The review of literature pertaining to the study entitled, “Gestational Glycemia and its impact on maternal and foetal outcome” is discussed under the following headings:

A. Gestational Diabetes Mellitus (GDM) – An Overview

B. Management strategies of GDM – “Road to Better Glycemic Control”

C. “Pre - Gestational Diabetes mellitus (PGDM) – Scenario in Pregnancy.

D. Outcomes in Gestational Diabetes - “The Essential maternal and foetal surveillance”.

A. GESTATIONAL DIABETES MELLITUS (GDM) – AN OVERVIEW

Glucose intolerance and gestational diabetes mellitus (GDM) result when pancreatic beta cell function cannot adequately compensate the degree of insulin resistance in pregnancy.

Pregnancy induces progressive changes in maternal carbohydrate metabolism. As pregnancy advances insulin resistance and diabetogenic stress due to placental harmones necessitate compensatory increase in insulin secretion. When this compensation is inadequate gestational diabetes develops (Desoyeet al, 2008).

JP Hoet, Belgian researcher, published a study on “Carbohydrate metabolism during pregnancy” and first used the term, “Meta-gestational diabetes” in 1954, which sparked a series of investigations later.

Gestational diabetes was originally defined by O ‘sullivan in a group of pregnant women in Boston as a degree of glucose intolerance greater than two standard deviations from the mean on a 100g oral glucose tolerance test.
Gestational Diabetes mellitus (GDM) is new defined as any degree of glucose intolerance with onset or first recognition during pregnancy. This definition acknowledges the possibility that patients may have previously undiagnosed diabetes mellitus, or may have developed, diabetes coincidentally with pregnancy.

A peep into the past

In earlier days before the discovery of insulin, diabetes in pregnancy was considered a complication of pregnancy, incompatible with life and therefore, pregnancy was not allowed in women with diabetes. The first reference to diabetes in pregnancy is available since 1823 and at that time diabetes was considered as a symptom of pregnancy, and not a serious disease entity (Ghosh, 2010).

In 1882, J Mathews Duncan, and obstetrician from London, first observed a few salient features of diabetes in pregnancy and focused this serious problem to the world. He came to the conclusion from his experience that diabetes may come on during the pregnancy, diabetes may occur only during pregnancy, being absent at other times, diabetes may disappear after pregnancy, recurring some time afterwards, pregnancy can occur during diabetes and pregnancy in diabetes is mostly associated with poor maternal and fetal outcome.

Whitfield Williams, Professor of Obstetrics in John Hopkins, USA concluded from his observations that diabetes may become manifest during pregnancy; either is a serious complication, although the prognosis is not as alarming as is frequently stated. In 1915, Elliott P. Joslin concluded with an optimistic comment. “It is certainly true that with the improvement in the treatment of diabetic patients (strict diet), diabetic women will be less likely to avoid pregnancy (Sullivan, 1961).

Priscilla White - a pioneer worker in the field of pregnancy diabetes and famous for her classification of GDM, became the beacon of hope to many diabetic women. In 1928, she made the spectacular and hopeful statement that “diabetes is no longer a contradiction to pregnancy”, as for diabetic women pregnancy was considered hopeless before insulin. She rightly pointed out that, “the degree of hyperglycemia seemed to be related to pregnancy outcome” and “controlled diabetes is essential to foetal welfare” (Hoet, 1954).
Jorgen Pederson was attracted with the problems of diabetes and pregnancy. He established the first committed centre for pregnancy diabetes, “The Copenhagen Centre for Pregnant Diabetics” in 1945. His aim was to diminish perinatal mortality by strict control of diabetes and special obstetric management. His efforts was widely successful as the perinatal mortality decreased from nearly 40% to 4% during his leadership.

Norbert Freinkel played the most crucial role in establishing GDM as a definite clinical entity. He illustrated that altered metabolism in GDM has both short and long-term impact on the mother, her child and even in subsequent generations. He also distinguished that the implications of metabolic change in GDM and in pre-existing diabetes are different (Sadikot, 2008). His centre - ‘Diabetes in Pregnancy Centre (DPC) conducted the “Prospective long-term follow-up study of offspring of diabetic mothers” and confirmed the hypothesis that intra uterine metabolic insults have long-term harmful effects on the tissues of the offspring.

National diabetes data group (NDDG) (ADA, 2000) gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Women with gestational diabetes are at increased risk of developing type 2 diabetes mellitus after pregnancy, as well as having a higher incidence of preeclampsia and caesarean section, their offspring’s are prone to developing childhood obesity with type 2 diabetes later in life (Seshiah, 2010).

To complement the NDDG classification of diabetes during pregnancy, the White classification named after Priscilla White who pioneered in research on the effect of diabetes types on perinatal outcome, is widely used to assess maternal and foetal risk. Herrera (2004) purports forth that this system separates patients into groups according to the age of onset and the years of duration of the disease as well as the presence or absence of micro and macro vascular changes.

Prevalence
Global Scenario

Worldwide, it is estimated that 70 million women in the reproductive age have diabetes or impaired glucose intolerance which puts them at risk of hyperglycemia
during pregnancy. The prevalence rates of GDM vary from between 3% to 15%, a variation that reflects variable risks related to ethnicity, lifestyle and environment (IDF Atlas, 2011).

The World Health Organization (WHO) has predicted that between 1995 and 2025, there will be a 35% increase in the worldwide prevalence of diabetes. Moreover, women born in Asian Countries display the highest prevalence of Gestational Diabetes mellitus (GDM), with upto 17% of women likely to develop GDM, in comparison to 4% of European and White American women (ADA, 2011). Among ethnic groups in South-Asian Countries, Indian women have the highest frequency of GDM (16.7%) followed by Chinese (15%), Vietnam-born (9.6%) and Australian – born (4.3%) as depicted in Table – A.

Table - A
Prevalence of Gestational diabetes according to ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>GDM Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglo – Celtic</td>
<td>3.0</td>
</tr>
<tr>
<td>Indian</td>
<td>16.7</td>
</tr>
<tr>
<td>Chinese</td>
<td>15</td>
</tr>
<tr>
<td>Arabic</td>
<td>7.3</td>
</tr>
<tr>
<td>Vietnamese</td>
<td>9.6</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Ross (2011)

Geographical variations in the prevalence of GDM in India

Prevalence varies between 1% to 16% depending on the geographical variation and ethnicity and from one region to another in the same country. The prevalence of GDM in India was 16.55% in the urban area and the frequency varied from 12% to 21% in different parts of the country (Seshiah et al, 2011) (Fig - A). The prevalence of GDM was 2% in 1982 which increased to 7.62% in 1991 and doubled to 16.55% in 2002, in a national survey performed. A low prevalence of GDM was observed in Kashmir 4.4% and a high prevalence of 16.55% in the southern part of India. It was observed in a national survey performed in 2002, the frequency of the occurrence of GDM was 16.55% which was closer to the prevalence of 1GT in the child bearing age group of women in India (Zargar et al, 2004). Parallel to the
increased prevalence of 1GT in the general population, the frequency of GDM had also increased.

Fig - A

Prevalence of GDM by age group in India (Seshiah et al, 2011)

In a community based prevalence data under the ‘Diabetes in Pregnancy Awareness and Prevention - DIPAP project where a total of 12,056 of pregnant women were screened in the urban, semi urban and rural areas of Tamilnadu, GDM was detected in 17.8% women in urban, 13.8% in semi urban and 9.9% in rural areas. The overall prevalence was 13.9% and the prevalence of GDM had increased from 16.55% to 17.8% in the urban areas in two years (Balaji et al, 2011).

There is a definite divide between the rural and urban areas in the prevalence, the possible cause for the low prevalence in the rural settings may be due to the less mechanized, agriculture based lift style. With the huge population of reproductive age in India, a significant segment of women with abnormal glucose tolerance during pregnancy needs cognizance.

In a study performed in an antenatal clinic of a government maternity hospital at Chennai, it was found that the prevalence proportion of GDM increased with gravida from 18 per cent in the primigravida to 25.8 per cent for the gravida ≥4 (Moses, 2008).
Risk Factors

Not every woman who becomes pregnant will develop gestational diabetes. However, all pregnant woman of Asian Indian ethnicity have an increased risk of GDM (Wahi et al, 2011). Over and above that risk, when the woman has certain other risk factors, the chances of her developing GDM are higher. The major risk factors for developing GDM are high maternal age, pre – pregnancy weight, pregnancy weight gain, high parity, previous delivery of a macrsonic infant, family history of diabetes, high BMI, Poly CysticOvarian Syndrome (PCOS), maternal GDM, previous obstetric history of still birth, congenital malformations, macrosomia, GDM and caesarean section.

Jang et al (2006) in a cohort study of Korean women found a 2.2% prevalence of GDM. They were older, had higher pregnancy weights, higher BMI, higher parities and higher frequencies of known diabetes in the family.

In India, both undernutrition and overnutrition exist during pregnancy. Fall et al (2008) speculate that the rise in type 2 diabetes in Indian urban populations may have been triggered by mild obesity in mothers, leading to glucose intolerance during pregnancy, macrosomic changes in the foetus and insulin deficiency in adult life. Study by Yagnik et al (2012) attributes high prevalence of type 2 DM and IGT in Indian people may be linked to poor foetal growth. Offspring of women with diabetes during pregnancy are at the higher risk of developing obesity and T2DM at young ages. The effects of maternal diabetes during childhood and subsequent life are a vicious cycle (Fig. B).

Fig - B
The Vicious Cycle of Diabetes in Pregnancy

(Banerjee.S, 2012)

Potential points of intervention are: A – to reduce the effect of the diabetic pregnancy on the offspring; B – to reduce the incidence of obesity and diabetes in
the offspring of the diabetic woman; C-to control the diabetes prior to and during pregnancy to lessen the impact of the diabetes throughout gestation (Vohr and Boney, 2008).

Pre pregnancy BMI, duration and severity of maternal hyperglycemia during pregnancy are most important predictors of the progression to abnormal glucose tolerance in the follow up (Sereday 2003).

**Cord blood Insulin:**

In genetically diabetes prove populations, maternal diabetes during pregnancy increases the risk of their children developing diabetes and obesity (vicious cycle of type 2 diabetes). Fetal hyperinsulinemia at birth acts as a marker of this risk and is characteristic of pregnancy complicated by maternal diabetes and underpins complications such as macrosomia. Davidson et al. (2006) state that exposure of the foetus to maternal diabetes results in characteristic changes in birth weight, adiposity and foetal insulin production. Notably, birth weight, skin fold thickness, insulin propeptides and leptin are significantly increased in our population, not only is offspring of mothers with type 2 diabetes also offspring of mothers with GDM.

The degree of fetal hyperinsulinum reflects the maternal fuel excess being provided to the foetus, and so it is difficult to determine whether maternal hyperglycemia or fetal hyperinsulinism is responsible for the observed abnormalities. There is evidence from human studies by Luo et al. (2010) that the degree of hyperinsulinism during fetal life is related to obesity during childhood. Among the Pima Indians, children who were exposed to abnormal maternal glucose tolerance while in utero had elevated fasting insulin levels at 5 - 9yrs of age compared to children born to mothers with normal glucose tolerance.

The diabetes in Pregnancy center at North Western University (Freeland, 2004) followed women with gestational or pre-existing diabetes and their offspring. Late in gestation, amniotic fluid was collected and stored for measurement of insulin levels. Amniotic fluid insulin levels reflect fetal insulin production. Childhood obesity...
at 6-8 yrs of age as measured by symmetry index was positively correlated with the amniotic fluid insulin levels in late pregnancy. Measurements of maternal glycemic control during pregnancy, on the other hand, were not related to childhood obesity. These results suggest that while fetal insulin secretion is stimulated by maternal glucose levels, it is the degree of fetal hyper insulinism that is directly correlated with later obesity. There may be additional fuel abnormalities beyond maternal hyperglycemia that contribute to fetal hyper insulinism in the diabetic intrauterine environment.

**Diagnosis**

**Rationale for Universal Screening**

In the Indian context, recognition of glucose intolerance during pregnancy is perhaps more relevant and necessitates universal screening as Indian women have an eleven fold increased risk of developing GDM compared to White Caucasian women (Simmons et al, 2009). It is important to detect these GDM cases, because if unrecognized, the pregnancy may end in foetal wastage or the child may be at higher risk of diabetes in adult life. Universal screening appears to be the most reliable and desired method for the detection of GDM, as it detects more cases and improves maternal and offspring prognosis, compared to selective screening (recommended by ADA – American Diabetes Association, 2011).

Cosson (2004) probably the undiagnosed gestational diabetes that has been occurring in the past has resulted in the increased prevalence of diabetes in India.

**Validation of WHO criterion as per DIPSI(Diabetes in Pregnancy Study in India) guidelines**

DIPSI group, after careful scrutiny, suggests the following for the diagnosis and screening of GDM in India.

When a glucose tolerance test is administered to a non pregnant individual, it is standard to use the 75-g 2-hr OGTT. To standardize the diagnosis of GDM, the WHO recommends using a 2-hr 75-g OGTT with a threshold PG (plasma Glucose) concentration of greater than 140mg/ dl at 2-hr, similar to that of IGT (Impaired Glucose Tolerance) >140 and <199 mg / dl outside pregnancy (Seshiah et al, 2009).
Gestational diabetes mellitus, based on 2hr 75g OGTT defined by either WHO or ADA Criteria, predicts adverse pregnancy outcome. There was no significant difference between prevalence of GDM using Carpenter and Coustan (ADA) and the WHO criteria. The WHO criteria of 2 hr PG >140 mg/dl identifying a large number of cases may have a greater potential for the prevention of diabetes (Franks et al, 2009). A pregnant woman, whose 2hr PG is 120 -139 mg/dl, needs follow up.

Retnakaren et al 2006 report that a number of prospective and retrospective studies have substantiated the observation that the frequency of adverse foetal outcome increases with 2 hr PG ≥ 120mg/dl and taking care of these women had resulted in a better foetal outcome.

A Single – Step produce to diagnose GDM

All the diagnostic criteria require women to be in fasting, but most of the time pregnant women do not come in the fasting state because of commutation and belief not to fast for long hours. Hence, for successful implementation of Universal screening, a casual and reliable test that would not impose any restriction was performed (Metzger et al, 2010). A 2-hr 75g oral glucose test performed in a non-fasting state, irrespective of last meal timing as efficacious as 2-hr 75g oral glucose test done in the fasting state recommended by WHO in detecting GDM, was done for 862 consecutive pregnant women. The observation this study was, all women diagnosed as GDM by 75g glucose test irrespective of the last meal timings also satisfied the diagnostic criteria of 75g oral glucose test performed in the fasting state recommended by WHO (Anjalakshi et al, 2009). This procedure is a modified version of WHO criteria in that, only 2 –hr PG is taken into consideration for the diagnosis of GDM and is being followed by the DIPSI.

Screening Recommendation

Practically all the pregnant women should undergo screening for glucose intolerance. The usual recommendation for screening is between 24 and 28 weeks of gestation. The recent concept is to screen for glucose intolerance in the first
trimester itself as the foetal beta cell recognizes and responds to maternal glycemic level as early as 16th week of gestation (Cosson, 2004). If found negative at this time, the screening test is to be performed again around 24th – 28th week and finally around 32nd – 34th week. Sendag et al 2004 state that management of GDM has altered markedly in recent years based on universal screening of blood sugar and to establish a tight control of blood glucose levels round the clock, serial measurements of blood glucose and HbA1c are recorded.

**Glycosylated hemoglobin – HbA1c levels**

If the glucose intolerance is detected in the early pregnancy A1c level is more that 6% (Balaji et al, 2007), the chances are that she may be a pre-GDM or GDM, in when the glucose intolerance was detected in the early weeks of pregnancy; all the more validating that the screening needs to be performed in the early weeks of gestation. The estimation of A1c may help in distinguishing a pre-GDM from an early onset GDM (Seshiah et al, 2007). But A1c is not estimated in the community health centres, barring a few tertiary care hospitals due to the difficulty in standardisation, inadequate technical support and the cost.

**Complications**

Women with GDM experience twice the number of urinary tract infections than women who do not have GDM. This increased infection incidence is thought to be due to the increased amount of glucose in the urine beyond the normal glucosuria that is present in pregnancy. There is also an increased risk of pyelonephritis, asymptomatic bacteriuria, and pre-eclampsia. There is a 10% risk of polyhydramnios that may increase the risk of abruption placentae and preterm labor as well as of postpartum uterine atony (Hod et al, 2007).

Congenital anomalies do not occur at an increased rate in patients with GDM. There is reportedly an increased incidence of stillbirth when glucose control is poor. There is also a 10% per year risk of developing type II diabetes after the pregnancy in which GDM occurred, with the greatest risk within the first 5 years following the index pregnancy (Haroush et al, 2004).
Macrosomia, if it occurs, typically becomes evident at 26 to 28 weeks gestation. Complications associated with macrosomia include fetopelvic disproportion leading to operative delivery, shoulder dystocia, and neonatal hypoglycemia. There is an increased incidence of hyperbilirubinemia, hypocalcemia, respiratory distress syndrome, and polycythemia in the neonate. Long-term complications can include obesity, diabetes during childhood, impaired motor function, and higher rates of inattention and hyperactivity (Merlob, 2008).

**Recurrence of Gestational Diabetes Mellitus**

Kim *et al* (2006) performed a study to examine rates and factors associated with recurrence of GDM among women with a history of GDM. They conducted a systematic literature review of articles published between January 1956 and November 2006, in which recurrence rate of GDM among women with a history of GDM were reported. Factors abstracted included recurrence rate, time elapsed between pregnancies, race/ethnicity, diagnostic criteria, and when available, maternal age, parity, weight or BMI at the initial and subsequent pregnancy, weight gain at the initial or subsequent pregnancy and between pregnancies, insulin use, gestational age at diagnosis, glucose tolerance test levels, baby birth weight and presence of macrosomia, and breastfeeding. Of 45 articles identified, 13 studies were eligible for inclusion.

After the index pregnancy, recurrence rates varied between 30 and 84%. Lower rates were found in Non-Hispanic White (NHW) populations (30-37%), and higher rates were found in minority populations (52-69%). Exceptions to observed racial / ethnic variations in recurrence were found in cohorts that were composed of a significant proportion of both NHW and minority women or that included women who had subsequent pregnancies within 1 year. No other risk factors were consistently associated with recurrence of GDM across studies. The rates of future pre-existing diabetes in pregnancy, socioeconomic status, postpartum diabetes screening rates after the index pregnancy, and the average length of time between pregnancies were generally not reported, Recurrence of GDM was common and may vary most significantly by NHW versus minority race/ethnicity (Larger *et al*, 2005).
Indian Experience of Diabetes Complicating Pregnancy

With improvement in antenatal care and routine screening of all pregnant women for carbohydrate intolerance, an increasing number of cases of diabetes are being detected. Of all cases of diabetes complicating, pregnancy, the majority (about 90%) are cases of gestation diabetes.

In studies on the effects of diabetes in pregnancy, the following pertinent observations were reported (Daftary and Desai, 2005).

The incidence of GDM (9.84%) was high in women undergoing spontaneous abortions, particularly in those poor glycemic control. The incidence of GDM varies widely even within the same metropolitan area. Excessive weight gain was observed in 32% of women with GDM as compared to 1.7% in controls. Fetal macrosomia was observed in 32% of GDM women as compared to 6.8% in controls. Incidence of pregnancy-induced hypertension was 48% in GDM group as compared to 18.8% in controls. Incidence of hydramnios reported was 28% in the GDM Group as compared to 4.3% in controls.

Candidal vulvovaginitis was reported in 4% in the GDM group as compared to 1.3% in controls. Incidence of intrauterine fetal deaths was 12% in the GDM group as compared to 1.7% in controls. Incidence of fetal malpresentations was 16% in GDM group as compared to 6% in controls. Cesarean section was required in 44% of GDM group as against 13.3% in controls. Postpartum complications are also much higher in the GDM group. Maternal mortality is 10 times higher in GDM patients. Perinatal morbidity increases in GDM patients. Strict glycemic control of GDM improves obstetric outcome significantly. The glycemic control should ideally precede onset of pregnancy. Prescribing pyridoxine 40 mg twice daily in GDM patients helps to reduce insulin requirements to control glycemic control.

B. Management strategies of GDM – “Road to better glycemic control”

The goal of treatment is to reduce the risks of GDM for mother and child. Schwarz (2012) reports that scientific evidence is beginning to show that controlling glucose levels can result in less serious foetal complications (such as macrosomia)
and increased maternal quality of life. Like primary prevention and early screening, the on-going management of women with GDM requires the involvement of a variety of stakeholders at different levels. The team would usually comprise an obstetrician, diabetes physician, a diabetes educator, dietitian, midwife and pediatrician.

Clinical management of women with GDM can be considered in three stages: before delivery, during delivery and immediate post partum, and after delivery (Gillies et al., 2008). Efficacy of clinical management is heavily dependent on food habits, stress free home environment and other supportive care at home. Therefore management of GDM is not directed at the pregnant women alone, but her family as a whole (Roman, 2011).

**Care before delivery**

The objective of care before delivery is to ensure that the blood sugar levels remain as much within normal limits as possible, so that foetal growth also remains within normal limits. If the blood sugar level is not controlled and is persistently high, the foetus may grow more than normal (macrosomia) which may result in complications for both mother and baby. If the blood sugar is too aggressively controlled, there is a risk of poor weight gain by the foetus.

**Patient Education**

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

Ceriello (2008) putforths that the compliance with the treatment plan depends on the patient’s understanding of:

- The implications of GDM for her baby and herself
- The dietary and exercise recommendations
- Self monitoring of blood glucose
- Self administration of insulin and adjustment of insulin doses
- Identification and treatment of hypoglycemia (patient and family members)
- Incorporate safe physical activity
- Development of techniques to reduce stress and cope with the denial

Care should be taken to minimize the anxiety of the women.
Diet

In preparation for pregnancy, a proper diet should provide all necessary macro- and micronutrients, minimize cholesterol, saturated fat and trans fat intake, promote euglycemia, and encourage an appropriate body weight (BMI 20-24.9). Artal et al (2010) reports that an appropriate diet would encourage weight gain for underweight women (BMI less than 20) and weight loss for overweight (BMI 25-29.9) and obese women (BMI 30 or more).

Reader (2007) recommends an appropriate daily distribution of dietary calories is approximately 40-50% of total calories from carbohydrate, 15-20% from protein (0.8g protein/kg bodyweight) and the remainder from fat.

Medical Nutrition Therapy (MNT)

All women with GDM should receive nutritional counseling. Franz et al. (2004) states the salient features (Goals of MNT) in counseling and diet therapy.

- Patient should be counseled for healthy nutrition for rest of life to avoid future GDM, DM, obesity and cardio vascular diseases. Food plans should be culturally appropriate and individualized to take into account the patients body habitus, weight gain and physical activity and be modified as needed throughout pregnancy to achieve treatment goals. Nutrition interventions should emphasize overall healthy food choices, portion control and cooking practices that can be continued postpartum and may help prevent later diabetes, obesity, cardio vascular disease and cancer.

- The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The expected weight gain during pregnancy is 300 to 400gm / week and total weight gain is 10 to 12 kg by term. The meal plan aims to provide sufficient calories to sustain adequate nutrition for the mother and fetus and to avoid excess weight gain and post prandial hyperglycemia. Calorie requirement depends on age, activity, pre pregnancy weight and stage of pregnancy. Approximately 30 to
40 Kcal/kg ideal body weight or an increment of 300Kcal / day above the basal requirement is needed.

- Carbohydrate intake can be manipulated by controlling the total amount of carbohydrate, the distribution of carbohydrate over several meals and snacks, and the type of carbohydrate. In recent years, the glycemic index and glycemic load has received attention as a nutrition intervention to improve glucose control (Jenkins et al 2001).

**Calorie Counting**

As per the recommendations of the Diabetes In Pregnancy Study Group (DIPSI) guidelines Seshiah et al (2006) states that as a part of the medical nutrition therapy, pregnant diabetic women are advised to wisely distribute their calorie consumption especially the breakfast. This implies splitting the usual breakfast into two equal halves and consuming the portions with a two hour gap in between. By this the undue peak in plasma glucose levels after ingestion of the total quantity of breakfast at one time is avoided. For example if 4 idlis / Chappathi / slices of bread (applies to all type of breakfast menu) is taken for breakfast at 8am and two hours plasma glucose at 10am is 140mg; the same quantity divided into two equal portions i.e., one portion at 8 am and remaining after 10am, the two hours post prandial plasma glucose at 10.00 am falls by 20-30 mg.

This advice has scientific basis as the peaking of plasma glucose is high with breakfast (due to Dawn phenomenon) than with lunch and dinner. Polonsky et al (2008) highlights that in a normal person, insulin secretion is also high with breakfast than with lunch or dinner. GDM mothers have deficiency in first phase insulin secretion and to match this insulin deficiency the challenge of quantity of food at one time should also be less.

**Insulin Therapy**

Insulin is essential if medical nutrition therapy fails to achieve euglycemia. Various criteria have been proposed for the initiation of insulin therapy. Fourth International Workshop on GDM recommended lowering capillary blood glucose concentration to 140 mg / dl at 1 hour and 120 mg / dl at 2 hours (Torlone,
Whereas ADA recommended the option of measuring one hour post meal values with cut off of 120mg / dl. These recommendations are based on one single determination, which reflects a “snap shot” of glucose evaluation rather than a “video” of continuous glucose profile (Kinsley 2007). The continuous glucose monitoring system has established that in normal pregnancy, peak plasma glucose occurs at 60 minutes and the value was 108.7±16.9mg/dl. In a woman with GDM, the peak occurs between 70-110 minutes (at approximately 90 minutes) and with a good glycemic control the value was 103± 26 mg/dl (Jovanovic 2005).

If the FPG concentration on the OGTT is ≥ 120mg / dl, then the patient is started on insulin immediately along with meal plan. Other GDM women are seen within 3 days and are also taught self monitoring of blood glucose (SMBG). SMBG is to be performed in fasting and 1 ½ hours after each meal. Zelindact (2011) in their study found that GDM women usually have high post breakfast plasma glucose level compared to post lunch and post dinner.

A few GDM women do have post dinner plasma glucose also high. Insulin is started within 1 to 2 weeks, if the majority (i.e., at least four of seven per week) of fasting values exceed 90mg/dl (Hod 2008). Similarly, if the majority of post prandial values after a particular meal exceed 120mg/dl, insulin is started. Pen injectors are very useful and the patient’s acceptance is excellent. Gupta (2004) putsforth that the requirement of insulin in addition to diet to maintain normal glycemia during the index pregnancy is also predictive of future diabetes.

### Target Blood Glucose Levels

Balaji et al (2010) in their pilot study found that maintenance of Mean Plasma Glucose (MPG) level ~105mg% is ideal for good fetal outcome. This is possible if FPG and post prandial peaks are around 90mg / dl and 120 mg/dl respectively.

### Oral Antidiabetic Drugs

Recently reports from Hebert (2009) have shown good fetal outcome in GDM women who were on glyburide (micronized form of Glibenclamide). A randomized unblinded clinical trial compared the use of insulin and glyburide in women with GDM who were not able to meet glycemic goals on meal plan. Treatment with either
agent resulted in similar perinatal outcomes. All these patients were beyond the first trimester of pregnancy at the initiation of therapy.

More studies are required before routinely recommending glibenclamide during pregnancy especially during the first trimester itself. Metformin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive (ADA, 2011). Continuing this drug after conception is still a controversy. But there are a few studies favouring continuation of metformin throughout pregnancy. Currently, oral agents are not routinely recommended during pregnancy through emerging data on glibenclamide and metformin is interesting (Coustan 2007).

**Monitoring Glycemic Control**

The success of the treatment for a woman with GDM depends on the glycemic control maintained with meal plan or pharmacological intervention. To know the effectiveness of treatment, monitoring of glycemic control is essential. Yoger et al (2004) demonstrated the following observations:

Once diagnosis is made, medical nutritional therapy (MNT) is advised initially for two weeks. If MNT fails to achieve control i.e., FPG≥90mg/dl and / or 1 ½ hrPPG ≥120mg/dl, insulin may be initiated. Once target blood glucose is achieved. Woman with GDM till the 28th week of gestation require lab monitoring of both fasting and 1 ½ hr post breakfast once a month and at other time of the day as the clinician decides. After the 28th week of gestation, the laboratory monitoring should be more frequent atleast once in 2 weeks If need be more frequently (Nicholson et al 2008).

After 32 weeks of gestation, lab monitoring should be done once a week till delivery. In high risk pregnancies, frequency of monitoring may be intensified with SMBG. Continuous glucose monitoring devices are available but these equipments need special training and are expensive. These devices may be useful in high risk pregnancies to know the glycemic fluctuations and to plan proper insulin dosage (Nuttall 1993).
Physical Exercise

It is well known that physical activity reduces glucose and insulin resistance in diabetic patients, thereby helping them to control their weight. Therefore the American Diabetic Association (ADA, 2011) has endorsed exercise as ‘a helpful adjunction therapy’ for GDM when euglycemia is not achieved by diet alone. Regular aerobic exercises with proper warm up and cool down has shown to lower fasting and postprandial glucose concentrations in several small studies of previously sedentary individuals with GDM and controls excessive gestational weight gain. Sewell (2006) state that women should monitor fetal activity and blood glucose levels before and after exercise and limit physical activity to 15-30 minutes.

Regular exercise, however, is a strategy that can help high-risk women prevent GDM and help women with GDM manage their GDM better, and it may help all high-risk women prevent the later onset of T2DM. Dietz (2009) point out that walking was the most frequently reported type of exercise during women’s first (58%) second (61%) and third (62%) trimesters and post partum (75%) followed by a combination of activities such as yoga, aerobic activity and swimming.

C) “Pre –Gestational Diabetes Mellitus (PGDM) – Scenario” in Pregnancy

Diabetes mellitus complicates approximately 3 to 5% of all pregnancies with 90% classified as gestational and 10% as pregestational. (M. B. Landon & Gabbe, 2010) Pregestational diabetes prevalence continues to rise largely due to increases in Type 2 diabetes associated with obesity. Pregestational diabetes is a major cause of maternal and perinatal mortality and morbidity which can be directly related to hyperglycemia and vasculopathy in the mother, although meticulous glycemic control reduces risks and can lead to successful pregnancy outcomes (Catalano, 2007).

Diabetes mellitus is classified by the American Diabetes Association (ADA, 2010) as Type 1, Type 2, or gestational. This classification is preferred as it reflects the underlying pathophysiology of the disease. Type 1 diabetes accounts for 5-10% of all diabetes in the general population and is a result of autoimmune destruction of pancreatic beta cells, leading to an absolute deficiency of insulin production. The
vast majority of Type 1 diabetics require insulin regardless of pregnancy status. Type 2 diabetes is the result of increased peripheral insulin resistance resulting in a relative, rather than absolute, deficiency of insulin. Type 2 diabetes may eventually result in failure of the pancreatic beta cells to produce insulin.

Gunningham et al (2010) point out that management of the non-pregnant Type 2 diabetic is directed at improving insulin sensitivity through diet, exercise, and oral hypoglycemic medications. Some patients with Type 2 diabetes will require insulin when conservative strategies cannot achieve adequate glycemic control. However, due to the stringent control required for optimal fetal outcomes and the increased insulin resistance associated with pregnancy, Type 2 diabetes is typically managed with insulin during pregnancy, even when reasonable control has been achieved with oral agents in the non-pregnant state.

Maternal Complications

Women with pregestational diabetes are at increased risk of preeclampsia compared to non-diabetic women (4-fold increase in risk) and at increased risk of primary cesarean delivery. Kitzmiller et al (2008) observed in their study that Diabetic Ketoacidosis (DKA) occurs in 5-10% of pregestational diabetics during pregnancy, with high rates of both maternal (2%) and fetal mortality (10%).

Fetal Complications

Major congenital anomalies occur in 6-12% of diabetic pregnancies. ACOG (2005) findings reveal that the risk for anomalies increases with increasing glycosylated hemoglobin (HgbA1c). A Hgb A1c level of approximately 5-6%, is associated with a fetal malformation rate close to that observed in normal pregnancies (2-3%), whereas a HbA1c concentration near 10% is associated with a fetal anomaly rate of 20-25%. Calusen et al (2008) complex cardiac defects, renal abnormalities, CNS and skeletal abnormalities are the most common. Diabetes also increases the risk of fetal demise, preterm birth, polyhydramnios, altered fetal growth (IUGR or macrosomia) and neonatal RDS, hypoglycemia, hypocalcemia,
hyperbilirubinemia, and cardiac hypertrophy. Glycemic control can reduce the risk for most if not all of these complications.

Preconception Counseling

Maternal hyperglycemia during the first trimester is a risk factor for abnormal fetal organogenesis; thus, diabetic women should be encouraged to have preconception counseling. The hyperglycemia and adverse pregnancy outcome. HAPO (2008) study put forth that visit should include discussions regarding fetal and maternal effects of diabetes, importance of maintaining euglycemic control before pregnancy, review of medications, and conversion of women on oral agents to insulin prior to conception.

Pregnancy Management

Looker et al (2006) point out that the initial prenatal visit all diabetics should have nutritional counseling with a diabetic educator, HbA1c to assess prepregnancy control, assessment of renal function using serum creatinine and urine protein/creatinine ratio, EKG for patients with diabetes for > 5 years or with co-morbid conditions, referral for comprehensive eye exam by an ophthalmologist if not performed in the last 6 months, and Type 1 DM patients should have thyroid function tests: TSH and free T4.

Diet modification, exercise, frequent blood sugar assessments, and insulin are the key management tools for glucose control. Scholl et al (2004) states that patients should be encouraged to keep a log of food intake to correlate with insulin dosages, exercise, and glucose values.

Hypoglycemia

Symptomatic hypoglycemia can be life threatening and must be prevented. Patients should be instructed on the use of emergency glucose. If hypoglycemia is complicated by stupor, inability to tolerate oral treatment or the patient is unconscious, glucagon 1mg1M should be administered. Fang et al (2009) documented the safety use of glucogon in Type 2 patients who are prone to hypoglycemia and all Type 1 diabetics.
Delivery and Postpartum Management

Early delivery may be indicated in some patients with vasculopathy, nephropathy, poor glucose control, or a prior stillbirth. Kaushal (2003) recommend that these patients have an amniocentesis to assess for fetal lung maturity for deliveries before 39 weeks. For patients with poor control or multiple co-morbidities, amniocentesis for fetal lung maturity at 36-38 weeks can be considered. For patients with well-controlled diabetes and reassuring antenatal testing, pregnancy can be allowed to continue until 39-40 weeks. Expectant management beyond the patient's Expected Delivery Date is not recommended. To prevent traumatic birth injury, cesarean delivery may be considered if the Expected Foetal Weight is 4200-4500 grams. (ACOG, 2005)

During induction of labor, maternal glycemia can be controlled with an IV infusion of regular insulin titrated to maintain hourly readings of blood glucose levels < 110 mg/dL. Patients using an insulin pump may continue their basal infusion during delivery. Simmons et al (2005) observed that intrapartum glycemic control is critical as it is a major determinant of neonatal glucose. Intrapartum maternal hyperglycemia increases the risk of neonatal hypoglycemia markedly.

Insulin requirements decrease rapidly after delivery. One half of the pre-delivery dose may be reinstituted after starting regular food intake. Breastfeeding should be encouraged and will require an additional 500 kcal/d more than the prepregnancy caloric intake. The frequency of long term breast feeding and the possible predictors for successful breast feeding were studied by Stage et al (2006).

D) Outcomes in Gestational Diabetes – “The Essential Maternal and fetal Surveillance”

The outcome of pregnancies in diabetes women is very important and the rates are always changing due to increase in the rates of diabetes mothers it self and availability of better treatment modalities. Pregnancy determines not only the immediate outcome of the fetus but also the future physiology and pathology of the child. GDM increase risk of poor pregnancy outcomes and often not diagnosed as women are not routinely screened for it. Maternal hyperglycemia is associated with
high risk of maternal and perinatal morbidity and mortality and poor pregnancy outcome. The relevance of diabetes and pregnancy is depicted in Fig - C.

**Fig - C**

**Diabetes and Pregnancy Relevance**

Maternal and Foetal risks

Gestational diabetes entails risks for mother as well as for child and contributes substantially to maternal and child morbidity and mortality. The risks increases with higher blood sugar levels.

**The maternal risks include**

- Gestational weight gain, hydraminos
- Hypertensive disorders of pregnancy (eg: gestational hypertension, pre-eclampsia, PIH)
- Caesarean delivery (including primary caesarean and repeat caesarean) and indication for caesarean delivery.
- Post partum hemorrhage (PPH)
- Post partum weight retention
- Post partum type 2 diabetes mellitus or glucose intolerance / Impaired fasting glucose.
- GDM in future pregnancies.

Jang *et al* (2005) in a cohort study, found that the diagnosis of GDM in the first half of pregnancy compared to later onset is associated with higher risk of future type 2 diabetes. This group shows higher incidence of hypertension, greater dose of insulin to combat higher range of glycemia, more perinatal death and neonatal
hypoglycemia. About half (54%) of the population presented one or more risk factors.

**Foetal Risks**

In addition to the high perinatal mortality and morbidity associated with diabetes complicating pregnancy, there is an increased risk of birth defects and stillbirths. Growth abnormalities and chemical imbalances after birth, may require admission to NICU - Neonatal Intensive Care Unit.

Ostlund *et al* (2003) found in their study that infants born to mothers with GDM are at risk of being both large for gestational age (macrocosmic) and small for gestational age. Macrosomia in turn increases the risk of instrumental deliveries or problems during vaginal delivery (such as shoulder dystocia).

Macrosomia may affect 12% of normal women compared to 20% of patients with GDM. Macrosomia (defined as a birth weight above 4kg/or >90\textsuperscript{th} percentile weight for gestational age or large for gestational age) which are associated with several obstetric complications like birth trauma, hypertrophic miocardiopathy. Murphy *et al* (2004) demonstrated that by allowing the pregnancies of women with diabetes to go to full term, there was a fourfold increase in the rate of spontaneous vaginal delivery.

Neonates are also at increased risk of low blood glucose (hypoglycemia) jaundice, high red blood cell mass (Polycythemia) and low blood calcium (hypocalcemia) and magnesium (hypomagnesemia). Mashiah *et al* (2009) point out that GDM also interferes with maturation, causing dysmature babies prone to respiratory distress syndrome due to incomplete lung naturation and impaired surfactant synthesis.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO, 2008) study - a large multinational prospective study that included 25,505 women, who underwent 2-hr OGTT with 75g glucose between 24 and 32 weeks of gestation and their glycemic levels, were investigated in relation to predefined adverse pregnancy outcomes. The four pre-defined primary out comes were primary caesarean
delivery, clinical neonatal hypoglycemia, birth weight and cord serum C-peptide above the 90th percentile.

Premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia and pre-eclampsia were chosen as secondary outcomes. The HAPO study demonstrated that there is a continuous association of maternal glucose levels with adverse pregnancy outcomes.

**Post partum management**

Subsequent diabetes after a GDM pregnancy is an upcoming health burden that needs urgent global attention. More than half of woman with gestational diabetes will develop type 2 DM in the ensuing 20 years. Post partum follow-up care aims at its primary prevention and early diagnosis.

Post partum glycemic scenario in India (C.S. Yagnik 2011)

- 10% continue to be diabetic
- 40% have type II Diabetes after 6 months
- 2/3rds of GDM women develop hyperglycemia within 4 years.

Women with history of GDM are at increased risk of future diabetes as are their children and GDM is the key factor in intergenerational transmission of diabetes-mother, foetus and reproductive cells in the foetus.

Das et al (2010) putforth that Indian women at a younger age are affected by GDM and rates of post partum screening among women with a history of GDM are low in a developing country like India, post partum blood glucose measurement is critical after 48 hours of delivery and at 6-8 weeks after delivery to detect persistent or overt DM. At 6-8 weeks of delivery an OGTT is repeated. If the women has an impaired glucose tolerance at 6-8 weeks post partum, she should continue diabetic diet and monitor her blood glucose every 6 months with FBS and PPBS. Diet, exercise and annual monitoring are recommended.

**Short - Term and Long-term implications of GDM**

**Short term** : The HAPO (2008) study observed a continuous relationship between maternal glycemia and neonatal outcomes, both for the primary (birth weight,
neonatal adiposity, and cord C peptide level >90th percentile) and secondary outcomes (premature delivery, birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia). Of these, the primary outcomes are important, as they are more likely to have permanent impact on the future development of obesity and type 2 diabetes in the offspring, whereas the secondary outcomes, which are treatable, have transitory influence on the newborn.

In the HAPO study, though the composite outcomes (which includes both primary and secondary outcomes) occur from 2h PG ≥153mg/dL, the primary outcome appears to manifest gradually from 2h PG 126mg/dL (7.0mm01/L) and is discernible from 2h PG 140 mg/dL (7.8mmol/L). In the DIPAP study, the prevalence of macrosomia was 8% with maternal glucose of 2h ≥120mg/dL, which increased to 15% from maternal glucose of 2h PG >140 mg/dL. A sub-study of DIPAP project also observed that the occurrence of macrosomia was a continuum, as the 2 h PG with 75 g OGTT increase above 120mg/dL.

**Long term:** Franks et al (2007) documented in their follow-up study of children born to mothers, who had third trimester 2 h PG 120-139 mg/dL, the cumulative risk of type 2 diabetes was 19% at age 24 years and the risk increased to 30% with respect to those women who had 2 h PG 140-199 mg/dL.

Thus, both short-term and long-term morbidities in the offspring occur as maternal plasma glucose increases and this trend is perceptible from 2h PG≥140mg/dL. As such, this level assumes a great clinical significance.

**Care of the Neonate**

Women with diabetes should be advised to give birth in hospitals where advanced neonatal resuscitation skills are available 24 hrs a day. Babies of women with diabetes should be kept with their mothers unless there is a clinical complication or there are abnormal clinical signs that warrant admission for intensive or special care. Blood glucose testing should be carried out routinely in babies women with diabetes at2 - 4hrs after birth. Blood tests for polycythemia, hyperbilirubinemia, hypocalcemia, and hypomagnesemia should be carried out for babies with clinical signs (Riskin et al., 2005).
Babies of women with diabetes should be admitted to the neonatal unit (NICU) if they have hypoglycemia associated with abnormal clinical signs, respiratory distress, signs of cardiac decompensation due to congenital heart disease or cardiomyopathy, signs of neonatal encephalopathy, signs of polycythemia and are likely to need parital exchange transfusion, need for intravenous fluids, need for tube feeding (unless adequate support is available on the postnatal ward), jaundice requiring intense phototherapy and frequent monitoring of bilirubinemia, and been born before 34 weeks (or between 34 and 36 weeks if dictated clinically by the initial assessment of the baby and feeding on the labor ward).

Study of Thomas et al (2013) revealed that in a cohort of GDM’s who required treatment with either insulin or OHA. There were few babies who developed complications with an overall good outcome.

Prevention of Diabetes after GDM

GDM by its merit demands close surveillance so that early lifestyle changes and preventive programs are instituted.

One of the important causes of DM developing after GDM is discontinuity of care as neglected by young women after delivery. Current American Diabetes Association Guidelines (ADA, 2008) recommend blood sugar estimation after childbirth, after 6-8 weeks and every 3 years thereafter. Women with high risk factors require more frequent testing.

GDM imparts lifelong risk for diabetes mostly in terms of T2DM. That modest weight loss and physical activity can delay or prevent diabetes is now of level A evidence, offspring can lower the risk by eating healthy foods, being active, and avoiding overweight or obesity. Women should reach pregnancy weight by 6-12 months in the postpartum period.

One of the barriers is the lack of perception and understanding after delivery on the part of the women (and perhaps, also that of the healthcare providers) of the seriousness and consequences of DM (Cheung et al, 2003). Among a selected
group of 217 mostly White, affluent, and well-educated women with a previous history of GDM, 7% believed that they had almost no chance of developing diabetes, 35% a slight chance, 41% a moderate chance, and 16% a high chance; only 31% reported engaging in lifestyle modification.

Ostlund et al (2004) puts forth that patient education in lifestyle modification and encouragement to return for glucose testing at regular intervals are important tools for the healthcare professional in the subsequent follow-up of women with GDM. Proper pregnancy counseling helps a lot in this process.

Physical inactivity and obesity are well-known risk factors for the development of T2DM. It was postulated that lifestyle modification, including weight loss, decreasing the total amount of ingested calories, increasing the amount of fiber in the diet, and increasing daily physical activity could delay or prevent the development of T2DM in those subject at higher risk. In the study by Helmrich et al (2008) among a group of women, the incidence of T2DM was reduced by a third through vigorous exercise independent of family history of diabetes.

Follow-up schedule after GDM, as recommended by Fifth International Workshop-Conference (2005) on GDM, is given in Table - B

<table>
<thead>
<tr>
<th>Time</th>
<th>Test</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>After delivery (1-3 days)</td>
<td>Fasting or random plasma</td>
<td>Detect persistent, overt diabetes</td>
</tr>
<tr>
<td>Early postpartum (around the time of post partum visit)</td>
<td>Glucose 75g 2-h OGTT</td>
<td>Postpartum classification of glucose metabolism</td>
</tr>
<tr>
<td>1-year postpartum</td>
<td>75g 2-h OGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Annually</td>
<td>Fasting plasma glucose</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Triannually</td>
<td>75g 2-h OGTT</td>
<td>Assess glucose metabolism</td>
</tr>
<tr>
<td>Prepregnancy</td>
<td>75g 2-h OGTT</td>
<td>Classify glucose metabolism</td>
</tr>
</tbody>
</table>

(Metzger et al, 2007)
Points to be considered after GDM are as follows:

- Evaluation of glucose metabolism and CV risk, such as hypertension, ischemic heart disease, etc., Breast feeding, appropriate use of contraceptives, prevention or delay of forthcoming diabetes.

**Gestational Diabetes Education and Diabetes Prevention Strategies**

Women with a history of GDM should try to achieve their pregnancy weight within 6-12 months after delivery. If they are still over weight (BMI>25kg/m^2) after 12 months, they should try to lose 7% of their body weight slowly and then strive to maintain that weight loss. Recommendations of the 5th International workshop on GDM (Metzger, 2007) reveal weight loss and maintenance strategies could include some of the following:

- Follow a balanced meal plan, try to include a carbohydrate food and a heart-healthy protein at each meal. Use the plate method to portion out meals, space meals throughout the day, use added fats in moderation, eat second helpings of no starchy vegetables instead of starchy food, such as rice, pasta, and potatoes, try to have two to three servings of calcium-rich food each day, drink water to reduce empty calories, use small (4 oz) glasses for fruit juice and other sugary beverages. If still thirsty, drink water, increase the fiber in the food plans, moderate physical activity 5 days per week for at least 30 min is also a very important risk-reduction behavior and limit sedentary activities.

The incidence of DM in future will reach unexpected level in our country. GDM is one of the forerunners of diabetes. Keeping aside the nonmodifiable factors, there are many modifiable factors, which, if targeted before, during, and after GDM, will impart good result. Proper detection and management of GDM and preventive measures thereafter are the affordable goals (Crowther et al., 2005).

Targeted management during a after pregnancy delays or prevents diabetes not only in the mother but also in the child for future. Keeping aside sophisticated experimental facts and observations, simple steps like early detection; regular monitoring and lifestyle modification can easier be implemented to prevent the huge explosion of diabetes in our country.