CHAPTER 1

INTRODUCTION

Diabetes is a chronic disease that occurs due to high sugar levels in the blood. Type 1 and Type 2 diabetes occur in a large number of people. World health Organization (WHO) has reported in year 2000 that about 172 million people around the world are suffering from diabetes and has estimated the numbers to increase in number to 367 million in forthcoming years. India has been reported as the country with the maximum diabetic patients.

Glucose is the source of energy for the body and enters the bloodstream from the digested food. The glucose then has to be taken up from the blood so as to enter various organs, where it will be used as fuel. The uptake of glucose is mediated by the hormone insulin and when the uptake is hampered it leads to increase in glucose concentration in the blood. This condition of chronic high sugar level in blood is known as diabetes.

1.1 Characteristic symptoms

- Thirst,
- Polyuria,
- Tiredness
- Polyphagia
- Blurring of vision, and
- Weight loss.

In its most severe condition it develops into

- Ketoacidosis
- Stupor,
- Non ketotic hyper osmolar state,
- Coma.

The long–term complications of Diabetes Mellitus are

- Diabetic retinopathy
Diabetic nephropathy

Diabetic neuropathy

People with long term diabetes are highly prone to cardiovascular and cerebrovascular disease.

1.2 Classification

The first widely accepted classification of diabetes mellitus was published by WHO in 1980 and, in modified form, in 1985. As per 1980 and 1985 classifications of diabetes mellitus and allied categories of glucose intolerance includes clinical classes and two statistical risk classes.

The 1980 Expert Committee proposed two major classes of diabetes mellitus and named them, IDDM or Type 1, and NIDDM or Type 2. In the 1985 Study Group report the terms Type 1 and Type 2 were omitted, but the classes IDDM and NIDDM were retained, and a class of Malnutrition–related Diabetes Mellitus (MRDM) was introduced.


The 1985 classification was widely accepted and is used internationally. A compromise between clinical and aetiological classification was represented and allowed classification of individual subjects and patients in a clinically useful manner even when the specific cause or aetiology was unknown. The recommended classification includes both staging of diabetes mellitus based on clinical descriptive criteria and a complementary aetiological classification.

The new classification contains various stages which reflects the degrees of hyperglycaemia in individual subjects with any of the disease processes which may lead to diabetes mellitus.

Diabetes mellitus can be categorized according to

(i) Clinical classification in which glycaemia may change over time depending on the extent of the underlying disease processes. The
(i) The disease process may be present but may not have progressed far enough to cause hyperglycaemia.

(ii) The aetiological classification reflects the fact that the defect or process which may lead to diabetes may be identifiable at any stage in the development of diabetes, even at the stage of normoglycaemia.

Adequate glycaemic control can be achieved with weight reduction, exercise and/or oral agents. These individuals, therefore, do not require insulin and may even revert to IGT or normoglycaemia. Other individuals require insulin for adequate glycaemic control but can survive without it. These individuals, by definition, have some residual insulin secretion. Individuals with extensive beta–cell destruction, and therefore no residual insulin secretion, require insulin for survival.

The aetiological type named Type 1 encompasses the majority of cases which are primarily due to pancreatic islet beta–cell destruction and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta–cell destruction and the mechanism is through the damage of the cell by cytokine mediated induction of intracellular oxidizing agents. The oxidizing agents include free radicals which have unpaired electrons, such as superoxide radicals (O$_2^-$), alkoxyl (RO$^.$) and peroxyl radicals (ROO$^.$), Hydrogen peroxide (H$_2$O$_2$) and lipid peroxides (LOOH).

The Type 2 Diabetes Mellitus (DM) includes the common major form of diabetes which results from defect(s) in insulin secretion with a major contribution from insulin resistance. It has been argued that a lean phenotype of Type 2 diabetes mellitus in adults found in the Indian sub–continent may be very distinct from the more characteristic form of Type 2 found in Caucasians.

Diabetes mellitus seen in undernourished populations and it appears that malnutrition may influence the expression of several types of diabetes, the evidence that diabetes can be caused by malnutrition or protein deficiency per se is not convincing.

Therefore, it is recommended that the class “Malnutrition–related diabetes” (MRDM) be deleted. The former subtype of MRDM, Protein– deficient Pancreatic Diabetes (PDPD or PDDM), may be considered as a malnutrition modulated or modified form of diabetes mellitus for which more studies are needed. The other former subtype of MRDM, Fibrocalculous Pancreatic Diabetes (FCPD), is now classified as a disease of
the exocrine pancreas, fibrocalculouspancreatopathy, which may lead to diabetes mellitus.

The class “Impaired Glucose Tolerance” is now classified as a stage of impaired glucose regulation since it can be observed in any hyperglycaemic disorder, and is itself not diabetes. A clinical stage of Impaired Fasting Glycaemia has been introduced to classify individuals who have fasting glucose values above the normal range, but below those diagnostic of diabetes.

The incidence of diabetes has also increased dramatically in women of reproductive age. In USA, the rate of diabetes has increased by 70% in women aged 30–39 years over the past decade. It was estimated that 12.6million women have diabetes, and of these 90–95% have type 2 diabetes. Death rates for women aged 25–44 years with diabetes are 3 times more than that for women without diabetes.

The magnitude of the reported risk varies widely it is under how much of the variation is explained by variations in ethnicity, length of follow up, selection criteria, and tests for GDM and type 2 Diabetes mellitus (DM) is a disease that prevails all over the world. Its prevalence rates differ from country to country (Groop, 1999). Khan and Ahmad (1993) have reported 1.49% prevalence of diabetes in Northwest Frontier Province and Pakistan. Type-2 diabetes is a chronic disease characterized by a disorder of the glucose metabolism associated with a reduced ability of tissues to respond to insulin.

The resulting chronic hyperglycemia damages blood vessels and nerve cells throughout the body, producing microvascular diseases such as retinopathy, neuropathy, and nephropathy. Moreover, the risk for cardiovascular disease is considerably elevated in patients with type-2 diabetes compared to the general population. Type-2 diabetes represents a major public health problem that causes high economic costs in industrialized countries.

One of the clinical research suggests that the homeostasis of trace elements can be disrupted by diabetes mellitus (Zargar et al., 2002). Conversely, research also suggests that early imbalances of specific elements may play an important role in upsetting normal glucose and insulin metabolism. With regard to essential trace elements, the main clinical
interest and the majority of publications focus on deficiencies of a single element or certain combinations of elements.

1.3 Gestational Diabetes mellitus

Gestational Diabetes is retained but now encompasses the groups formerly classified as gestational Impaired Glucose Tolerance (GIGT) and Gestational Diabetes Mellitus (GDM). GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for the treatment and whether or not the condition persists after pregnancy.

GDM is a form of diabetes affecting only pregnant women. If a pregnant woman develops diabetes for the first time during pregnancy, the condition is termed as gestational diabetes mellitus.

GDM occurs in pregnant women who need 2–3 times more insulin than normal and the body is unable to produce the needed insulin. If gestational diabetes is not cared properly, it may result in problems such as miscarriage or a large baby.

GDM occurs in nearly 5 percent pregnancies. A total of 200,000 cases of gestational diabetes mellitus are reported every year. A majority of women suffering from gestational diabetes give birth to babies who are healthy. This is true when such women maintain appropriate bloodsugar levels, consume a healthy diet, exercise adequately, and maintain a proper weight.

GDM affects at least 7 percent and possibly as many as 18 percent of pregnancies in the United States. Using new diagnostic criteria, an international, multicenter study of gestational diabetes found that 18 percent of the pregnancies were affected by gestational diabetes (Coustan et al., 2010).

As in Type 2 diabetes, GDM is associated with both insulin resistance and impaired insulin secretion (Ryan et al., 1985; Catalano et al. 1993; Kuhl, 1991). This is especially true in high-risk populations in which Type 2 diabetes occurs at an early age (King et al., 1998).

GDM has not only associated with acute risk for complications of pregnancy but also long-term disease risks for both mother and baby. Perinatal morbidity includes hyperinsulinaemia, macrosomia, hypoglycaemia, hyperbilirubinaemia, and respiratory
distress syndrome which in turn may generate subsequent complications. Longer-term morbidity for the offspring includes obesity and diabetes independent of genetic factors (Van Assche et al., 1992; Van Assche et al., 1991a; Van Assche et al., 1991b; Van Assche et al., 2001). GDM in the mother is associated with increased risk of overt diabetes later in life. A higher risk of developing metabolic and cardiovascular disease has been reported for women who develop GDM during pregnancy.

Dooley et al. (1991) demonstrated that ethnicity as well as maternal age and degree of obesity must be taken into an account in comparing the prevalence of GDM in different populations. Their adjusted relative risk for GDM was higher in Black and Hispanic women than in White women. Furthermore, ethnicity had a significant independent effect on birth weight, with maternal body weight as a significant co-variate. These findings were supported by a more recent study showing that Asian woman were more likely to have GDM than White woman (Gunton et al., 2001).

Several mechanisms for the progression to chronic insulin resistance in GDM have been proposed: abnormal sub-cellular localization of glucose transporter protein-4 (GLUT4) (Garvey et al., 1993), alterations in the insulin-signaling pathway (Catalano et al., 2002; Shao et al., 2000), reduced expression of PPARγ (Catalano et al., 2002;), increased expression of the membrane glycoprotein PC-1 (Shao et al., 2000), and reduced insulin-mediated glucose transport (Garvey et al., 1993).

GDM may impart a risk for type 2 diabetes. In addition it was typically identified by the oral glucose tolerance test (OGTT) in non pregnant individuals. Long- term follow-up studies, reviewed by Kim et al. (2002) reveal that most women with GDM do progress to diabetes at some time after the index pregnancy; GDM is therefore considered as a pre-diabetic state because of its high conversion rate to type 2 diabetes (Kjos et al., 1995).

Recent studies demonstrated that an approx. 30 percent reduction in basal rates of muscle mitochondrial ATP synthesis (due to reduced mitochondrial numbers and/or function) in a group of healthy, young, lean, and insulin-resistant offspring of parents with type 2 diabetes (Petersen et al., 2004).
Subjects with GDM have signs of autoimmunity, with insulin autoantibodies and anti-islet cell antibodies, although the prevalence is extremely low (Damm et al., 1994; Catalano et al., 1990). The inheritability of GDM was studied in 100 women with previous GDM 11 years postpartum.

Harder et al. (2001) reported a significantly higher prevalence of Type 2 diabetes in mothers than in fathers of women with GDM, and a significant aggregation of Type 2 diabetes in the maternal-grand maternal line compared with the parental –grandparental line.

An investigation has shown that there is an inherited reduction in the mitochondrial content in skeletal muscle of insulin-resistant pre-diabetic offspring of parents with type 2 diabetes, and this reduction may be responsible for decreased oxidative phosphorylation, decreased lipid oxidation, and lipid accumulation (Peterson et al., 2004; Peterson et al., 2005; Mootha et al., 2003; Patti et al., 2003).

In addition, reduced β-oxidation of free fatty acids (FFAs) may produce a decreased cis-FFA / total FFA ratio over several years. For example, arachidonic acid and other polyunsaturated fatty acids are primarily processed to so-called local hormones, including prostaglandins, thromboxanes, leucotrienes, and other hydroxyeicosanoic acids, whereas saturated FFAs are taken up and stored as triacylglycerols by adipocytes, which in turn release the original saturated FFAs in response to hormone messengers. The fatty acids profile of serum lipids, especially phospholipids, reflects the fatty acid composition of cell membranes (Dougherty et al., 1987).

Thus, long-standing decreases in mitochondrial activity may ultimately contribute to an increase in the percentage of saturated fatty acids or a decrease in the percentage of polyunsaturated fatty acids in membrane phospholipids. This concept is consistent with the results of Min et al. (2004) studied the membrane phospholipid fatty acids in control individuals and women who developed diabetes during pregnancy, because insulin resistance, a characteristic of gestational diabetes, is correlated with the fatty acid profile of the erythrocyte and skeletal muscle cell membrane.

It was found that appreciable reductions in arachidonic acid and docosahexaenoic acid were associated with a substantial increase in saturated fatty acids in erythrocyte
membrane phosphatidyl choline and phosphatidyl ethanolamine of GDM women, compared with control individuals (Min et al., 2004).

Micronutrients have been investigated as potential preventive and therapeutic agents for type 2 diabetes and for common complications of diabetes (Mooradian et al., 1994; Retnam et al., 1981). In particular, diabetes has been shown to be associated with abnormalities in the metabolism of Zinc, Chromium, Copper, Magnesium and Manganese (Walter et al., 1991; El–Yazige et al., 1991).

The effect of diabetic pregnancy on fuel metabolism is one of underutilization of exogenous fuel in the fed state and over production from endogenous source in the fasted state (hyper-accelerated starvation). The first sign of pregnancy in a diabetic (particularly in type 1 diabetes) as early as the first week of gestation and even before nausea or vomiting sets in may be early morning fasting ketonuria. The minor proportion of women lack the B-cell reserve to maintain euglycemia during pregnancy, and develop impaired glucose tolerance (IGT). They have significantly lower insulin responses at 30 and 60 min after oral glucose load compared with glucose-tolerant controls (Nicholls et al., 1995), while insulin sensitivity is similarly reduced in the second trimester (Nicholls et al., 1995; Kuhl et al., 1991).

The G-peptide response to intravenous glucagon is also significantly reduced in women with IGT in pregnancy (Jacobs et al., 1994), while serum low insulin concentrations are increased. The need for insulin treatment in gestational diabetes mellitus (GDM) is associated with raised circulating pro-insulin levels, implying that greater B-cell dysfunction leads to glucose intolerance (Nicholls et al., 1994).

Impaired Glucose Tolerance (IGT) in pregnancy can vary in severity but even mild degrees are accompanied by other disturbances, including abnormalities of glycerol and non-esterified fatty acid metabolism (Metzger et al., 1980). Women with a previous history of GDM who become glucose tolerant postpartum show continuing B-cell dysfunction, characterized by impaired insulin release in response to oral glucose, and impaired lipolysis despite normal insulin sensitivity (Chan et al., 1992; Dornhorst et al., 1990). Carbohydrate intolerance deteriorates early in pregnancy diabetic pregnant women, in parallel with the physiological decrease in insulin sensitivity.
1.3.1 Risk Factors

- Immediately after pregnancy 5 to 10 percent of women with GDM are found to have diabetes, usually type 2.
- Women with a history of GDM have a 35 to 60 percent chance if developing diabetes, in the next 10 to 20 years.
- Non-Caucasian and Hispanic women with a history of GDM appear to be at particularly high risk for developing diabetes (England et al., 2009).
- Children born from pregnancies affected by GDM may be at increased risk for obesity and type 2 diabetes compared to other children (Hillier et al., 2007, Silverman et al., 1995).

1.3.2 Screening and Diagnosis

Kjos and Buchanan (1999) and Hanna and Peters (2002) evaluated the screening and diagnosis protocol for GDM. The final diagnosis of GDM is based on the results of the OGTT. There is no agreement on the performance or interpretation of the OGTT in pregnant women, but two or more pathological glucose values are required for a diagnosis of GDM. In 1979, the National Diabetes Data Group recommend a 3-h, 100-g test using predefined criteria to quantify the risk of subsequent diabetes in the pregnant mother (O’Sullivan et al., 1964).

The fourth international Workshop and Conference on Gestational Diabetes mellitus (Metzger et al., 1998), the World Health Organization (WHO Diabetes mellitus, 1985), and the European Diabetic Pregnancy Study Group (Lind and Phillips, 1991) proposed different criteria for interpreting the results of the 100-g 3 hour OGTT or 75-g 2 hour OGTT.

According to the American College of Obstetricians and Gynecologists (American College of Obstetricians and Gynecologists, 2001), there is insufficient evidence to determine the optimal antepartum testing regimen for women with GDM with relatively normal glucose levels on diet therapy and no other risk factors and either the plasma or serum glucose level established by (Carpenter and Coustan, 1982) or the
plasma level designated by the (National Diabetes Data Group, 1979) conversions are appropriate for use in the diagnosis of GDM.

Nord et al. (1995) evaluated the accuracy of diagnosing GDM by a 2-h blood glucose value of nearly 9.0 mmol/l in the 75-g OGTT. They showed that using the 75-g 2-h OGTT with a blood glucose limit of 9.0 mmol/l instead of 8.0 mmol/l to diagnose GDM during pregnancy (Hanna et al., 2002).

1.3.3 Complications:

- The body of the baby is abnormally large, a condition known as macrosomia. Such babies are more likely to be delivered through caesarian section rather than vaginal birth.
- The baby may have low blood sugar levels, a condition known as hypoglycemia.
- If the baby still lacks glucose in the blood, a tube may be used to transport glucose.
- The skin of the baby gets a yellowish blue. The white region of the eye will also change color. These are symptoms of jaundice. This condition can be treated effectively and is not serious in nature.
- The newly born baby may experience discomfort while breathing. Oxygen may have to be supplied and this condition is known as Respiratory Distress Syndrome. The baby may possess low levels of minerals may be administered to the baby in such situations.

1.3.4 Adverse consequences of GDM

GDM can have deleterious consequences for the mother as well as the offspring. These consequences may be observed at the time of delivery, which will be referred as immediate consequences or they may appear later in life, which will be referred to as long-term consequences.

Women with uncontrolled plasma glucose levels during pregnancy have immediate adverse consequences, in the form of obstetric complications, such as pre-eclampsia, preterm deliveries, still births, caesarian sections and insulin treatment (Carr, 1998; Xiong et al., 2001).
In Asian Indian women diagnosed with GDM up to 8.2% preterm deliveries have been reported (Shefali et al., 2006). Moreover, in another Indian study one in six women who were diagnosed as having GDM continued to have diabetes even after the pregnancy was over (Kale et al., 2004).

During pregnancy, the women develop the changes in their fasting lipid level, blood pressure, large and small vessel function which causes hypertensive complications such as pregnancy induced hypertension and eclampsia. Metabolic syndrome is a condition which involves central obesity along with any two of the following factors such as raised triglyceride levels, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose. During pregnancy there is development of insulin resistance causing a transient increase in lipid levels, in a short a metabolic syndrome (Sattar et al., 2002).

At birth, offspring of women with GDM are at an increased risk of developing congenital malformations, macrosomia, respiratory distress and hyper-bilirubinaemia (Carr, 1998). Several studies have shown the association of GDM with congenital malformations such as cardiac defects, hypospadias, polydactyl and central nervous system defects (Schaefer et al., 2000).

It has been reported that 20% - 30% of births in women with GDM are complicated with macrosomia due to high values of amino – acids, glucose and lipid levels in the blood. Also increased insulin secretions in the pancreas of the foetus causes macrosomia (Carpenter et al., 2001). Neonates of women with GDM had greater than average head, chest and abdominal measurements compared to neonates of women without GDM (Hill et al., 2005).

Women with a history of GDM are at a greater risk of developing various chronic diseases later in life such as Diabetes Mellitus (DM), metabolic syndrome and cardiovascular disease compared to women who did not develop GDM in a pregnancy. (Lauenborg et al., 2004; Lauenborg et al., 2005).

The women with GDM progressed to type 2 DM, when women were followed up from 6 weeks post partum to 28 years post partum. Furthermore it was observed that the highest increase in the development of type 2DM took place in the first five years after the index pregnancy and then increased slowly (Kim et al., 2002).
The cumulative incidence for type 2 DM and abnormal glucose tolerance was 13.8% and 42.2% respectively in women who had GDM and 0 and 2.8% respectively in women without GDM (Albareda et al., 2003).

Reported progression rate for type 2 DM in women with GDM indicate wide variation and inconsistencies. There is controversy about the role of ethnicity in the development of type 2 DM in women with GDM. In a recent study in the UK 35% of the Indo – Asians had persistent glucose tolerance 3 months post partum compared with 7% of Caucasians and 5% of the Afro – Carribbean subjects (Sinha et al., 2003). Women with GDM are also at a greater risk of developing metabolic syndrome and coronary vascular disease later in life.

A cross sectional analysis of data collected on parous women who had participated in the genetics of non-insulin dependent diabetes study showed that women with prior GDM were more likely to the metabolic syndrome compared to women who did not had GDM. They also had a higher prevalence of CVD that occurred at a younger age and was independent of metabolic syndrome and type 2 DM (Carr et al., 2006). Furthermore, the vascular changes which developed during GDM led to vascular diseases in women during later years of life (Carr, 1998).

Most studies done on offspring of GDM mothers have assessed the association of birth weight and in-utero exposure to a diabetic environment with obesity and metabolic syndrome in childhood. Adiposity was assessed by skin fold measures found to higher in offspring of women with GDM compared to offspring of women without GDM (Wright et al., 2009).

In a comparison of offspring of mother with GDM, with those of diabetic fathers and offspring of parents who did not have diabetes in India, the BMI of offspring of mothers with GDM was significantly higher than that of the other two groups (Krishnaveni et al., 2005). In another investigation a positive dose response relationship was observed between degrees of maternal hyperglycaemia during pregnancy adjusted for birth weight, maternal weight gain, age, parity, ethnicity and obesity in children at 5 to 7 years of age (Hiller et al., 2007).
There are several plausible biological mechanisms through which GDM increases the risk of offspring to have obesity or DM. In the early phase of intrauterine development of the foetus in women with GDM, there is increased vulnerability of having a defect in organogenesis and physiologic function development when exposed to increased levels of metabolic substrates, such as amino acids, glucose and fatty acids (Van et al., 2001; Thapar et al., 2007). It has been estimated that 5-7 year old children of mothers with GDM have increased prevalence of obesity and metabolic syndrome, especially when there are heavier at birth (Boney et al., 2005).

In the case of women with diabetes complications, during pregnancy there are risks that diabetic retinopathy and diabetic nephropathy could deteriorate and ketoacidosis could increase.

Obstetric complications that occur are increased incidence of pregnancy-induced hypertension, caesarean section, bradycardia due to macrosomia and induction of childbirth

Perinatal complications exhibited are increased incidence of macrosomia, delayed intrauterine fetal development, neonatal complications. In the case of GDM, there is an increased risk of the mother developing type 2 diabetes in future.

1.3.5 Management of GDM

The importance of educating women with GDM (and their partners) about the condition and its management cannot be overemphasized.

The compliance with the treatment plan depends on the patient’s understanding of:

- Diet and exercise
- Monitoring of blood glucose
- Self administration of insulin
- Identification and treatment of hypoglycemia
- Physical activity
- Reduce stress and anxiety
1.3.5.1 GDM management during labor and delivery

Timing and mode of delivery

In the case of diabetes or GDM alone, caesarean section is not indicated, but at the present time it cannot be said that there is sufficient data to support this. For example, it has been reported that in the case of a GDM patient undergoing insulin therapy where fetal development is thought to be within the normal range.

There is no difference in the caesarean section rate between women for whom labor is induced at 38 weeks and those for whom labor is not induced. Moreover, it has also been reported that there is no difference in the incidence of macrosomia or caesarean section between insulin-treated GDM patients for whom labor is induced at 38–39 weeks and insulin treated GDM patients who electively waited for labor and childbirth to take their natural course. Although in general the rate of caesarean section for GDM patients is high, there are some reports that this is due to the concern of physicians about shoulder dystocia occurring as the result of macrosomia, which has a high rate of frequency amongst GDM patients.

However, much of the data is from the United States, and the average birth weight of infants born in the United States is higher than that in Japan. Thus it is thought to be impossible to use overseas data as the Japanese standard from the standpoint of infant birth weight.

So far, in the case that the GDM patient has good blood glucose control and fetal development is thought to be within the normal range, as a general rule it is considered that the pregnancies of GDM patients may be managed in the same manner as those of normal glucose-tolerant women. In the case that birth weight is estimated at 4,000g or higher, an elective caesarean section is considered. However, in the case that the patient has poor blood glucose control, induced delivery at 38 weeks onward is considered.

When carrying out insulin therapy, special care is needed as the amount of insulin required during pregnancy, during delivery, and after birth differs tremendously. Thus, insulin requirements at the end of pregnancy increase by approximately two-fold.

During first-stage labor the required amount decreases, while in second-stage labor it increases slightly and after birth decreases rapidly. Accordingly, attention needs
to be paid to such changes in required insulin amounts during pregnancy and the amount of insulin administered reduces by half following delivery.

In particular, since it becomes difficult for the patient to eat during first stage and second-stage labor, especially careful management of blood glucose levels is necessary in the case that labor and delivery are prolonged.

In many cases at Mie University, at the onset of labor the patient is administered an electrolyte fluid containing 5% glucose at a rate of 100 to 120 ml/hr, then administered insulin intravenously via an infusion pump. Depending on the individual case, blood glucose is measured at intervals of 1 to 2 hours. Insulin administration begins with a dosage of 0.5 units/hr and the insulin dosing rate is determined based on fluctuations in blood glucose levels.

**Factors that can be ameliorated before and after pregnancy**

In the case of women with diabetes complications and especially in the case that diabetic retinopathy is present the patient needs to undergo evaluation and treatment by an ophthalmologist. For example, if the patient was being treated using photo-coagulation therapy, pregnancy is possible. In addition, it is necessary to educate the patient about points to be careful about with regard to further pregnancies.

Obesity is an important risk factor for GDM, and so prior to pregnancy not only it is necessary for patients to take special care with their lifestyle, especially diet, but it is also vital that women suffering from infertility be checked for glucose intolerance. For women with carbohydrate intolerance as complication of obesity, it is also necessary that the patient make lifestyle improvements after the birth.

**1.3.5.2 Treatment**

In the majority of GDM cases, the frequency of the various complications that may affect mother or child can be controlled with appropriate diagnosis and management. The subjects who received treatment like diet therapy, self-monitoring of blood glucose, insulin therapy have a lower incidence of complications for both the mother and newborn than for subjects receiving no treatment intervention.
1.3.5.3 Self-monitoring of blood glucose

Depending on the degree of hyperglycemic disorder in pregnancy, self-monitoring of blood glucose is carried out by the patient at a frequency of 4 to 7 times per day. As explained above the target blood glucose levels are venous plasmaglucose values of 100mg/dl or lower before meals and of 120mg/dl or lower 2 hours after meals. In the case that these target values cannot be achieved, the diet and insulin therapies described below are implemented. Furthermore, while the patient is hospitalized, regular check ups should be made to ensure that the difference between blood glucose levels obtained through self-monitoring and by laboratory testing is no more than around 10%.

1.3.5.4 Diet therapy

The key strategies for achieving strict control of blood glucose levels are first of all frequent self-monitoring of blood glucose, followed by appropriate diet therapy, which is extremely important. During pregnancy, as pregnant women patients need to consume adequate energy, protein, and minerals.

In Japan, according to the diet therapy recommended by the JSOG Committee on Nutrient and Metabolism Problems in 1985, dietary intake for ideal pregnancy weight is 25–30 kcal/kg +150 kcal for the first half of pregnancy and 25–30 kcal/kg +350 kcal for the second half of pregnancy, with “+150 kcal” and “+350 kcal” the additional calorie intake recommended for pregnant women according to the dietary reference intakes prescribed by the then-Ministry of Health and Welfare.

Under the nutritional guidelines recommended by the Ministry of Health, Labour and Welfare in 2010 - 12 an additional calorie intake of 50 kcal, 250 kcal, 450 kcal is recommended for pregnant women during the first, second, and third trimester, respectively. Thus using these recommendations, it is reasonable to regard the currently recommended calorie intake for pregnant women as 25–30 kcal/kg+50 kcal, 25–30 kcal/kg+250 kcal, and 25–30 kcal/kg+450 kcal for the first, second, and third trimester, respectively.
1.3.5.5 Insulin therapy

In the case that target blood glucose levels cannot be achieved, insulin therapy should be actively implemented. Although there are RCTs indicating that the oral antidiabetic, glyburide, does not affect the fetus but its safety cannot be said to have been established, and so as a rule treatment is changed to insulin therapy.

In the case that a woman becomes pregnant while taking an oral antidiabetic, it is explained to the patient that there is no evidence that oral antidiabetics increase the incidence of congenital malformations. In the case of insulin therapy, due to the need for strict blood glucose control, it is important to keep blood insulin concentrations as close as possible to physiological insulin secretion patterns.

Basal insulin secretion and after-meals insulin secretion, intensive insulin therapy is carried out by means of multiple injections of intermediate-acting and rapid-acting insulin or ultrarapid-acting insulin analog.

The benefits of treating mildly elevated blood glucose are supported by the results of two large randomized controlled trials conducted in Australia and the United States. The vast majority of women (80% to 90%) in these trials were managed solely with meal planning and lifestyle changes. The results showed that women receiving treatment had a reduction in birth weights, lower frequency of large-for-gestational age births, and less preeclampsia compared with women receiving usual care.

Although it is clear that nutrition-based interventions are effective for GDM, there is little evidence to guide decisions about the optimal energy or macronutrient content of diets for women with GDM. The Institute of Medicine (IOM) recommends weight gain of 25 to 35 lbs for normal-weight women 15 to 25 lbs for women who are overweight and 11 to 20 lbs for women who are obese.

Many organizations recommend moderate physical activity, including brisk walking or arm exercises while seated in a chair, as part of the treatment program for women with GDM who are capable of participating.

These recommendations are based on small studies suggesting that exercise lowers fasting and postprandial glucose concentrations and may reduce the number of women with GDM requiring insulin therapy. Although 30 minutes per day of activity is
recommended, there is currently not enough evidence to determine the appropriate duration, frequency, intensity, or type of exercise to perform for optimal outcomes.

Women with GDM who performed self-monitoring of blood glucose (SMBG) showed lower rates of macrosomia compared with women with GDM who did only weekly office testing of blood glucose levels. Most experts recommend conducting SMBG daily upon waking and at 1- or 2-hour intervals after meals.

The goal of GDM treatment is to maintain blood glucose at levels that will minimize risk of adverse perinatal outcomes, but there are no evidence-based cutoffs at which benefits of treatment clearly outweigh harms. Existing consensus recommendations include targets of ≤95 mg/dL for fasting glucose, ≤140 mg/dL for one-hour postprandial measurements, and ≤120 mg/dL for two-hour postprandial measurements.

The use of insulin during pregnancy heavily depends on provider and patient treatment preference and the success of other lifestyle interventions. Diagnosis of GDM may depend on the screening protocols at a particular site which may explain why gestational age was associated.

1.4 Relationship between type II Diabetes mellitus and Gestational Diabetes Mellitus

Detailed studies of women with glucose intolerance, which is first detected during pregnancy, provide 3 types of information regarding the relationship between GDM and type 2 diabetes. First, virtually all women with GDM appear to have a large β-cell defect against a background of chronic and exaggerated resistance to insulin’s ability to stimulate glucose utilization (Buchanan and Xiang, 2005).

Women with GDM have a 17 to 63% risk of Type-2 diabetes within 5-16 years (Hanna and Peters, 2002). Greenberg et al. (1995) in a study of 94 patients with GDM are reported that the most significant predictor of 6-weeks postpartum diabetes was insulin requirement followed by poor glycaemic control. All these factors probably represent the magnitude of the insulin resistance, which is the hallmark of future diabetes and other vascular complications.