini *et al.* 1994).

3.7.6. 6. Obstructive cardiomyopathy

Fetuses of women with pregestational diabetes have an increased risk of developing cardiac septal hypertrophy (Walther *et al.* 1985, Vela-Huerta *et al.* 2000). This may be due to fetal chronic hypoxia as indicated by elevated amniotic fluid EPO levels (Teramo and Widness 2008). Newborn infants with obstructive cardiomyopathy often have cyanosis or cardiac failure during the first days of life (Gutgesell *et al.* 1980).

3.7.6. 7. Preexisting Diabetes-Related Complications

As previously stated, Type 1 and Type 2 DM are linked to several co-morbidities such as cardiovascular disease, neuropathy, nephropathy, and retinopathy. Pregnancy can lead to further complication of these disorders, especially eye and kidney disease (Harvard Health Publications 2002, Thoenen *et al.* 2001). Brown and Hare (1995) stated that these conditions increase the risk for poor gestational outcomes for both mother and baby. Several researchers have suggested that in order to prevent or lessen the effects of these conditions the first important step is early diagnosis, preferably before pregnancy, and the second important step is optimal glycemic control (American Diabetes Association 2002, Rosenn & Miodovnik 2000.)

CHAPTER-4

MATERIALS AND METHODS

4. MATERIALS AND METHODS

4.1. Target population

The principal aim of the present study is to observe and assess the outcome of pregnancy of diabetic mothers admitted into a tertiary level hospital. For this purpose, the hospitalized diabetic mothers required follow up till delivery of the baby. The target population was pregnant women with GDM and PDM in Rajshahi and adjoining areas in the Northern region of Bangladesh.

4.2. Study population

The study population was pregnant diabetic mothers attending obstetrics OPD and indoor department of Rajshahi Medical College Hospital, Rajshahi, Bangladesh for delivery.

4.3. Study design

A hospital based case study was designed to collect data for this research which was fully quantitative and observational. Rajshahi Medical College Hospital, a tertiary level Government owned public hospital in Rajshahi, a divisional city in the Northern part of Bangladesh was chosen for the collection of data. To collect necessary information, a face to face interview with the mothers and a retrospective clinical chart review of all the cases (GDM and PDM) were done in postnatal phase. Data for GDM and PDM were collected from the women who came to attend delivery in this hospital.

4.4. Study Hospital

Rajshahi Medical College Hospital is a tertiary level Government owned public hospital in Rajshahi, a divisional city in the Northern part of Bangladesh. It has a large hospital that is the central provider for advanced health care in the northern part of Bangladesh.

Quite a significant number of patients come to this hospital from Rajshahi district and adjoining districts. This hospital is not a specialized hospital for diabetes care but it mostly renders obstetric services to pregnant women. This hospital has been accredited and reputed for holding well-maintained antenatal care services in the OPD of Ob and Gynecology. All of the women who deliver here usually have been on their regular antenatal check up. The hospital conducts about 10-15 deliveries a day. These are mostly GDM and pregestational diabetic deliveries (source: hospital registry).

Cases other than referred ones are usually screened off early in third trimester or in second trimester based on the suspicion of the attending doctors in obstetric outpatient unit. Thus these women start to receive treatment for diabetes from the hospital. Their demographic and medical history, clinical and laboratory findings and treatment on diabetes are recorded systematically in a book developed by Bangladesh Diabetic Association. At the same time they also go for antenatal checkup in the same unit which is recorded in the antenatal card.

The practice of screening for diabetic pregnancies is different in Rajshahi Medical College Hospital, Rajshahi. During the first or second antenatal check up in the OPD of Obs & Gynecology, it performs a routine test of random blood glucose (RBG) irrespective of time of meal to all pregnant women. If that is found equal or more than 7 mmol/l, they take another RBG test. If that again came the same as before they are asked to take a GCT/ OGTT. If the result of the test confirmed GDM they are referred to the hospital for better and proper management of diabetes. BIRDEM hospital is one of those referral hospitals. This is how Rajshahi Medical College Hospital Rajshahi screens out diabetic pregnancies and intends to provide routine pregnancy care for the women not detected as diabetic according to their criteria.

4.5. Period of study: August, 2008 to September, 2011.

4.6. Research instrument

The following research tool was used in this study for collection of data.

   a). Questionnaire (Appendix-II).

   Sources for data

   a). Answers from the participants in interview (Appendix- II)

   b). Antenatal cards.

   c). Diabetic book of the women with GDM

   d). Hospital files for delivery and birth records.

4.7. Inclusion criteria and exclusion criteria

Inclusion criteria

1. Women with any degree of glucose intolerance with onset or first recognized during pregnancy.

2. Women with a diabetic book and antenatal card with necessary information for this study.

 Exclusion criteria

1. Women without a diabetic book and antenatal card lacking necessary information for the study.

2. Women who are unwilling to participate in the research work.

4.8. Sample size

We collected data from 187 diabetic (GDM and PDM) pregnant during the study. In the planning phase we estimated a total sample size of 400 cases. Calculation was performed by a statistician. But in place due to shorter period of time and limited logistic support we could not reach up to that many samples.

4.9. Sampling procedure

We underwent random (continuous) sampling for selection of cases for this study. Two hundred (200) women who fulfilled inclusion criteria were asked to take part in the study. Among them 13 refused to participate. The rest 187 women with GDM and PDM, willing to participate, were selected as cases for the study. These women were already diagnosed GDM and PDM patients by OGTT. They had been on treatment by hospital outpatient service for control of their diabetes and pregnancy care.

4.10. Data collection procedure

Along with principal investigator two doctors belonging to Rajshahi Medical College hospital, Rajshahi took part in data collection. They followed the sampling technique to select the sample for the study. Assistance of the doctors from the hospital was sought because of their easy access to the necessary information.

A two days training was provided to the assisting doctors by the principal investigator. The training focused on the demonstration of the questionnaire, collection of information from the records, approach of communication and ethical issues. This training was conducted before the pilot phase of testing the questionnaire. Data were collected from Aug 2008 to Sep 2011 with a structured questionnaire. Women selected as cases were interviewed by an investigator in their apparently stable situation after the delivery in post natal ward.

The purpose of the study was clearly explained to them. All the pregnant women gave consent to take part, in face to face interview (Appendix-II) and antenatal card and delivery records were reviewed to collect the necessary information. Sometimes husband and other family person accompanied the woman during the interview and helped her providing information to the interviewer. An interview took about 20-30 min. The data were regularly cross checked by the principal investigator.

4.11. Diagnostic criteria used

We depended on the method adopted by Rajshahi Medical College Hospital for screening of GDM and PDM. We followed the guideline for diagnosis and screening of DM proposed by the clinical research division BIRDEM to set a cut off value for screening DM women.

4.12. Variables

In this study GDM and PDM were the only dependent variables. All others are independent variables

4.13.1 Risk factor variables

i) Socio demographic risk factors: Maternal age, First recorded maternal weight in this pregnancy, Height, BMI, Level of education of the women, monthly expenditure of the family and occupational status of the women.

ii) Familial risk factor: Family history of diabetes and first and second degree relatives.

4.13.2. Time of diagnosis of DM

Gestational week at which DM was diagnosed

4.13.3 Type of treatment in DM

Diet control or insulin whichever was received by the women with DM for longer duration.

4.13.4. Pregnancy outcome variables

i). Pregnancy complications: Hypertension in pregnancy, anaemia

ii). Delivery outcome: Gestational age at delivery, Mode of delivery.

iii). Fetal and neonatal Outcome: Birth weight of the newborn, Normal live or abnormal birth of fetus or babies.

4.13.5. Data handling and analysis

Individual case was given a case number to avoid mixing up of data. In the field data were entered into Microsoft Access 98 according to pre-coded categories. Later this data were converted into the software package SPSS 16.0 (Statistical Package for Social Sciences) for windows operating platform. The data were checked by going through each and every questionnaire.

SPSS 16.0 was used to examine the frequency distributions of maternal socio-demographic characteristics, family and obstetric histories, pregnancy and neonatal outcomes according to case and control status. For a general description of the study population group differences were recorded in x^2 test, while individual t-test was employed to identify differences for some of the continuous variables.

4.1.3.6. Ethical issues

Approval to carry out the study was sought from the Human Research Ethics Committee, Institute of Biological Sciences, University of Rajshahi, Rajshahi, Bangladesh. Before the commencement of the study the purpose, objectives of the study and possible benefits of the study were explained to the relevant authorities at Rajshahi Medical Collage Hospital, Rajshahi, Bangladesh. In order to have access to patients' information and to use patient materials and laboratory medical records for this study permission and Ethical approval was sought from the Principal of Rajshahi Medical Collage Hospital, Rajshahi, Bangladesh (Appendix-III).

Prior to interview, the purpose and objectives of the study was explained to the prospective participants. Decision to join in the study was made on the basis of informed consent. Written consent to take part in this study was sought prior to their inclusion to this study in presence of a witness (Appendix-I). Participation in

this study had been voluntary and participants had the right to withdraw at any period of the investigation. No penalty was attached to such decisions. The findings were treated with highest possible degree of confidentiality. Each participant was given a separate identity number.

In cases of adverse pregnancy outcome like complicated delivery, mother's and baby's illness or in any emergency situation psychological effects of the participants had been taken care of while asking question or collecting information. Researchers were available for counseling bereaved people if they need such assistance.

CHAPTER-5

RESULTS AND OBSERVATIONS

5. RESULTS AND OBSERVATIONS

The findings in this study imparts the data collected from Rajshahi Medical College Hospital, Rajshahi, Bangladesh, a tertiary level hospital in Northern part of Bangladesh from August, 2008 to September, 2011.

A total of 187 women were interviewed during this period. The data were based on the answers that came from interviews and medical records registered in the antenatal cards, diabetic booklet and delivery notes in hospital files. Medical records were reviewed retrospectively for information on medical history, physical findings, course of the disease, treatments, complications, and outcomes in accordance with the objective of the study.

5.1. Sample of the study:

This observational retrospective study included 187 diabetic (both Pregestational diabetes and Gestational diabetes) pregnant women who got admitted, treated and delivered at Rajshahi Medical College Hospital (RMCH), Rajshahi, Bangladesh from August, 2008 to September, 2011.

The sample of the present study has been shown in Table 3. Out of the total 187 pregnant women, 113(60.43%) women had gestational diabetes (GDM) and the rest 74 (39.57%) women had pregestational diabetes (PDM).

Table 3. Sample of the study (n=187).

	Diabetes type	Frequency	Percent
	Pregestational diabetes (PDM)	74	39.57
	Gestational diabetes (GDM)	113	60.43
	Total	187	100.0

5.2. Distribution of women according to age and parity

The age and parity distribution of diabetic pregnant women of the present study has been shown in Table 4.

Table 4. Distribution of women according to age and parity (n=187).

Age group	PDM	GDM	Total
18-29 yrs	29	46	75 (40.10 %)
30-39 yrs	39	63	102 (54.54 %)
>40 yrs	6	4	10 (5.35%)
Total	**74**	**113**	**187 (100%)**
Primi gravida	24	40	64 (34.22%)
2nd gravida	42	71	113 (60.42%)
3rd gravida	08	02	10 (5.34%)
Total	**74**	**113**	**187 (100%)**

As shown in Table 4, of the study, majority (54.54 %) *i.e.* 102 of the diabetic pregnant women belonged to the 30- 39 years age group; while 40.1% *i.e.* 75 women within the 18- 29 years age group and only 10 *i.e.* (5.34%) women were of the >40 yrs group.

Again, as evidenced from Table 4 above, nearly 34.22% women were primi gravida, 60.42% women 2nd gravida and only 5.34% women were 3rd gravida; while there were no 4th gravid women.

5.3. General characteristics the patient's

Out of the total 187 pregnant women with diabetes of the study, 113(60.42%) had gestational diabetes (GDM) and the rest 74 (39.57%) women had pregestational diabetes (PDM).

Among the pregnant women with diabetes nearly fifty-eight percent (58.22%) i.e. 109 women progressed to term pregnancy where as in 41.78 % i.e. in 78 diabetic pregnant women it ended before 37 weeks of gestation. Average pregnancy duration (gestational age) was calculated to be 36.75 ± 0.9 (28-41) weeks. The mean age of pregnant women i.e. maternal age was calculated to be 28.9 (18-45) years. The general characteristics of the patients have been presented in Table 5.

Table 5. The general characteristics of the patients.

Variables	No of patients (n=187)
Maternal Age (Mean+ SD)	28.9 ± 3.2 (18-45)yrs
Average parity (X+SD)	1.38 ± 0.01
Gestational age (weeks) (X +SD)	36.75± 0.9 (28-41)
Term	109 (58.22 %)
Preterm	78 (41.78 %)
Gestational diabetes(GDM)	113 (60.42%)
Pregestational diabetes (PDM)	74 (39.57%)

SD= Standard deviation

5.4. Pregnancy outcome depending upon type of diabetes, n=187

5.4.1. Maternal outcome of the study population based on the type of diabetes

The maternal outcome based on the type of diabetes of the current study; has been shown in the Table 6 (a). As presented in the Table, hypertensive disorder of pregnancy (PIH and Pre-eclampsia (PE) developed among 24 (12.9%) women; while Eclampsia developed among 04 (2.2%) women out of total 187 pregnant diabetic women.

Among women having GDM, 9 (7.96%) developed PE in comparison to 15 (20.3%) women of PDM. The prevalence rate of Pre-eclamsia (PE) therefore, was comparatively higher in pre-gestational diabetic (PDM) mothers than in GDM mothers. This difference was also found to be statistically significant as evidenced by χ2/Fisher's Exact Test and the value of p> 0.014; as shown in Table 6 (a). Similarly, the incidence of Eclampsia was also higher among women having PDM than GDM (3 vs 1). However, the differences among them were statistically insignificant (p=0.172).

Table 6 (a). Association between maternal outcome and type of diabetes (n =187).

Parameters	GDM (n=113)	PDM (n = 74)	Total (n = 187)	χ^2/Fisher's Exact Test, p-value	Inference
Maternal outcome					
Pre-eclampsia (PE) Yes	9(7.96)	15(20.3)	24(12.9)	6.053, 0.014	Preclampsia was significantly higher in PDM group
No	104(92.0)	59(7.9)	163(87.1)		
Eclampsia Yes	1(0.9)	3(4.05)	4(2.2)	2.145(FE), 0.172	Difference is not significant.
No	112(97.3)	71(97.3)	183(97.8)		

Table 4 (a). Contd. From previous page

Table 6 (a). Association between maternal outcome and type of diabetes (n =187).

Parameters	GDM (n=113)	PDM (n = 74)	Total (n = 187)	χ2/Fisher's Exact Test, p-value	Inference
PROM Yes	17(15.0)	6(8.1)	23(12.3)	1.994, 0.158	Difference is not significant
No	96(84.9)	68(91.9)	164(87.7)		
Fetal distress Yes	27(23.9)	16(21.6)	43(23.0)	0.130, 0.718	Difference is not significant
No	86(76. 1)	58(78.4)	144(77.0)		
Polyhydramnios	33(29.2)	44(59.5)	77(41.2)	16.900, < 0.001	Polyhydramnios significantly higher in PDM group
Abortion	6(5.3)	14(18.9)	20(10.7)	8.671, 0.003	Abortion was significantly higher in PDM group
Cesarean section CS	88(77.8)	47(63.5)	135(72.1)	0.227, 0.634	Difference is not significant
Vaginal delivery	16(14.2)	4(5.4)	20(10.7)	3.901, 0.048	Vaginal delivery significantly higher in GDM group
Vulva and vaginal candidiasis	47(41.6)	30(40.5)	77(41.2)	0.020, 0.886	Difference is not significant
UTI	51(45.1)	35(47.3)	86(46.0)	0.084, 0.771	Difference is not significant

The incidence of preterm rupture of membrane (PROM) was found to be comparatively higher (15.0%) in pregnant women having GDM as compared to 8.1% women of PDM but the differences did not reach to statistically significant level (p= 0.158).

Ante-partum fetal distress developed in 27 (23.9%) women of GDM in comparison to 16 (21.6%) women in PDM but the difference among them was statistically insignificant (p= 0.718).

Polyhydramnios i.e**.** excessive amounts of amniotic fluid throughout pregnancy were found to be comparatively higher (59.5%) in pregnant women having PDM as compared to 29.2% having GDM. This difference was found to be statistically highly significant as the value of p was calculated to be < 0.001 as shown in Table 6 (a).

Total 135 (72.1%) women were delivered by cesarean section (CS) as compared to 20(10.7%) by vaginal delivery. Eighty eight (77.8%) women of GDM and 47(63.5%) women of PDM were delivered by cesarean section and the difference is not statistically significant ($\chi^2 = 0.227$, p>0.634). The results of statistical analyses also revealed that rate of vaginal delivery was significantly higher in GDM mothers than the PDM mothers ($\chi^2 = 3.901$, p=0.048).

Proportion of women who underwent abortions was 14 (18.91%) in PGDM and 6 (5.03%) in GDM *i.e.* the rate of abortion was significantly higher in the PGDM women as compared to GDM women. Statistical analyses also showed that abortion rate was significantly higher in PDM mothers ($\chi^2 = 8.671$, p= 0.003) than the GDM.

As shown in Table 6 (a), in the present study, the incidence of Vulva and vaginal candidiasis was found to be almost very similar in pregnant women having GDM and PDM; was 41.6% and 40.5%, respectively and the difference is not statistically significant (p>0.886). Similarly, the incidence of urinary tract infection (UTI) was found to be almost same in pregnant women having GDM and PDM; 41.6% and 40.5%, respectively and the difference is also found to be statistically insignificant (p>0.771) as shown in Table 6 (a).

5.4.2. Fetal and Neonetal outcome on the type of diabetes

Fetal and Neonetal outcome on the type of diabetes of the present study has been presented in Table 6 (b). As shown in the Table, there were 155 (82.88%) normal live birth, 05 (2.67%) live birth with congenital malformations and 12 (6.4 %) intrauterine death (IUD).

A case of live birth delivery with congenital malformation in mother with pre-gestational diabetes of the present study has been shown in Fig. 3.

Fig. 3. Photograph of live birth delivery with congenital malformation.

Among 12 intrauterine deaths (IUD) the occurrence of IUD was higher among PDM as compared to that of GDM (9 and 3, respectively). Statistical analyses of the above findings indicated that intrauterine death was frequently common in pregnant women having PDM than GDM. However, the differences between them didn't reach to significant level (p >0.022) as shown in Table 6(b). Among 12 intrauterine deaths eleven (11) had developed preeclampsia and in one women the cause was unknown.

Table 6 (b). Association between Fetal/Neonatal outcome and type of diabetes (n =187).

Parameters	GDM (n=113)	PDM (n = 74)	Total (n = 187)	χ2/Fisher's Exact Test, p-value	Comment
Fetal/Neonatal complications					
Live birth			155 (82.88%)		
Intrauterine death (IUD)	3(2.7)	9(12.2)	12(6.4)	5.240, 0.022	Intrauterine death was frequently common in PDM
Congenital malformation	2(1.7)	3(4.1)	5(2.7)	0.234, 0.308	Difference is not significant
Large for gestational age (> 4000 g)	30(26.5)	52(70.3)	82(43.8)	34.717, <0.001	Birth of large baby is significantly higher in women having PDM than GDM group
Maternal death	**0**	**0**	**0**	**Not computable**	

Data are given as number (percentage).

Regarding congenital malformation, the prevalence was almost the same in pregnant women with PDM and GDM and were 3(4.1%) and 2(1.7%), respectively. The above differences were found to be statistically insignificant as the calculated p value was >0.308 (Table 6(b).

In the present study, the prevalence of 'large babies' i.e. Macrosomic babies was much higher (70.3%) in pregnant women having PDM as compared to that of GDM (26.5%) groups. PDM group therefore gives birth to large baby more frequently than the GDM group does. The above difference was found to be statistically highly significant p <0.001 (Table 6 b). Photograph of a Macrosomic baby delivered by a diabetic mother of the current study has been shown in Fig. 4. A photograph of

another macrosomic baby delivered by an uncontrolled diabetic mother versus and a normal weight baby delivered by a better diabetes controlled mother of the study has been shown in Fig. 5.

Fig. 4. Photograph of a Macrosomic baby (>10 lbs) delivered by a diabetic mother.

Fig. 5. Photograph of Macrosomic baby versus normal body wt baby delivered by diabetic mothers.

5.5.0. Socio-demographic characteristics of the study population

5.5.1. Socio–economic status of the patients

The socio-economic statuses of the participants of the study have been presented in Table 7. From the data presented in the Table it is evident that the highest numbers of the patients (60%) were from the lower middle class group while the lowest number patients (08%) belonged to the poor class.

Table 7. Socio–economic status of the patients (n=187).

Socio economic status	Number of patients	Percentage
Rich	20	10 %
Middle class	44	22 %
Lower middle class	120	60 %
Poor	16	08 %
Total	187	100%

5.5.2. The educational level the respondents

The educational level the respondents of the study has been depicted in Table 7. Data presented in Table 8 indicated that majority of the patients (nearly 44%) had educational levels less than S.S.C. and the least number of patients (only 4.81%) were graduates.

Table 8. Educational level of the patients (n =187).

Educational level	Number of patients	Percentage
Less than S.S.C.	82	43.8%
S.S.C.	65	34.75 %
H.S.C.	31	16.57 %
Graduates	09	4.81%
Total	187	100%

5.5.3. Diabetes and pregnancy and family history:

The Frequency and percentages of diabetes mellitus and their relation to previous family history of diabetes have been presented in Table 9.

Table. 9. The Frequency and percentages of diabetes mellitus and their relation to previous family history of diabetes (n =187).

			Family history of diabetes			
			1st degree relatives	2nd degree relatives	No family history	Total
Diabetes mellitus	Pregestational Diabetes (PDM)	Count	54	14	6	74
		% within DM	72.92%	18.97	8.11	100%
	Gestational diabetes (GDM)	Count	87	10	16	113
		% within DM	76.99	8.85	14.15	100%
Total		Count	141	24	22	187
		% within DM	75.40	12.84	11.76	100%

Data presented in the Table 8 indicated that 72.92% of PDM patients had first degree relatives, 18.97% second degree relatives and 8.11% no family history. And of those who had gestational diabetes, 76.99 of them had first degree relatives, 8.85% second degree relatives, and 14.15% had no family history.

5.5.4. Diabetes and pregnancy and residence

The Frequency and percentage of diabetes mellitus (depending upon their type) and their possible relation to location of resident areas have been showed in Table 10. Data presented indicates that 51.35% of those who had PDM had lived in the city, and 36.49% lived in villages, and 12.16% had lived in slums. Pertaining to gestational diabetes, 57.52% had lived in the city, 37.18% had lived in villages, and 5.3% had lived in slums.

Table 10. Frequency and percentage of diabetes mellitus and residence (n =187).

			Residence			
			City	Village	Slums	Total
Diabetes mellitus	Pregestational diabetes	Count	38	27	9	74
		% within DM	51.35%	36.49%	12.16%	100%
	Gestational diabetes	Count	65	42	6	113
		% within DM	57.52%	37.18	5.3	100%
	Total	Count	103	69	15	100
		% within DM	55.08%	36.98%	8.02%	100%

CHAPTER-6

DISCUSSION

6.0. DISCUSSION

Historically, the perinatal mortality rates due to diabetic pregnancy were as high as 65%, but after the development of specialized maternal and neonatal care, the outcome of diabetic pregnancies has improved tremendously in the western world (Diagnosis and classification of diabetes mellitus, 2006). Unfortunately, in our set up in developing countries there is still a high perinatal mortality among infants of diabetic mother due to poor antenatal care, non compliance of therapy and lack of adequate neonatal services (Tahir and Aleem 2006, Shefali *et al.* 2006). This problem is compounded by the lack of general awareness of the problem.

Diabetes is a fairly common medical complication of pregnancy. The presence of diabetes (gestational and pre gestational diabetes) in pregnancy has been associated with adverse effects on maternal and neonatal outcomes (Gillmer & Hulrey 1999). The incidence of obstetrical and metabolic complications increased, and a continuum has been observed between maternal blood glucose levels and perinatal outcome perinatal mortality, severe congenital malformations, prematurity, and macrosomia (Justin 2004, Pickup and William 1997).

Though there are studies in Asian Indians on the prevalence of PGDM and GDM among pregnant mothers (Ramachandran *et al.* 1994, Banerjee *et al.* 2004) there have been very few studies comparing the outcomes in these two groups. The present study was conducted to compare the pregnancy outcomes in mothers with PGDM and GDM i.e. determine the maternal and fetal outcomes of pregnancies in women with diabetes mellitus in a tertiary level Hospital in the Northern region of Bangladesh.

In the present study, total number of pregnant diabetic women was 187 and among them 113(60.43%) were diagnosed to have gestational diabetes mellitus (GDM)

and 74 (39.57%) women had pre-gestational diabetes (PDM) as shown in Table 3 (Page 61 in Results and observation chapter 5 of this dissertation).

This finding of ours is very close to that reported earlier by Mahmood and Keyes (2008) in Bangladesh who reported that 59.61% of their patents had GDM and 40.38% had PDM. Our results are also very close to the findings of two other studies conducted earlier in Bangladesh by Begum (1997) and Begum (1998).

Khan *et al.* (2007) reported that Diabetes mellitus is prevalent among 4.8% people of Bangladesh and prevalence of IGT is 8.5%. Among them a significant number are female. In western world 2 to 3% of all pregnancies are currently being diagnosed as GDM (Kuhl 1991). Gestational diabetes mellitus (GDM) develops among 6.7% of all pregnancies in our population (Tofail *et al.* 1997).

In our study, among diabetic pregnant women, nearly fifty-eight percent (58.22% i.e. (109) women progressed to term pregnancy where as in 41.78 % *i.e.* in 78 pregnant women it ended before 37 weeks of gestation (Table 5, page 63 in Results and observation chapter 5 of this dissertation). The above findings clearly showed that in a quite large proportion of pregnant diabetic women (41.78 %) among our study population had to be delivered prematurely.

This finding of ours agree very well with the observations of Mark and Steven who reported that pregnant diabetic women may need to be delivered prematurely due to maternal or fetal problem (Mark and Steven). Mahmood and Keyes (2008) in Bangladesh and Ranade *et al.* (1989) in India reported 7.6% and 36% of preterm delivery respectively, in their study.

Among different pregnancy complications, pre-eclampsia is the commonest and dangerous (Justin 2004, Mark & Steven, Carla *et al.* 1994, Gillmer & Hurley, Andrea & Jude 2000). In the present study, the prevalence rate of Pre-eclamsia

(PE) was comparatively higher (20.3%) in pre-gestational diabetic (PDM) mothers than in GDM mothers (7.96%) and this difference was found to be statistically significant (p> 0.014.).

Our above finding is are very close to the observations of Akhter *et al.* (2012) who in their study on the Immediate Outcome of Pregnant Diabetic Women in Bangladesh reported that occurrence of PE was higher among PDM mother as compared to that of GDM mother (35% and 19% respectively); but however, unlike our study; the difference was statically insignificant (p>0.076).

Our findings are also in good agreement with the report of Andrea and Jude (2000) and Mark & Stevens (1994) who also observed that occurrence of PE was higher among PDM mother as compared to that of GDM mother (Medical Disorder During Pregnancy).

Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor. In most cases, this occurs near term, but when membrane rupture occurs before 37 weeks' gestation, it is known as preterm PROM. PROM complicates approximately 3 percent of pregnancies and leads to one third of preterm births (Meis *et al.* 1987). It increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death (Mercer 2003). It can lead to significant perinatal morbidity, including respiratory distress syndrome, neonatal sepsis, umbilical cord prolapse, placental abruption, and fetal death. Appropriate evaluation and management are important for improving neonatal outcomes.

PROM is very common in the obstetric wards. We face problem in diagnosis, monitoring and adopting treatment policy. There were very limited studies about PROM in our country and no national statistics is available about the incidence of

PROM or incidence of maternal and perinatal mortality and morbidity from PROM. Incidence of preterm PROM in Bangladesh is not known but Incidence of PROM in Dhaka Medical College Hospital is 8.12% (Tasnim & Bhuiyan 1998 and 1.94% at Holy Family Red Crescent Hospital (Shaheen Rahman Chowdhury *et al.* 2005).

In the current study, the incidence of preterm rupture of membrane (PROM) was found to be comparatively higher (15.0%) in pregnant women having GDM as compared to 8.1% women of PDM but the differences did not reach to statistically significant level (p= 0.158).

The finding of higher incidence of PROM (15%) in our study is very near to the findings of 8.12% of the study of Tasnim & Bhuiyan (1998) at Dhaka Medical College Hospital Dhaka. Our result of 15% incidence of PROM is also very close to the observations of Akter *et al.* (2012) who in their study on the immediate outcome of pregnant diabetic women in Bangladesh reported that 13% women developed preterm rupture of membrane (PROM). However, Singh Uma *et al.* (2007) in their study in India reported a much higher incidence (25.96%) of premature rupture of membranes (PROM) and it was the most common cause of preterm labor. It can be concluded that pregnant diabetic women of our study population had received poor antenatal care which might be due to lack of awareness and/ or knowledge.

Fetal distress is the compromise of a fetus during the antepartum period (before labor) or intrapartum period (during the birth process). The term fetal distress is commonly used to describe fetal hypoxia (low oxygen levels in the fetus), which can result in fetal damage or death if it is not reversed or if the fetus is not promptly delivered. Fetal distress can be detected via abnormal slowing of labor,

changes in fetal heart rate, the presence of meconium (dark green fecal material from the fetus) or other abnormal substances in the amniotic fluid, or fetal monitoring with an electronic device that shows a fetal scalp pH of less than 7.2.

In the current study, ante-partum fetal distress was found to develop in (23.9%) women of GDM and 21.6% women in PDM. Our obtained results show good agreement with the study Akhter *et al.* (2012) who reported that 23.25% pregnant diabetic women admitted to Dhaka Medical College Hospital developed fetal distress.

Polyhydramnios i.e**.** excessive amounts of amniotic fluid throughout pregnancy - is somewhat less common. Published data showed incidence of polyhydramnios was 20% (Adeed 1999). Mahmuda (2005) in a clinical study in Dhaka Medical College Hospital, Dhaka, Bangladesh reported incidence of polyhydramnios to be 6.97%. Dutta & Kulenthran (1998) working on outcome of pregnancy with diabetes mellitus in Kualalumpur, Malaysia reported 7.2% incidence of polyhydramnios.

In the present study, the prevalence rate of polyhydramnios was comparatively higher (41.2%) than any other previous studies. Aside from the discomfort of an overly distended belly, polyhydramnios rarely has harmful consequences. However, it is a sign that the diabetes has not been under optimal control. The fluid builds up because the baby is urinating large quantities due to elevated glucose levels. Polyhydramnios in diabetes is probably related to fetal polyuria due to fetal hyperglycemia. Polyhydramnios complicating diabetic pregnancies is associated with higher perinatal mortality and morbidity rates than diabetics with normal amniotic fluid (Pikee *et al.* 2011).

Women with diabetes type 1 DM, type 2 DM, or GDM are more likely to suffer one or more complications of labor and/or delivery such as cesarean section,

preterm delivery or induction of labor than are women who do not have diabetes (Blatman & Barss 1995, Dunne *et al.* 2003, Harvard Heath Publishers 2002, Jensen *et al.* 2000, Svare *et al.* 2001, Thoenen *et al.* 2001, Wylie *et al.* 2002). Blatman and Barss (1995) reported that maternal diabetes by itself is not a certain indication for cesarean section, however, macrosomia and large for gestational infants along with the associated problem of shoulder dystocia are indications for cesarean section. Women with GDM (Sermer *et al.* 1998, Langer *et al.* 2005a) and Type 1 diabetes (El-Sayed and Lyell 2001) have an increased risk of cesarean section delivery. Fetuses of diabetic women are frequently macrosomic (Bradley *et al.* 1988, Schwartz and Teramo 2000), which increases the rate of cesarean section deliveries.

The rate of Caesarean delivery in Bangladesh is not known but thought to have increased markedly in recent years. A study conducted by Abdul Latif Bhuiya (2009) in a referral hospital in Dhaka, Bangladesh reported that among study participants 1509 (55.6%) had a history of normal delivery and 1150 (42.4%) underwent Caesarean sections.

The overall incidence of delivery of baby by caesarean operation in the present study was significantly higher. The rate of cesarean delivery was 72.1% in diabetic pregnancies and only 10.7% baby were born by vaginal delivery (Table 6 (a) page 65 in Results and observation chapter 5 of this dissertation).

Our above finding of higher delivery rate of babies by caesarean operation of is supported by the increased prevalence of caesarean section in GDM in a recent study done in Bangladesh (Khatun *et al.* 2005). The above results are also in good harmony with the finding of some other studies in Srilanka (Siribaddana *et al.* 1998) in India by Strehlow and Mestman (2005) and in Pakistan by Rizvi *et al.* (1992).

In women with type 1 DM 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. These anomalies can be prevented by tight control of maternal glycemia before gestation and during the early weeks of pregnancy.

Pregnancy outcomes in diabetic women have improved dramatically over years with temporal trends showing a decline in rates of spontaneous abortions in diabetic mothers (Greene 1999). However, diabetic mothers still carry a higher risk for fetal morbidity and mortality. A recent prospective study has shown that inspite of planned pregnancies with good glycemic control, diabetic mothers still had higher rates of maternal and perinatal complications (Evers *et al.* 2004b).

In the presents study, the cumulative rate of abortion among pregnant diabetic women (Both GDM and PDM) was calculated to be 10.7% as shown in Table 6 (a) of Results and Observation chapter 5 page 65 of this dissertation. In the context of available modern management strategies in diabetic pregnancy Now-a-days our estimated abortion rate of 10.7% in pregnant diabetic women is quite higher. However, in a previous study in Bangladesh conducted by Sayeed *et al.* (2005) the abortion rate in diabetic pregnant women was reported to be 19.9%.

The proportion of women who underwent abortions in our study was 14 (18.91%) in PGDM and 6 (5.03%) in GDM i.e. the rate of abortion was significantly higher in the PGDM women as compared to GDM women. Abortion rate was significantly higher in PDM mothers than the GDM as per our study. This finding is similar to the study of Shefali *et al.* (2006) in neighboring India who found that proportion of women who underwent abortions was 10.1% in PGDM and 2.7% in

GDM. However, the difference between PGDM and GDM in their study was statistically significant [p = 0.04].

From earlier literature review it is established that UTI and Vulva vaginal candidiasis is a common infection observed in diabetic patients. DM alters the genitourinary system where UTI can be a cause of severe complications ranging from dysuria (pain or burning sensation during Urination) organ damage and sometimes even death due to complicated UTI (pyeleonephritis). Again also pregnancy is another risk factor for developing UTI.

As expected, in the present study, the incidence of Vulva and vaginal candidiasis was found to be almost very similar in pregnant women having GDM and PDM; was 41.6% and 40.5%, respectively as shown in Table 6 (a) page 65 in Results and observation Chapter 5 of this dissertation. Similarly, the incidence of urinary tract infection (UTI) was found to be almost same in pregnant women having GDM and PDM; 41.6% and 40.5%, respectively.

From literature it is an established fact that maternal hyperglycemia often causes intrauterine death in women with GDM and PDM who have poor glycemic control. Pikee Saxena *et al.* (2011) in India reported three cases of intrauterine deaths (IUD) in their study that all had poor glycemic control and were not on insulin therapy at the time of admission.

In the present study, Twelve (12) intrauterine deaths in diabetic pregnant women's were observed which accounted for 6.4% incidence of IUD of the study population. Careful examination of the patient's diabetic book and hospital medical records revealed that – nearly all of them had records of poor or extremely bad glycemic control and were not under insulin therapy before and during the time of admission.

Congenital malformations are common among infants born to diabetic mothers (American Diabetes Association 2002, Dunne *et al.* 2003, Harvard Health Publications 2002, Langer and Conway 2000). Major fetal malformations are often associated with poor glycemic control before or during early pregnancy (Mills *et al.* 1979, Kitzmiller *et al.* 1996). Fetal malformations represent one of the main causes of increased perinatal mortality among pregnant women with pre-gestational diabetes (Gabbe and Graves 2003). The prevalence of major congenital malformations in Type 1 and Type 2 diabetic pregnancies is 2–4 times higher than in the general population (Macintosh *et al.* 2006, Yang *et al.* 2006).

In our study, the cumulative prevalence rate (Both PDM and GDM) of congenital malformation was found to be 2.7% while prevalence in pregnant women with PDM and GDM were 3 (4.1%) and 2 (1.7%), respectively which is quite higher. This finding of ours shows good harmony with an earlier study of Begum *et al.* (2004) reporting that the frequency of congenital malformations and low birth weight also appeared to be higher in Bangladesh.

Fetal macrosomia is defined in many different ways in the literature, e.g. as an absolute birth-weight, over 4000 g or over 4500 g, or as a relative birth-weight, either above the 90th percentile or above +2 SD of the mean (97.7th percentile) of a standard population. Fetal macrosomia is one of the main perinatal complications in all types of diabetic pregnancy, especially in women with poor glycemic control (Gabbe and Graves 2003). It has been suggested that all infants of women with Type 1 diabetes are actually macrosomic (Bradley *et al.* 1988).

Ozumba *et al.* (2004) in their study on diabetes mellitus in pregnancy in an African population found that in women with gestational diabetes the incidence rate of fetal macrosomia was more than 28.7% and resulted in high (36%) cesarean

section operation. Very recently in neighboring India, Pikee Saxena *et al*. (2011) reported that macrosomia was diagnosed in one-in-five diabetic pregnancies. Gasim (2012) in his study on Maternal and Perinatal Outcomes in 220 Saudi women also reported a high incidence (58%) of macrosomic babies. Barakat *et al.* (2010) in Oman also reported 48% incidence of large i.e. macrosomic babies in diabetic pregnancy which resulted in higher rates of Cesarean delivery.

In the current study, the prevalence of 'large babies' i.e. Macrosomic babies was much higher (70.3%) in pregnant women having PDM as compared to that of GDM (26.5%) groups. Birth of large baby was significantly higher in women having PDM group than GDM group.

CHAPTER-7

CONCLUSION AND RECOMMENDATIONS

7. CONCLUSION AND RECOMMENDATIONS

Conclusion:

The observation and results of the present study clearly indicated that most of the patients had no planning for pregnancy with diabetes – including gestational diabetes –whose blood sugar was controlled (by diet or insulin). The results of outcome of the pregnant patients with controlled blood sugar level were better than those whose blood sugar were not controlled. Quite a number of the babies were macrosomic. So the incidences of caesarean section were higher among the study population i.e. diabetic pregnant women. If we can grow more awareness about diabetes among pregnant patients then, we can expect better pregnancy outcome.

7.1. Recommendations

1. Diagnosis and treatment of GDM are to be put into national antenatal check up program so that 5-8% of the risk pregnancy from GDM can be identified. Thus measures are to be taken to avoid preventable consequence to the mother and fetus/newborn.

2. Pregnant women at their first antenatal check up needs to be checked for gestational diabetes.

3. As quite a large number of women were diagnosed early in pregnancy screening of GDM needs to be carried out in early trimester. We suggest that this subgroup of women with gestational diabetes is to be promptly identified. Their situation can be considered equivalent to that of women with pregestational diabetes mellitus and managed as such.

4. A standard treatment guideline including referral instruction is to be prepared and available to the health professional so that they can identify GDM as well as make a birth plan for GDM in pregnancy.

5. Particular attention needs to be given to the women who are diagnosed early in pregnancy as they are more likely to develop hypertension in pregnancy; need insulin treatment and their newborn are prone to develop hypoglycemia. In this regard all health personnel concerned with conducting diabetic delivery are to be trained off on management of hypoglycemia in newborn to prevent grave and undesired effect of hypoglycemia in newborn.

6. Women who are treated with insulin need particular attention as they may lead to birth of relatively larger baby if their blood glucose was not controlled in a proper way.

7. Women with GDM should be followed after delivery in order to monitor hyperglycemic status and so advised accordingly.

CHAPTER-8

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8. REFERENCES

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CHAPTER-9

APPENDICES

9.0. APPENDICES

Appendix-I

SAMPLE INFORMED PATIENTCONSENT FORM:

RAJSHAHI MEDICAL COLLEGE & HOSPITAL
RAJSHAHI, BANGLADESH

RESEARCH INFORMED CONSENT FORM

TITLE OF THE RESEARCH PROJECT: PREGNANCY OUTCOME OF DIABETIC MOTHERS
ATTENDING A TERTIARY HOSPITAL IN RAJSHAHI

SUPERVISOR'S NAME: **PROFESSOR DR. MD ANWAR-UL ISLAM**

INVESTIGATOR: **SHAMIMA AKHTER HOSSAIN (**MBBS)

PURPOSE OF RESEARCH:
I have been explained about the reason for doing the study and selecting me as a subject of the study. This study is for the better understanding of pregnancy outcome of Diabetic mothers attending Rajshahi Medical College Hospital, Rajshahi, Bnagladesh..

RISK AND DISCOMFORTS:
I understand that I may experience discomfort during my examination or during my treatment. This is mainly the result of my condition and the procedure of the study is not expected to exaggerate these feeling which are associated with the usual course of treatment.

BENEFITS:
I understand that my participation in the study will have no direct benefits to me other than potential benefit of treatment.

ALTERNATIVES:
Even if you decline the participation in the study, you will get the routine line of management.

CONFIDENTIALITY:

I understand medical information produced by this study will become part of my hospital record and will be subject to the confidentiality and privacy regulations of the said hospital.

If the data are used for publication in the medical literature for teaching purposes, no names will be used, and other identifiers, such as photographs and audio or videotapes, will be used only with my special written permission. I understand I may see the photographs and videotapes and hear the audio tapes before giving this permission. For this purpose every effort will be made by publishing person to contact me in the address furnished by me through postal communication. If no response is received within a reasonable time, all the identities will be removed from the photographs and case report before being submitted for publication.

REQUEST FOR MORE INFORMATION:

I understand that, I may ask more questions about the study at any time. Researcher is available to answer my questions or concern in this research period. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or my withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that researcher may terminate my participation in the study at any time after I have been explained the reasons for doing so and has been helped to arrange for my continued care by my own physician, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study. If such injury were reported promptly, then medical treatment would be available to me, but no further compensation would be provided. I understand that my agreement to participate in the study I am not waiving any of my legal rights.

I have explained to _____

(Patient/Guardian Name)

The purpose of research, procedures required the possible risk and benefits to the best of my ability.

  Investigator   **Date:**   /   /

     I have been explained clearly about the reason for doing this study, reason for selecting me as a subject in the study. I also have been explained about the risks, benefits and confidentiality of the study. Alternative procedures that might be used in the treatment of my disease also explained to me. I am willing to attend any follow up requested to me at a future date. Freedom is given to me for the participation in the study or discontinues participation at any time without prejudice.

     All the above explained in detail to me clearly in my own language. I am giving consent voluntarily for inclusion of me in the study as a subject.

Participant/Guardian

Appendix - II (Questionnaire)

Date of interview:	Hospital	RMCH:	Others:	Place of Interview: ....
Questionnaire checked by: .... Date:				

Name:	Contact Address: ....

Demographic Characteristics

Age	(in years)	Record	Interview	Clinical investigation
Ht	(m)			
Wt	(kg)			
Highest level of education attained	Years of Schooling			
Main occupation	House wife			
	Others			
Monthly expenditure	Local currency (BDT)			

Family and Obstetric History

Diabetes in the family(first, second and third degree relation)	Yes			
	No			
	Unknown			
EDD				
LMP				
Previous history of GDM	Yes			
	No			
	Unknown			
	Not applicable			
Previous bad obstetric history	Miscarriage			
	Still born			
	Premature Birth			
	Gravida			
	Not applicable			
Time of diagnonsis of GDM	Weeks of gestation			
	Not diagnosed			
	Not applicable			
Main treatment til delivery	Diet and exercise			
	Insulin			
	No treatment			
Blood sugar level On diagnosis	Mmol/L			
Range of blood glucose level during pregnancy	Mmol/l			
RBS During Pregnancy				
RBS within 24 hours before delivery				
Hypertension	yes			
	No			
Hb mg/dl				

Pregnancy Outcome

Gestation at delivery	<32 wks			
	32-36 wks			
	37-39 wks			
	Full term			
	Post dated			
	Post term			
Mode of delivery	Normal			
	Vaginal			
	Assisted			
	Caesarean			
Outcome of delivery	Live birth			
	Live birth with injury			
	Live birth with injury			
	Still born			
	IUD			

Records from Antenatal Checkup card:

Newborn Status:

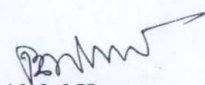# Appendix-III

Ethical Committee (EC)
Rajshahi Medical College, Rajshahi-6000
Bangladesh

To

Dr Shamima Akhtar Hossain   24.05.2010
Medical Officer
Model Family Planning Clinic
Rajshahi Medical College Hospital
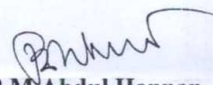
A protocol is submitted by Dr. Shamima Akhtar Hossain entitled **" Pregnancy outcome of diabetic mothers attending a tertiary hospital in Rajshahi "** supervised by Prof. Dr. Md. Anwar-ul-Islam, Professor of Pharmacy, University of Rajshahi and Professor A R M Saifuddin Ekram, Professor of Medicine, Rajshahi Medical College. The Ethical Committee (EC) of Rajshahi Medical College has gone through the protocol thoroughly and after careful scrutiny, the committee has come to the decision that the work would not be harmful to the patients. So, the committee is satisfied to grant permission of the stated work as per protocol.

Prof. A B M Abdul Hannan
Principal & Chairman
Ethical Committee (EC)
Rajshahi Medical College

Copy forwarded to :

1. Prof. Dr. Md. Anwar-ul-Islam, Professor of Pharmacy
   University of Rajshahi - Supervisor.

2. Professor A R M Saifuddin Ekram, Professor of Medicine
   Rajshahi Medical College - Co-Supervisor.

3. Office copy.

Prof. A B M Abdul Hannan
Principal & Chairman
Ethical Committee (EC)
Rajshahi Medical College