Chapter 2:
Literature Review
2.1. Gestational diabetes:

2.1.1. History and prevalence:

“One hundred years ago the medical literature on diabetic pregnancy was very limited. Pregnancy outcomes was affected by so many other major problems that the influence of a medical disorder with a chronic nature was unrecognized and disregarded” (Hod, M, et.al, 2008).

Dr. H.G. Bennewitz, in 1823, considered that the diabetes was actually a symptom of the pregnancy and since the symptoms and the glycosuria disappeared after at least two successive pregnancies, he had some evidence to support his views (Hadden RD, 2008). The idea that lesser degrees of maternal hyperglycemia could adversely affect pregnancy outcome dates back to 1940s in the United states and Scotland. Those showed increased perinatal mortality some years before the recognition of clinical diabetes mellitus.

This led to the term pre-diabetes in pregnancy, and to the poorly defined concepts of temporary and latent diabetes. The first prospective study of carbohydrate metabolism in pregnancy was conducted in Boston in 1954. It involved ingesting 50 grams of carbohydrates and performing a one hour screening test. The procedure has subsequently been widely adopted in the U.S. O’Sullivan first used the name ‘gestational diabetes’ in 1961, based on the term meta gestational diabetes used by Dr JP Hoet in 1954 after his early studies in Louvain, Belgium (Hod, et.al, 2008).

About first evidences and recognition of GDM Hadden (1998) discussed the old case of Frederica Pape; aged 22 was admitted to the Berlin Infirmary at 7th month of her pregnancy in 1823. Dr Bennewitz has described her symptoms as unquenchable thirst, weak voice, dry skin, cold face, beer like urine smell and detection about 2 oz of sugar in 16-lb of urine. Pape had recurrent sore throat and increased abdominal distention during 32-36 weeks of pregnancy. She had an obstructed labor and her infant died intrapartum, though Bennewitz had found:”the baby was of such robust and healthy character that you would have thought Hercules had begotten.”

Historically this case recognized as the first recorded case of diabetes during pregnancy, for gestational diabetes mellitus (GDM) described today as “carbohydrate
intolerance of varying severity with onset or first recognition during pregnancy (Hadden, 1998).

Although GDM is a milder form of glucose intolerance than type 1 and type 2 diabetes, maternal hyperglycemia has the potential to adversely affect the well-being of the fetus as well as the mother (Langer & Hod, 1996).

Priscilla White was a pure clinician who devoted her entire professional career to the treatment of diabetic patients. In particular, she had an interest in Type 1 diabetes in women and in youths. This interest led her to the treatment of diabetes in pregnancy, and helped establish formal discipline (Hare JW, 2008).

“As early as 1945, Jørgen Pedersen started his work on diabetes and pregnancy. He managed to build up a center for pregnant women with diabetes, which over the years has become well-known as the Copenhagen centre for pregnant diabetics. His aim was to diminish perinatal mortality through strict control of diabetes and special obstetric management.” (Molsted-Pedereson, L, 2008) These efforts were widely successful, as the perinatal mortality during his leadership decreased from nearly 40 percent to 4 percent. Pedersen was also one of the founders of the European Diabetic Pregnancy Study Group (DPSG) (Molsted-Pedereson, L, 2008).

In his thesis Pedersen, in 1952, quoted the hypothesis of first mentioned the hyperglycemia (maternal) – hyperinsulinism (fetal), but at that time direct measurements of plasma insulin were not possible (Molsted-Pedereson, L, 2008). In the second edition of his book the Pregnant Diabetic and Her Newborn, he hypothesized that maternal hyperglycemia would result in fetal hyperglycemia and, hence, in hypertrophy of fetal islet tissue with insulin hypersecretion. Over the years, its consequences and explanatory powers have been intensively discussed, especially in papers from the Copenhagen Centre (Molsted-Pedereson, L, 2008).

Nearly two decades later, in 1980, Norbert Freinkel proposed “the fuel mediated teratogenesis” hypothesis. He considered additional long-term effects on growth and development of the child following a diabetic pregnancy. He hypothesized that the fuels of maternal origin may influence developmental events by modifying phenotype gene
expression in terminally differentiated, poorly replicating cells during intrauterine development (Banting lecture, pregnancy and progeny, N. Freinkel, 1980).

Freinkel initiated and chaired the first two International Workshop Conferences on GDM (B.E Metzger, 2008).

GDM is the one of medical complication of pregnancy- (Car DB et al, 1998) occurring in 4% of all pregnancies or 100,000 women in the United States annually (all ethnicities) (King H, 1998). In addition, it is increasing in prevalence globally (King H, 1998). Although pregnancy is a carbohydrate-intolerant state, only a small proportion of pregnant women (3–5%) develop GDM (Hod, et al, 2008).

Based on demographic projections made by United Nations population division for the year 2025, WHO issued estimates of adults with diabetes in all countries and reported that there will be more women with diabetes than men and we may anticipate a considerable increase in the burden of gestational diabetes mellitus especially in less prosperous countries (King H, et. al, 1998). During last two decades, there has been a marked increase in the prevalence of diabetes among urban Indian (Ramachandran A, et. al, 1998). A similar though slower trend is occurring amongst semi-urban and rural populations due to changes in life style, aging and low birth weight leading to diabetes during adult hood. India has the largest number of diabetic patients in the world (IDF), and among ethnic groups in South Asia, the Indian women have the highest prevalence of GDM (Beischer NA, et. al, 1991).

The incidence of GDM has increased dramatically globally (IDF2013) over the past 20 years from 2.9% (the average reported in the 1980s) to 8.8% and 12% (Catalano, et.al, 2003; Diabetes Prevention Program, 1999; Mokdad et al., 2001). The reported worldwide prevalence of GDM varies between 0.6-13.7 percent (Aberg A, et.al, 2001; Sadikot SM, et. al, 2004).

The International Diabetes Federation (IDF) reports in 2007 that there were 46.5 million people in India with diabetes and that this number is expected to be 60.9 million by 2025. (IDF2006; API-ICP diabetes guideline, 2007; Metzger BE, et. al, 2006). The IDF estimated that worldwide there were 194 million people with diabetes in 2003 and this will increase to 334 million by 2025. Prevalence of GDM as a percentage of all
pregnancies for Indian-Australian is 15% and for American-Zuni Indians is 14.3\(\text{Hod M, et. al, 2008; King H, 1998; Kousta E ,et. al, 2000, Branchtein L, et. al, 2000). Prevalence of GDM in India is high but variable in different states, with 16-17% recorded in Tamil Nadu and 10% in Punjab (World Diabetes Federation, GDM projects in 2011).}

In a study of the prevalence of diabetes and IGT in diverse populations of women aged of 20 and 39 the World Health Organization ad hoc diabetes reporting committee, noted a lower rate of diabetes (<1%) in rural India (WHO ad hoc diabetes reporting group, 1992). However overall Indian women had the highest prevalence of GDM (15%), followed by Chinese (13.9%), Vietnam-born (7.8%) and Australian-born (4.3%)(King H,1998). In a study in Australia 35 % of subjects with a positive family history of diabetes who also had GDM developed diabetes mellitus, compared to 22% cases with a negative family history of diabetes mellitus (Henry OA, et.al, 1991).

Among Indians the prevalence of impaired glucose tolerance (IGT) in the age groups of 20-29 years and 30-39 years was found to be 12.2 and 15.3%, respectively. No gender difference was observed in the prevalence of IGT (Ramachandran A, et. al, 2001).

“The National Urban Diabetes Survey (NUDS) was a population based study was conducted in six metropolitan cities across India and it recruited 11,216 subjects aged 20 years and above who were representative of all socio-economic strata. The study reported that the age standardized prevalence of type 2 diabetes was 12.1%. This study also found that the prevalence in the southern part of India was higher-13.5% in Chennai, 12.4%, in Bangalore, and 16.6% in Hyderabad; compared to eastern India (Kolkata) had 11.7%; northern India (New Delhi) had 11.6%; and western India (Mumbai) had 9.3%” (Mohan V, 2007).

The study also suggested that there was a large pool of subjects with impaired glucose tolerance (IGT) and 14% had a high risk of conversion to diabetes. A study done in western India found an age-standardized prevalence of 8.6% in urban population. A more recent study reported a higher prevalence (9.3%) in rural Maharashtra (Mohan V, 2007, Deo SS, et. al, 2006).

The overall crude prevalence of diabetes using WHO criteria in CURES was 15.5 per cent (age-standardized: 14.3%), while that of IGT was 10.6 per cent (age-
standardized: 10.2%). A low prevalence of GDM was observed in the hilly areas of Jammu and Kashmir (Uvaraj MG, et. al, 2007) of North India (4.4%), while Imphal in North-East India had a prevalence of 2.2% and Yercaud (ADA, 2003) in South India had 3.5%. This low prevalence could be attributed to the life style adapted by the people living in the hostile terrain. The prevalence of GDM in other developing countries also showed regional variations.

The current diabetes epidemic affects pregnant women on a large scale, not only in high-income countries but also in developing countries (Hotu S, et al, 2004, national service framework for diabetes, 2001) Studies show that there are wide differences in the prevalence of diabetes in different ethnic groups, giving regional estimates of prevalence varying from lowest in Africa (2.4%) to highest in Europe and North America (7.89%) (IDF, global burden of diabetes, 2003).

The most recent reports on prevalence of diabetes the Indian Health ministry’s first ever large scale study in 2012 to check for diabetes and hypertension has revealed that highest rate of diabetes are in the following states: Sikkim (14%), Tamil Nadu (11.7%), Karnataka (10.3%), West Bengal (9.8%), Kerala (9.3%), Odissa (9%), Jammu & Kashmir (8.8%), Punjab (8.5%), Andra Pradesh (8.3%). Low rate of diabetes was in Madhya Pradesh (2.9%), Assam (3.7%), Chhattisgarh (3.9%), Haryana (4%), Jharkhand (4.6%), Uttarkhand (5.7%), and Uttar Pradesh (5.9%) (Times of India, Pune Monday, December, 17, 2012).

Also according to IDF recent report diabetes caused death of 10 lakh Indians in 2011, India is presently home of 63 million diabetics (Times of India, Pune. Monday, December, 17, 2012).

IDF 2013 has reported that by international prevalence of diabetes which was 8.3% in 2011, India in 2011 had 61.3million diabetes and it will be 101.2 million by 2030.

The incidence of GDM worldwide is estimated to be 2%–14% (Forsbach F, et al, 1988, Coustan DR, et al, 1989). However, data vary from country to country. Comparing epidemiological data is not an easy task because of the varying diagnostic criteria in GDM currently being used. Usually, the incidence of GDM reflects the incidence of T2DM in the background population (Willibald Z, et al, 2008).
A random survey was performed for the first time in 2002 to determine the prevalence of GDM in India. Of the total number of pregnant women (n=3674) screened, 16.55% were found to have GDM. In the Chennai urban population, the prevalence of GDM was found to be 16.2% (Seshiah V, et al 2004).

The prevalence of GDM usually reflects the prevalence of type 2 diabetes in the underlying population (Mohan V, et al, 2007). Established risk factors for GDM are advanced maternal age, obesity, and family history of diabetes. Unquestionably, there are ethnic differences in the prevalence of GDM.

The overall prevalence of GDM in India was 16.88%, ranging from 12 to 21% in different parts of the country (Seshiah V, 2008). A trend of increased prevalence of GDM
was observed in women with less physical activity, but this was not statistically significant. In this community-based study, the prevalence of GDM varied in the urban, semi urban and rural areas. Age >= 25 years, BMI >= 25 and family history of diabetes were found to be risk factors for GDM.

“In the U.S, Native Americans, Asians, Hispanics, and African-American women are at higher risk of GDM than non-Hispanic white women. In Australia, GDM prevalence was found to be higher in women whose country of birth was china or India than in women whose country of birth was in Europe or Northern Africa. GDM prevalence was also higher in Aboriginal women than non-aboriginal women. In Europe, GDM has been found to be more common among Asian women than among European women” (Ferrara A, 2007).

![Figure2.2. Prevalence of GDM by BMI (Seshiah, V, et.al, 2005)](image)

The proportion of pregnancies complicated by GDM in Asian countries has been reported to be lower than the proportion observed in Asian women living in other continents. In India, GDM has been found to be more common in women living in urban areas than in women living in rural areas (Ferrara, A, 2000) also adiposity and hyper-insulinemia in some Indian was observed at birth (Yajnik CS, et. al, 2002).

It was reported that two to three percent of all pregnant women may develop GDM (Freinkel N, 1980) . Another study (MIG) cited that 5 % of all pregnancies are with GDM (Janet A, et. al, 2008). Three other researchers believe that GDM occurs in 2-9% of all pregnancies (Crowther CA, et. al, 2005, ACOG no30, 2001, Blank A et. al, 1995) .
standardized prevalence of DM and IGT were 12.1% and 14% respectively, with no gender difference (DESI,NUDS).

![Graph showing the prevalence of GDM by gravidity.](image)

Figure 2.3. Prevalence of GDM by gravidity, (V Seshiah, et. al, 2005)

2.1.2. Definition of gestational diabetes:

Gestational diabetes mellitus (GDM) is carbohydrate intolerance of variable severity at the onset or first recognition of pregnancy (Metzger BE et.al, 1998). GDM is usually identified in mid- to late-pregnancy and seems to relate to increased levels of anti-insulinemic hormones, specifically estrogen, prolactin, progesterone, cortisol, and human placenta lactogen (Pesicka D et.al 1996).

The definition applies to whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy (ADA, 2008; ADA, 2009; Buchanan TA, et. al, 2005; Harisson, et. al, 2005). IGT and IFG are intermediate tolerance condition in the transition between normality and diabetes (WHO).

GDM is considered a transient abnormality of glucose intolerance during pregnancy (O’ Sullivan JB, et al, 1970). Women with GDM are at increased risk of diabetes in future as are their children and the subsequent generations (Girling, J, et al, 2003). This fact should alert physicians about the necessity of devoting special attention to this segment of population especially in developing countries (Avi Ben Haroush, et al, 2003).
“Gestational diabetes mellitus (GDM) is characterized by carbohydrate intolerance of variable severity, with the onset or first recognition during pregnancy. This definition applies whether or not there is a need for insulin and whether or not it disappears after the pregnancy. It does not apply to gravid patients with previously diagnosed diabetes” (Yoge Y, et.al, 2008).

Because women with the history of GDM have a greatly increased subsequent risk for diabetes they should be screened for diabetes 6-12 weeks post partum, using standard criteria and should be followed up with subsequent screening for development of diabetes or pre-diabetes(ADA 2008; ADA 2009; Pan American Health Organization (PAHO) diabetes fact sheet, 2008).

GDM mothers in urban India are more obese and are more adipose than non-diabetic mothers. Frequently they have a familial history of diabetes and show metabolic features of insulin resistance syndrome, suggesting high cardiovascular risk. Neonates of GDM mothers are heavier, longer and more adipose than those born to non-diabetic mothers, and suffer higher rate of morbidity (Kale S. D, et.al, 2005).
“The dietary changes that characterize the “nutrition transition” include both quantitative and qualitative changes in the diet. The adverse dietary changes include shifts in the structure of the diet towards a higher energy density diet with greater amounts of fat and added sugars in foods, greater saturated fat intake (mostly from animal sources), reduced intake of complex carbohydrates and dietary fiber, and reduced fruit and vegetable intakes” (WHO, 2003). These dietary changes are compounded by lifestyle changes that reflect reduced physical activity at work and during leisure time (Ferro-Luzzi A, et al., 1996; Popkin BM, et al., 2001) which can be the cause of many non-communicable disease like diabetes.

To sum up, in gestational diabetes, there is a combination of factors that may affect the nutrient supply to the fetus (Hod, et al, 2008).

2.1.3. Risk factors for gestational diabetes:

1. A family history of diabetes
2. Higher age (over 30)
3. Higher parity (number of kids, 3-4 or more)
4. Previous pregnancy with GDM is very strongly associated with recurrence, obesity, a previous child over 4000g (almost 9 lbs), women whose own birth weights were over 9 lbs,(Kale S.D, et. al, 2005; King H, 1998) unexplained multiple miscarriages, stillbirths, or birth defects (so-called “poor obstetric history”) may be due to undiscovered GDM in some cases, non-white ethnicity native Americans, African-Americans, women from India, Arabic women, American –Indian/Alaskan native, Asian American, pacific Islander or Latino descent, etc. However Europeans had the lowest rates overall of any population.

Weight gain especially in early pregnancy is associated with higher rates of GDM (Haderson MM et.al, 2010).

Central fat distribution, in some studies, “apple shape” (women with larger waist or larger waist/hip ratios) was found to have an increased risk of GDM. PCOS (Poly Cystic Ovarian Syndrome) is definitely associated with higher risks. Cigarette smoking, multiple pregnancies, history of skin, urinary tract, infection, hypertension, and chronic steroid use may also be associated with higher rate of GDM.

Glucocorticoids such as prednisone often decrease glucose tolerance markedly. Other medications such as terbutaline, progestin, etc. can decrease glucose tolerance as
well. Polyhydraminos (excessive amniotic fluid) is sometimes associated with GDM pregnancies. Glycosuria, previous cesarean section (ADA 1994, Taylor JS, 2005; Marshall JA, et.al. 1993). Teenage mothers and women who drank alcohol was less likely to have GDM (Xiong X, et. al, 2001.)

Body fat percentage, physical activity and possibly, diet quality are important modifiable risk factors for GDM (Iqbal R et. al., 2006). Several mechanisms, involving fiber, antioxidants or poly phenols, are thought to be responsible for the inverse association between diet and the risks of the metabolic syndrome and type2 diabetes or its complications (Schroder H, 2007, F. J. Gortari B et.al, 2008).

Some have attributed the risk of adverse outcomes associated with GDM to confounding characteristics such as obesity, advanced maternal age with GDM, or other medical complications, rather than glucose intolerance (Jarret RE et.al 1981, Hunter DJS 1989, Spellacy WN 1985).

2.1.4. Diabetes screening:

Different screening methods have been introduced depending on the suitability of the test to the population characteristics, cost and screening accuracy. However consideration has been given to the existing screening practices for GDM including universal screening, risk factor-based screening, and the option of not screening for GDM. Yet there are plenty of debates on which test to be used, when should be the screening be done, and on whom it should be applied (Nigam A et.al, 2010).

Screening for GDM is important because studies have shown that treating even mild GDM reduces morbidity for both the mother and newborn (Landon et al, 2009). Also another importance of any screening procedure is not only to identify women with GDM but also to exclude NGT (normal glucose tolerance) women. In other words, universal screening for GDM detects more cases and improves maternal and offspring prognosis.
Figure 2.5.—Disorders of glycemia: etiologic types and stages. *Even after presenting in ketoacidosis, these patients can briefly return to normo-glycemia without requiring continuous therapy (i.e., “honeymoons” remission); **in rare instances, patients in these categories (e.g., Vacor toxicity, type1 diabetes presenting in pregnancy) may require insulin for survival.
Diagnosis and Classification of Diabetes Mellitus (American Diabetes Association 2010)

2.1.4.1. Different screening methods:

Different screening methods have been introduced depending on the suitability of the test to the population characteristics, cost and screening accuracy. The following methods are used in different medical contexts.

Oral glucose tolerant test (OGTT), oral glucose challenge test (OGCT), HbA1c, fasting plasma glucose (FPG), has been explained elaborately in the following context.

Urine test (Glycosuria): only has 30% accuracy and thus is not used during pregnancy.

Random blood sugar (RBS): ADA recommends 50 gm of oral glucose for screening without regard to time of the last meal and the plasma glucose of ≥ 140 mg/dl 1 h after the glucose load is considered to be a positive screen test (ADA clinical practice recommendations 2002). However this result needs confirmation which is tested by 100 grams glucose load and conducting OGTT. This two step procedure is cumbersome since the woman has to visit the antenatal clinic twice (Seshiah Vet al, 2005, De Aguiar LG, et al, 2001).
Serum feructosamine estimation is another screening tool which is not in common use and considered insensitive as a screening test in pregnant patients with clinical risk of gestational diabetes (Comtois R et.al, 1989).

2.1.4.2. Comparison of methods in different studies:

Fifty years ago, screening for GDM was done by taking patients’ history alone. In 1973, Mahan and O’Sullivan proposed using oral glucose tolerance test (OGTT) after giving 50 gram oral glucose load for screening. Now there is variety of standard tests for screening but huge debates to choose a unique universal technique worldwide.

Erika F Werner et.al 2012, in a study compared three methods of screening to find out efficiency of International association of diabetes in pregnancy study group (IADPSG) method. They enrolled three groups. In one group there was no screening; in second group 1 hour 50g oral glucose challenge test (OGCT) between 24-28 weeks of gestation followed by 3 hours 100g OGTT when indicated and the last group underwent the IADPSG method. They concluded that the IADPSG criteria for glucose screening in pregnancy are cost effective. This model is used in post-delivery counseling and intervention, which may help to prevent future diabetes in patient identified with GDM.
Table 2.1: Diagnostic criteria for GDM: The ADA adopted the IAPDSG criteria in 2010 (Holt et al, 2011) and ADIPS is modified WHO criteria.

<table>
<thead>
<tr>
<th>Glucose load</th>
<th>Glucose tolerance test (mg/dl)</th>
<th>Abnormal values for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fasting</td>
<td>1hour</td>
</tr>
<tr>
<td>ADA(^1)</td>
<td>75g</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>100g</td>
<td></td>
</tr>
<tr>
<td>ADIPS(^2)</td>
<td>75g</td>
<td></td>
</tr>
<tr>
<td>CDA(^3)</td>
<td>75g</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO(^4)</td>
<td>75g</td>
<td>126</td>
</tr>
<tr>
<td>DIPSI(^5)</td>
<td>75g</td>
<td></td>
</tr>
<tr>
<td>IADPSG(^6)</td>
<td>75g</td>
<td>&gt;92</td>
</tr>
<tr>
<td>EASD(^7)</td>
<td>75g</td>
<td>108</td>
</tr>
<tr>
<td>NZSSD(^8)</td>
<td>75gm</td>
<td>100</td>
</tr>
</tbody>
</table>

1. American Diabetes Association
2. Australain Diabetes In Pregnancy Society
3. Canadian Diabetes Association
4. World Health Organization
5. Diabetes In Pregnancy studygroup in India
6. International Association of Diabetes in Pregnancy Study Group
7. European Association for study of Diabetes
8. New Zealand Society for Study of Diabetes

Aldasouqi et al. did a retrospective study in 2008 in the United States and examined HbA1c as a screening tool for GDM. They compared HbA1c and OGTT with diagnostic results and concluded that HbA1c is a reasonably sensitive screening measure of GDM among high risk population. But the limitation of their study was retrospective in nature and various methods were used.

IADPSG recommend routine testing for GDM for all pregnant women during 24-28 weeks of gestation. They believed that OGCT lacks both sensitivity and specificity and is no longer part of diagnostic algorithm.
<table>
<thead>
<tr>
<th></th>
<th>ADA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ADIPS&lt;sup&gt;2&lt;/sup&gt;</th>
<th>CDA&lt;sup&gt;3&lt;/sup&gt;</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; International workshop on GDM,1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended glucose targets(mg/dl):</td>
<td>105</td>
<td>155</td>
<td>130</td>
<td>96</td>
</tr>
</tbody>
</table>

1. American Diabetes Association  
2. Australian Diabetes In Pregnancy Society  
3. Canadian Diabetes Association

Cheng YW, Block Kubrisch and Caughey AB carried out a 13 years retrospective cohort study of 14693 women screened for GDM. Women diagnosed with GDM according to the Carpenter and Coustan thresholds, but not by the NDDG criteria were compared to women without GDM by either criterion.

The Carpenter and Coustan criteria are recommended because of higher sensitivity compared to national diabetes data group (NDDG).

At the fourth International workshop and conference of GDM in 1998, for the first time, Metzger et.al presented a strategy. This strategy offered that rather than performing blood glucose testing for all pregnant women, potential ‘exclusion from blood glucose testing’ on the basis of below average risk for GDM, should be considered.

The Carpenter and Coustan criteria were recommended for interpretation of the 100-g OGTT (Carpenter and Coustan et.al 1982). The WHO recommends that levels of glycemia during pregnancy should be interpreted according to the criteria used outside pregnancy (Alberti KGMM, et al, 1998). However the one-step procedure of WHO serves the dual purpose of both screening and diagnosis of GDM (Seshiah Vet al, 2005).

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

Agarawal MM, et.al 2007 in a study on 1172 pregnant women tried various screening criteria namely W.H.O, ADA and ADIPS. They concluded that the WHO criteria by universal acceptance and ability to detect over half the women with DM earlier during pregnancy, was ideally suited to identify women with GDM.

Berger H, et.al had reached to the same conclusion in 2002 that the WHO criteria will approximately double the number of women diagnosed with GDM without an apparent clinical benefit.

Also they recommend OGCT of 50g glucose for women in 24-28 weeks of gestation with threshold of 140 mg/dl, except in low risk women which included: maternal age less than 25, Caucasian or member of other ethnic group with low prevalence of diabetes, pregnant body mass index (BMI) ≤ 27, no previous history of GDM or glucose intolerance, no family history of diabetes in first-degree relative, no history of GDM-associated adverse pregnancy out-comes. Yet a single approach of testing for GDM cannot be recommended at the present.

If the new diagnostic criteria extrapolated from the O'Sullivan and Mahan data (By Carpenter and Coustan as suggested by the 4th International Workshop-Conference on GDM) are accepted and widely used, the incidence of this metabolic complication of pregnancy will also notably increase (Metzger BE, Coustan DR, 1998). Of all the screening tests, the WHO procedure is simple and cost-effective. The only disadvantage is that the pregnant women have to come in the fasting state, to undergo OGTT. (C. Anjalakshi C, et al, 2009).

Blatto AJ, et al, 2011 in their study concluded that the GDM positivity rates for all ages were higher with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria than with the Carpenter-Coustan criteria. This study has mentioned that the IADPSG criteria utilizes slightly lower threshold values for the fasting and 2-hour blood draws, and this was responsible for a 118% increase in the number of positive fasting results.
Table 2.3: Summary of recommendations for detection and treatment of diabetes in pregnancy in various health care contexts

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>High income countries</th>
<th>Middle income countries</th>
<th>Low income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early pregnancy testing for overt diabetes</td>
<td>Random VPG, fasting VPG, or HbA1c</td>
<td>Random VPG, evaluate early OGTT, in relevant populations</td>
<td>Variable, depending on local diabetes prevalence and resources formal prevalence studies recommended</td>
</tr>
<tr>
<td>Diagnosis of gestational Diabetes</td>
<td>Universal 75 g OGTT at 24-28 weeks of gestation</td>
<td>Universal 75 g OGTT at 24-28 weeks of gestation</td>
<td>Variable, depending on local resources</td>
</tr>
<tr>
<td>Treatment of Diabetes in pregnancy</td>
<td>Urgent medical evaluation and treatment of newly detected overt diabetes GDM: dietary and lifestyle measures pharmacologic treatment based on maternal glycemic and fetal growth pattern</td>
<td>Urgent medical evaluation and treatment of newly detected overt diabetes GDM: as for high income countries, depending on local sources</td>
<td>Urgent medical evaluation and treatment of newly detected overt diabetes GDM: dietary and lifestyle measures, increased use of oral anti-diabetic agents, insulin depending on availability</td>
</tr>
<tr>
<td>Follow up post pregnancy</td>
<td>Repeat OGTT in most cases encourage breast feeding dietary and lifestyle behavior change counseling</td>
<td>Re-evaluation of glycemic status depending on local resources encourage breast feeding dietary and lifestyle behavior change counseling</td>
<td>Develop strategies to detect and treat ongoing overt diabetes encourage breast feeding develop personal and population measures to reduce prevalence of obesity and diabetes</td>
</tr>
</tbody>
</table>


The Australasian Diabetes in Pregnancy Society (ADIPS) originally formulated recommendations for the testing and diagnosis of gestational diabetes mellitus (GDM) in 1991 and is modified WHO criteria. The ADIPS recommends that screening for GDM should be considered in all pregnant women. However, if resources are limited, screening may be reserved for those at highest risk.

Hillier T.A. et al, 2008, after comparing standard methods they concluded that there was limited evidence about early screening before 24 weeks’ gestation for GDM. More research is required.

Conversely, others believe that all systematic efforts to identify the condition should be stopped unless more data become available to link significant morbidities to specific degrees of glucose intolerance. Hunter DJS, et.al, 1989).

<table>
<thead>
<tr>
<th></th>
<th>100gm, 3hours</th>
<th>100gm, 3hours</th>
<th>100gm, 3hours</th>
<th>75gm, 2hours</th>
<th>75gm, 2hours</th>
<th>75gm,2hurs</th>
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<tbody>
<tr>
<td>O Sullivan and Mahan 1973</td>
<td>90</td>
<td>105</td>
<td>95</td>
<td>95</td>
<td>126</td>
<td>92</td>
</tr>
<tr>
<td>NDDG (national diabetes data group) 1997</td>
<td></td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>140</td>
<td>180</td>
</tr>
<tr>
<td>Carpenter and Coustan 1997</td>
<td></td>
<td></td>
<td>155</td>
<td>155</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>ADA 1998</td>
<td></td>
<td></td>
<td></td>
<td>140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO 1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>IADPSG 2010 (International association of diabetes in pregnancy group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>90</td>
<td>105</td>
<td>95</td>
<td>95</td>
<td>126</td>
<td>92</td>
</tr>
<tr>
<td>One hour</td>
<td>165</td>
<td>190</td>
<td>180</td>
<td>180</td>
<td>-</td>
<td>180</td>
</tr>
<tr>
<td>2hours</td>
<td>145</td>
<td>165</td>
<td>155</td>
<td>155</td>
<td>140</td>
<td>153</td>
</tr>
<tr>
<td>3hours</td>
<td>125</td>
<td>145</td>
<td>140</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Any two</td>
<td>Any two</td>
<td>Any two</td>
<td>Any two</td>
<td>Any two</td>
<td>-</td>
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</tr>
</tbody>
</table>

National institute for clinical excellence (NICE) recommends no routine screening. Whereas ACOG recommends selective screening with 50 g GCT followed by 100g OGTT for confirmation of GDM in pregnant women.
Table 2.5: The IADPSG proposal for the screening and diagnosis of GDM:

**First prenatal consultation**

- Fasting glucose level or hemoglobin A1 (HgA1) or random measurement in women
- If clinical diabetes => Treatment and follow up for pre-existing diabetes
- If results are non-diagnostic for clinical diabetes:
  - And fasting glucose level is >92mg/dl and <126mg/dl => diagnosis of GDM
  - And fasting glucose level is <92mg/dl => test at 24-28 weeks with OGTT, 75g

**24-28 weeks of pregnancy**

- OGTT 75 g: Fasting glucose measurement/1hour/2hour
- Consider clinical diabetes if fasting glucose >126mg/dl
- Consider GDM if one or more measurements are above the cut-off points
- Consider normal if all the values are below the cut-off points
Table 2.6: The IADPSG proposal for the screening and diagnosis of GDM (cut-points):

<table>
<thead>
<tr>
<th>For diagnosis of GDM (OGTT, 75g)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>&gt;92mg/dl</td>
</tr>
<tr>
<td>Glucose level at 1 hour after overload</td>
<td>&gt;180mg/dl</td>
</tr>
<tr>
<td>glucose level at 2 hours after overload</td>
<td>&gt;153mg/dl</td>
</tr>
</tbody>
</table>

| For diagnosis of clinical diabetes during pregnancy (any one of the following tests) |
|------------------------------------------|------------|
| Fasting glucose                          | >126mg/dl  |
| Hemoglobin A1                            | >6.5%      |
| Random plasma glucose measurements       | >200mg/dl  |

According to Metzger et.al (fifth international workshop-conference on GDM in 2005), GDM risk stratification is done at first antenatal visit. The pregnant females are divided into low, middle and high risk and managed accordingly. For low risk group no blood glucose test is done:

“**Low risk group** is comprising of women with age less than 30, BMI less than 27, no history of GDM or glucose intolerance, no family history of diabetes in first degree relative, no history of GDM associated adverse pregnancy outcome.

**Average risk group** are including of neither low nor high risk. For this group blood glucose testing is done at 24-28 weeks of gestation. Indian, Hispanic, African-American, Asian ethnic group were in this category.

**High risk group**: blood glucose test is done at the earliest and if found normal, then repeated at 24-28 weeks of gestation or at any time when there are features of hyperglycemia is recognized (e.g. glycosuria). Obese pregnant subjects, with family history of type 2 diabetes or previous history of GDM, or impaired glucose tolerance or glycosuria are categorized in this group”.

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1. All pregnant women between 24 and 28 weeks’ gestation.
2. If multiple risk factors for GDM are present, screen during the first trimester of pregnancy and reassess during subsequent trimesters.

Gestational Diabetes Screen (GDS):
a 50-g glucose load followed by a 1hPG, given at any time of day

1hPG = 7.8 - 10.2 mmol/L

75-g OGTT*
Measure FPG, 1hPG and 2hPG levels

FPG ≥ 5.3 mmol/L
1hPG ≥ 10.6 mmol/L
2hPG ≥ 8.9 mmol/L

If 2 values are met or exceeded
GDM

If 1 value is met or exceeded
IGT of pregnancy

1hPG ≥ 10.3 mmol/L

1hPG < 7.8 mmol/L

Normal

Reassess during subsequent trimesters if multiple risk factors for GDM are present

*In view of controversies about diagnostic tests, other accepted methods maybe used.

Figure 2.7: Screening for and diagnosis of GDM, CDA, 2008
## Table 2.7: Summary of different GDM screening methods in different studies:

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Title of the article</th>
<th>Authors/Journal/year</th>
<th>Objectives/methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Screening for GDM: Are the Criteria Proposed By the IADPSG Cost-Effective?</td>
<td>Erikaf. Werner, et.al/ Diabetes care, 2012</td>
<td>Compared 3 methods of screening: no screening, 50g OGCT, 100g OGTT when necessary, and IADPSG criteria</td>
<td>IADPSG criteria for glucose screening in pregnancy is cost effective and most sensitive to the likelihood of prevention future diabetes in patients identified with GDM using post-delivery counseling and intervention</td>
</tr>
<tr>
<td>2.</td>
<td>Glycohemoglobin A1c: a promising screening tool in GDM</td>
<td>Aldasouqi, S.A. et.al/ Ind J diab Dev Ctries, 2008</td>
<td>Using HbA1c as a screening tool for GDM</td>
<td>HbA1c is a reasonably sensitive screening measure of GDM in tested high risk population</td>
</tr>
<tr>
<td>3.</td>
<td>Carpenter-Coustan criteria compared with the national diabetes data Group thresholds for GDM</td>
<td>Cheng YW, et.al/ Obstet Gynecol, 2009</td>
<td>Women diagnosed by GDM according to the carpenter and coustan thresholds but not by NDDG criteria were compared with women without GDM by either criteria</td>
<td>Carpenter and Coustan criteria are recommended due to more sensitivity in compare with NDDG.</td>
</tr>
<tr>
<td>4.</td>
<td>Screening and diagnosis of gestational diabetes</td>
<td>The American college of obstetrics and gynecologists, women’s health care physicians, committee opinion, 2011</td>
<td>Two step test for 24-28 weeks of gestation pregnant women first 50g OGCT and if necessary 100g 3hour OGTT, which GDM will be confirmed</td>
<td>One step IADPSG criteria is not recommended since there is no evidence that diagnosis using this criteria leads to clinically significant improvements in maternal and newborn outcomes and it would lead to a significant increase in health care costs</td>
</tr>
<tr>
<td>5.</td>
<td>GDM: time to change our approach to screening, diagnosis and postpartum care</td>
<td>Donovan LE, Faculty of medicine, University of Calgary, Alberta, 2010</td>
<td>Screening and diagnostic testing for GDM Key differences and impact of the IADPSG guidelines For Canada</td>
<td>A reason to pause only use of IADPSG criteria as a screening tool in Canadian context is stem from the recognition that, the outcome upon which they are based, are not necessarily serious negative outcome</td>
</tr>
<tr>
<td>Serial no.</td>
<td>Title of the article</td>
<td>Authors/Journal/year</td>
<td>Objectives/methods</td>
<td>Results</td>
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</tr>
<tr>
<td>6.</td>
<td>Diagnostic criteria for gestational diabetes in relation to pregnancy outcome</td>
<td>De Sereday M, et.al, Journal of Diabetes and its Complications, 2009</td>
<td>To determine which of the American Diabetes Association (ADA) or World Health Organization (WHO) plasma glucose criteria for gestational diabetes mellitus (GDM) best predicts poor fetal outcome</td>
<td>WHO criteria was optimal for predicting macrosomia</td>
</tr>
<tr>
<td>7.</td>
<td>Efficacy and Cost of Postpartum Screening Strategies for Diabetes Among Women With Histories of Gestational Diabetes Mellitus</td>
<td>Kim C, et.al/ Diabetes care, 2007</td>
<td>To compare the cost and time to diagnosis associated with several screening strategies for diabetes (FPG, OGTT, HbA1c) in women with histories of gestational diabetes mellitus (GDM)</td>
<td>Screening every 3 years with OGTTs results in the lowest cost per case of detected diabetes</td>
</tr>
<tr>
<td>8.</td>
<td>An evaluation of the latest ADA criteria for screening and diagnosing gestational diabetes at a tertiary care hospital in the United Arab Emirates</td>
<td>Laila O. et.al/ Int J Diabetes &amp; Metabolism, 2006</td>
<td>Reports on the appropriateness of applying the latest ADA Diagnostic criteria when screening for gestational diabetes mellitus (GDM) in a tertiary care facility in the United Arab Emirates.</td>
<td>Application of the latest ADA criteria to the two-step OGTT was determined to be appropriate for UAE pregnant women tested for GDM in the tertiary care setting. Older (age &gt;30 years), multi-parous (parity &gt;4), and obese women (BMI &gt;30) were at greater risk of GDM Diagnosis by the latest ADA criteria.</td>
</tr>
<tr>
<td>9.</td>
<td>Diagnosing gestational diabetes mellitus; is the gold standard valid?</td>
<td>David Naylor CD Diabetes care, 1989</td>
<td>Is the gold standard valid?</td>
<td>Although NDDG criteria merit continued use for lack of a better alternative, new diagnostic criteria for GDM should be derived and validated</td>
</tr>
<tr>
<td>10.</td>
<td>Gestational diabetes screening and glycemic management; National survey on behalf of the Association of British Clinical Diabetologist</td>
<td>Hanna FWF, et.al, Oxford University press, 2008</td>
<td>To evaluate routine practice for GDM management across the UK.</td>
<td>Standards for GDM screening/management vary significantly across the UK. Although most centers utilize the 75g OGTT to confirm the Diagnosis, there is no consistency in its interpretation. This survey confirms the urgent need for Consensus guideline development</td>
</tr>
<tr>
<td>Serial no.</td>
<td>Title of the article</td>
<td>Authors/Journal/ year</td>
<td>Objectives/ methods</td>
<td>Results</td>
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<tr>
<td>11.</td>
<td>The Ante-partum Glucose Values that Predict Neonatal Macrosomia Differ from Those that Predict Postpartum Pre-diabetes or Diabetes: Implications for the Diagnostic Criteria for Gestational Diabetes</td>
<td>Retnakaran, R, et.al,  The Journal of Clinical Endocrinology &amp; Metabolism,2009,Canada</td>
<td>Is that the glucose values that define gestational diabetes mellitus on the OGTT relate to both of maternal GDM and neonatal LGA in the same way?</td>
<td>On ante-partum 3 hour OGTT, the FPG value best predicts LGA risk, whereas post-load glucose (2 hour) values predict postpartum pre-diabetes/diabetes.</td>
</tr>
<tr>
<td>12.</td>
<td>The Glucose Challenge Test for Screening Gestational Diabetes in Pregnant Women with No Risk Factors</td>
<td>Wong, L. et.al, Singapore Med J 2001</td>
<td>To evaluate the 50g GCT as a screening tool for gestational diabetes in pregnant women with no risk factors, to determine the prevalence of GDM in this population and to determine the perinatal outcomes of pregnancy according to the glucose challenge test</td>
<td>The 50g glucose challenge test is a useful screening test for diabetes in Singaporean Women with no risk factors.</td>
</tr>
<tr>
<td>13.</td>
<td>One step procedure for screening and diagnosis of gestational diabetes mellitus</td>
<td>V Seshiah, et.al,  J Obstet Gynecol India,2005</td>
<td>To study the merits and demerits of different screening and diagnostic procedures that is used at present And to find a one step procedure which serves both as a screening as well as a diagnostic tool.</td>
<td>Diagnosis of DM by OGTT based on initial GCT screening leaves 21.5% undiagnosed. The two step procedure of screening with GCT and then diagnosing GDM based on the cut off values with 100 g or 75 g OGTT is not practical as the pregnant women have to visit the clinic at least twice and the number of blood samples drawn vary from 3 to 5. Hence, we suggest a single glucose challenge test with 75 g of oral glucose load and diagnosing GDM if 2 hour PPG is &gt; 140 mg/dl as recommended by WHO. This method serves both as a one step screening and a diagnostic Procedure, and is easy to perform besides being economical.</td>
</tr>
<tr>
<td>14.</td>
<td>Postpartum Diabetes Screening</td>
<td>Arahkwong, R. et.al,  Diabetes care,2009</td>
<td>To determine the rate of adherence to postpartum glycemic testing in women with gestational diabetes mellitus (GDM) and the performance of fasting plasma glucose (FPG) versus the 75-g oral glucose tolerance test (OGTT) in detecting postpartum glucose intolerance</td>
<td>The rate of postpartum diabetes screening is low, and FPG lacks sensitivity as a screening test in comparison with OGTT</td>
</tr>
<tr>
<td>Serial no.</td>
<td>Title of the article</td>
<td>Authors/Journal/ year</td>
<td>Objectives/methods</td>
<td>Results</td>
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<tr>
<td>15.</td>
<td>Trends in Postpartum Diabetes Screening and Subsequent Diabetes and Impaired Fasting Glucose Among Women With Histories of Gestational Diabetes Mellitus</td>
<td>Ferrara,S.,et.al, Diabetes Care,2009</td>
<td>To examine trends in postpartum glucose screening for women with gestational diabetes mellitus (GDM), predictors of screening, trends in postpartum impaired fasting glucose (IFG) and diabetes, and diabetes and pre-diabetes detected by postpartum fasting plasma glucose (FPG) versus a 75-g oral glucose tolerance test (OGTT)</td>
<td>Postpartum screening has increased over the last decade, but it is still sub-optimal. Compared with FPGs alone, the 2-h values identify a higher proportion of women with diabetes or pre-diabetes amenable to intervention.</td>
</tr>
<tr>
<td>16.</td>
<td>Gaps in Diabetes Screening During Pregnancy and Postpartum</td>
<td>Blatt, A.J.et.al, Obstetrics &amp; Gynecology,2011</td>
<td>To estimate the screening rate and prevalence of gestational diabetes mellitus (GDM) and the screening rate and prevalence of postpartum diabetes</td>
<td>Many women may not be receiving GDM screening during pregnancy. Postpartum diabetes Screening rates after pregnancy remain low. Adoption of the new IADPSG criteria would require a significant change in current clinical practice.</td>
</tr>
<tr>
<td>17.</td>
<td>Comparison of Screening Methods for Pre-diabetes and Type 2 Diabetes Mellitus by Race/Ethnicity and Gender</td>
<td>Ashleigh E. H cath, Georgia State University Digital Archive2012</td>
<td>To compare the effectiveness of screening methods for type 2 diabetes mellitus (T2DM) and pre-diabetes by race/ethnicity and Gender.</td>
<td>This study revealed that the HbA1c test might be an effective method for Screening for pre-diabetes in racial and ethnic minorities instead of the FPG test alone. Screening in High-risk populations will help delay the onset of T2DM, with increased prevention during the pre-clinical phase.</td>
</tr>
<tr>
<td>18.</td>
<td>Specific information about the WHO guidelines for gestational diabetes screening improves clinical practices.</td>
<td>Gayet-Ageron A, et.al, J Eval Clin Pract. 2008</td>
<td>To evaluate the impact of specific information on World Health Organization (WHO) guidelines for gestational diabetes mellitus (GDM) screening on clinical practices and to estimate its acceptance by women</td>
<td>Specific information about WHO screening guidelines improves doctor practices. Moreover, the high rate of acceptance by women is an argument to promote more widespread WHO screening for GDM during pregnancy.</td>
</tr>
<tr>
<td>19.</td>
<td>Selective versus universal screening for gestational diabetes mellitus: an evaluation of predictive risk factors</td>
<td>Davey, R.X, The medical J of Australia</td>
<td>Selective screening for GDM based on prior risk assessment can reduce the need for testing, with negligible loss of diagnostic efficiency.</td>
<td>Selective screening for GDM based on prior risk assessment can reduce the need for testing, with negligible loss of diagnostic efficiency.</td>
</tr>
<tr>
<td>20.</td>
<td>Screening for biomarkers predictive of gestational diabetes mellitus</td>
<td>Georgiou, H.M, et.al, Acta Diabetologica,2008</td>
<td>To identify potential biomarkers for impending gestational diabetes that appears in the plasma before impaired glucose tolerance.</td>
<td>Both insulin and adiponectin are associated with subsequent development of gestational diabetes. Plasma insulin and adiponectin concentrations, when measured at 11 weeks, may be predictive of impending gestational diabetes.</td>
</tr>
<tr>
<td>Serial no.</td>
<td>Title of the article</td>
<td>Authors/Journal/year</td>
<td>Objectives/methods</td>
<td>Results</td>
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</tr>
<tr>
<td>21.</td>
<td>Cost-Effectivity Analysis of One-Step Versus Two-Step Screening for Gestational Diabetes</td>
<td>Sevki Celen, et.al, EAJM 2012</td>
<td>He present study aimed to investigate the difference in the cost and duration of hospital stay of a one-step procedure compared to a two-step procedure, which is routinely performed in our hospital</td>
<td>The one-step method may be preferred over the two-step (Or glucose challenge) test due to its diagnostic value and lower cost.</td>
</tr>
</tbody>
</table>
2.1.4.3. Screening in brief:

Screening procedure can only be properly evaluated when both negative and positive screenees in an adequate population are given the full diagnostic test (John O’Sullivan, 1980). But the lack of international uniformity in the approach to ascertain and diagnosis of GDM has been a major hurdle (Metzger BE, et.al).

Screening could be considered as a preventive tool. During pregnancy, women have to be screened for GDM, by assessing risk factors, by doing blood glucose testing, or both. A diagnosis of GDM identifies women at high risk for diabetes. This clinical identification provides a unique opportunity and responsibility for caregivers to educate the patient and for health care system and to equip primary diabetes prevention.

Consensus regarding optimal diagnostic criteria among the many groups and professional organizations will further much need further research regarding the benefits and harms of screening and diagnostic of GDM. Hence till that time the universal recommendation for the ideal approach for screening and diagnosis of GDM remains elusive.

In Indian context, universal screening in 24-28 weeks of gestation for all pregnant women is essential since Indian women have 11 fold increased risk of developing glucose intolerance during pregnancy as compared with Caucasian women (Dornhorst A et.al, 1992). Also the overall prevalence of GDM in India was 16.88%, with varied frequency in different parts of country from 12 to 21%.

Finally Universal in comparison with selective screening in early pregnancy, universal screening will be ideal. Even though limited studies suggest the screening to diagnose GDM in first trimester.
Table 2.8. GDM risk assessment should be ascertained at the first prenatal visit (Metzger BE and Kim YL 2008)

<table>
<thead>
<tr>
<th>LOW risk: Blood glucose testing not routinely required if all of the following characteristics are present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Member of an ethnic group with a low prevalence of GDM</td>
</tr>
<tr>
<td>No known diabetic in first degree relatives</td>
</tr>
<tr>
<td>Age &lt; 25 years</td>
</tr>
<tr>
<td>Weight normal at birth (According to local standards)</td>
</tr>
<tr>
<td>Weight normal before pregnancy</td>
</tr>
<tr>
<td>No history of abnormal blood glucose metabolism</td>
</tr>
<tr>
<td>No history of poor obstetric outcome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average risk: Perform blood glucose testing as soon as feasible after booking if one or more of the following characteristics are present</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects not classified at low risk or high risk</td>
</tr>
<tr>
<td>Subjects initially designated high risk that did not have GDM at early testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk: Perform blood glucose testing as soon as feasible after booking if one or more of the following characteristics are present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe obesity according to local standards</td>
</tr>
<tr>
<td>Strong family history of diabetes mellitus</td>
</tr>
<tr>
<td>Previous history of GDM or glucose intolerance outside of pregnancy</td>
</tr>
<tr>
<td>Glucosuria</td>
</tr>
<tr>
<td>If GDM is not diagnosed blood glucose testing should be repeated at 24-28 weeks or at any time a patient has symptoms or signs that are suggestive of hyperglycemia</td>
</tr>
</tbody>
</table>

2.1.5. Side effects of GDM on mother:

“GDM mothers in urban India are more obese and are more adipose than non-diabetic mothers. Frequently has a familial history of diabetes and show metabolic features of insulin resistant syndrome, suggesting high cardiovascular risk” (Kale, S.D, et.al, 2005).

Women with a history of GDM are at increased risk of future diabetes predominantly type2 diabetes as are their children (Kim C, et. al, 2002) approximately 7% of all pregnancies are complicated by GDM, results in more than 200,000 cases annually.
The prevalence may range from 1 to 14% of all pregnancies depending on the population studied and the diagnostic test adopted (Persson B, et.al, 1997). Mothers with GDM were at increased risk of presenting with preeclampsia, premature rupture of membranes, cesarean section, and preterm delivery.

In the classical studies by O’Sullivan, diabetes was diagnosed in 36% of women 22-28 years after a pregnancy with GDM (Hod, M et. al, 2008; O’Sullivan JB, 1989).

GDM mothers have higher of metabolic risk factors, which qualify them for the developing of the metabolic syndrome and an increased cardiovascular risk (Kale, S.D et. al, 2005; Luis FP, et. al, 2003; Sattar N, et. al, 2002).

2.1.5.1. Fetal and neonatal complications of maternal hyperglycemia:

GDM increases the risk of bad outcome in the pregnancy for both mother and the baby, and also increases the risk of “permanent” diabetes for the mother (Kale SD, et. al, 2005; Damm P, et. al, 1992; Caustan DR, et. al, 1993; Kim C et. al, 2002).

Glucose intolerance during pregnancy predisposes the offspring for increased risk of developing glucose intolerance in the future (Seshiah V, et. al, 2008). Infants born to mothers with GDM were at higher risk of being macrosomic or large-for-gestational-age (Xiong X, et. al, 2001).

Uncontrolled diabetes during the first three months of pregnancy increases the risk of abortion and congenital malformation in the fetus. Also elevated maternal blood glucose level has a direct effect on the increased susceptibility of the fetus developing diabetes later.

Neonates of GDM mothers are heavier, longer, and more adipose than those born to non-diabetic mothers, and suffer higher rate of morbidity (Kale SD, et. al, 2005).

In 1952, Jorgen Pedersen postulated that maternal hyperglycemia led to fetal hyperglycemia, which evoked an exaggerated fetal response to insulin. Since then, the Pedersen hypothesis has formed the basis for understanding the patho-physiological consequences of diabetes during pregnancy (HAPO study, 2008).

Knowledge about the role of maternal diabetes in fetal programming owes itself to Jorgen Pedersen from Copenhagen and Norbert Freinkel and colleagues from Chicago. A combination of their ideas saw the birth of the concept of fuel-mediated teratogenesis.
(Freinkel N, 1980) and extended the use of this term from disfiguring birth defects to a wide range of changes in the body habits of the developing fetus (Yajnik, CS 2010).

Fuels included glucose, fatty acids, and amino acids and were components of the culture medium bathing the fetus. Non-glucose metabolites have been forgotten in clinical practice and the importance of micronutrients was realized only recently (Yajnik CS, et al, 2008).

According to fuel-mediated teratogenesis (N. Freinkel, 1980) by changing in maternal insulinization fairly wide-ranging changes in the fetus could be seen.

Infants born to mother with type 2 diabetes are at increased risk of having congenital malformation (Dunne F, et. al, 2003, Carpenter MW, et. al, 1982).

High blood glucose levels in newborns of diabetic mothers induce oxidative stress, which in turn evokes the production of highly reactive oxygen radicals, toxic to cells, particularly to the plasma membranes where these radicals interact with the lipid bilayer (Yessoufou A et al, 2005).

The intra uterine environment assumes a great significance in determining the long-term prospects of the fetus (Gluckman PD, et. al, 2004). Maternal hyperglycemia has a direct effect on the development of fetal pancreas and is associated with increased susceptibility to future diabetes in the infant, an effect which is independent of genetic factors (Seshiah V, et. al, 2005; Dorhorst A, et. al, 1993; Jarrett RJ, 1994).

The HAPO study indicates strong, continuous association of maternal glucose levels with increased birth weight and increased cord-blood serum C-peptide levels (HAPO2008). A cross-sectional study found that pre-gestational maternal diabetes was associated with an increased risk of a major congenital anomaly, but obesity itself was not (Walsh N, 2010).

Neonatal hypoglycemia is considered blood glucose value of less than 44 mg/dl (2.6 mmol/) (Koh THHG, et.al, 1998). The prevalence of hypoglycemia in infants of GDM mothers is reported to be 25% (Agarwal RK et.al, 2000).

Development in the intrauterine environment of diabetic mother results in excess fetal growth. While maternal glucose freely crosses the placenta, maternal insulin does not (Freinkel N, 1980). The developing fetal pancreas responds to this increased glucose load.
by producing additional insulin, which in turn, acts as a fetal growth hormone promoting growth and adiposity (Freinkel N, 1980).

Other side effect of maternal hyperglycemia on mother and fetus could be: obesity, insulin resistance, hypoglycemia, jaundice, which is prevalent among 5% of neonates of GDM mothers (Engelagau MM et.al, 1995), respiratory distress syndrome (RDS) which manifest by tachynea, costal retraction, nasal flare, cyanosis, and metabolic acidosis (Robert MF, et.al, 1976) and hypocalcaemia (Lindsey RS, 2009).

Studies in Chicago also showed that children of diabetic mothers had a higher risk of glucose intolerance at a young age; this was related to higher concentration of insulin in amniotic fluid (Krishnaveni GV, et. al, 2005).

FFA uptake by the placenta and transfer to the fetus increase over gestation in response to a gestational increase in placental lipoprotein lipase activity, which appears to be increased by glucose and insulin. (Magnusson AL, et al, 2006).

Placental expression of the fatty acid transporter binding protein L-FAB also is increased in diabetic pregnancies. (Magnusson AL, et al, 2004) Together, these changes perhaps contribute significantly to the greater lipid transport to the fetus and resultant macrosomia in gestational diabetics.

Studies in India have confirmed the high risk of glucose intolerance in 5 year-old children of mothers with GDM (Yajnik CS, et. al, 2008). Other perinatal risks include shoulder dystocia, birth injuries such as bone fractures and nerve palsies and hypoglycemia.

Long-term adverse health outcomes include sustained impairment of glucose tolerance, subsequent obesity (Innes KE, et. al, 2002) (although not when adjusted for size (Rizzo Ta, et. al, 1997)), and impaired intellectual achievement (IDF, 1998).

Pronounced hyperglycemia in relation to pregnancies of women with type 1 diabetes as well as mild hyperglycemia, as seen among women with GDM are both associated with increased fetal growth and prenatal morbidity (Crowther CA, et. al, 2005; Jensen DM, et. al, 2001). Also less severe forms of glucose intolerance are associated with increased feto-maternal morbidity (Shaefer-Graf UM, et. al, 2000).
Maternal under-nutrition of calories, protein and a number of micro nutrients has a profound “programming” effect on the fetus and increase its risk of metabolic and vascular disease (Yajnik CS, 2008).

Deficiency or imbalance of vitamin B12 and folate associated with a spectrum of fetal out comes, early abortion, congenital anomalies (neural tube and cardiac defects), intra uterine growth restriction, neuro-cognitive affection, adiposity and insulin resistance (Yajnik CS, 2008). In thrifty phenotype hypothesis, proposed that “poor” maternal nutritional status increases the risk of type 2 diabetes in the off spring (Hales CN, et. al, 1992).

In developing countries like India the majority of LBW infants because of IUGR are born small at term (>37 wk of gestation) with only 6.7 % born prematurely. (Sumithra M.2009). IUGR can complicate 3-10% (Malhotra N, et.al, 2010), of all physiological pregnancies. Other causes could include maternal infections, low maternal nutrient intake, higher nutrient losses and/or increased nutritional requirements during pregnancy (Tomkins A 1989), as well as low maternal size.

Pre-pregnancy weight, BMI and gestational weight gain all have strong positive effect on fetal growth suggesting that energy balance is an important determinant of birth outcome (WHO1995) However among presented factors maternal nutrition is an important factor because it is modifiable and therefore susceptible to modifications.

So Effects of maternal diabetes on fetus and neonate can be categorized as follows: (Hod M, et al, 2008, pg352)


2.1.6. Diabetes prevention:

During pregnancy, women have to be screened for GDM, by assessing risk factors, performing blood glucose testing, or both. This clinical identification provides a unique opportunity and responsibility for caregivers to educate the patient and health care system for early management of diabetes prevention. There is substantial research evidence that lifestyle change can prevent or delay the progression of IGT to type 2 diabetes after GDM (Metzger BE, et.al, 1998; API-ICP guidelines on diabetes, 2008; Indian diabetes educator project, 2008; Douglas C.H, 2009; Cooper DH, et. al, 2007).

Improvement in glycemia by dietary modification and promotion of physical activity, and sometimes pharmacological agents, is called “diabetes prevention” (Yajnik CS, 2008)

2.1.7. Diabetes treatment:

In order to provide high-quality care a multidisciplinary team approach is essential, including a diabetologist, a nurse who specialize in diabetes, a dietitian, obstetrician, midwife and neonatologist (IDF 1998).

- Specific treatment for gestational diabetes is determined by the physician based on:
  Patient’s age, overall health, and medical history, extent of the disease, patient’s tolerance for specific medications, procedures, or therapies, expectation for the course of the disease and patient’s opinion or preference.

- Treatment of gestational diabetes focuses on keeping blood glucose levels in the normal range. Treatment may include: Special diet, exercise, daily blood glucose monitoring, insulin injections and smoking cessation (API-ICP guidelines on diabetes, 2008; India diabetes educator project, 2008; Douglas C.H, 2009; Daniel HC, et. al, 2007).

The initial post partum management of women with GDM should focus on maternal-infant well-being, encouragement and training for healthy nutrition, planned physical activity, weight reduction as needed, continued smoking cessation, breastfeeding, self-monitoring of blood glucose levels, and provision of appropriate contraception (John LK, et.al, 2008; Karter AJ, et.al, 2001).
The first line of treatment for GDM is usually dietary changes. If fasting glucose levels are unusually elevated, insulin may be started immediately. In addition to insulin therapy, diet therapy will be essential for the total care of the patient. (Pesicka D, et. al, 1996).

Insulin requirements go up one to three times in pregnancy. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset (pure GDM) or first recognition of pre-GDM, which was not diagnosed before pregnancy (Kale SD, et. al, 2005, Metzger BE, et. al, 1998, HAPO study, 2008, Anjalakshi C, et.al, 2009, Hoffman L, et. al, 1998).

2.2. Maternal metabolic changes during pregnancy in GDM vs. NGT subjects:

Pregnancy is a state of changing hormonal milieu that alters maternal metabolism. Maternal blood glucose levels decrease by 14.4 to 19.8mg/dl from normal level (0.8-1.1 mmol/lit) during pregnancy because glucose is the basic energy for fetus and placenta and also due to urinary glucose loss. The normal fasting blood glucose level in pregnancy is 59.4 to 90 mg/dl (3.3.-5.0 mmol/l) (Gillmer MDG et.al, 1975).

The second half of pregnancy is considered a diabetogenic state because the elevated gestational hormones and increased maternal weight place a demand on the body for extra insulin (Freinkel N, et al, 1985).maternal metabolism usually compensates for this altered state by secreting extra insulin. Women with GDM however decompensate from a euglycemic state to a hyperglycemic state.
Figure 2.8. Barker hypothesized that nourishment in utero can stress the fetus in ways that permanently affected development, creating a “reprogramming” of the fetus’s developing phenotype—for example, by creating a different insulin response to the nourishment available in utero, which expressed itself in later life as chronic disease. The ‘Barker hypothesis’ has become widely accepted and grown into the field of developmental origins of health and disease, which seeks to delineate the mechanisms by which unbalanced nutrition in utero and during infancy can permanently affect health (DeBoo HA, et al 2006).

Pregnancy causes alteration in maternal metabolism. This is to ensure a continuous supply of nutrients to the fetus to support the growth of fetus, despite intermittent maternal food intake. These metabolic alterations might be accentuated in pregnancies complicated with GDM. The metabolic alteration during pregnancy include: carbohydrate, lipid and protein metabolism.

Glucose, amino acids, fatty acids, as well as other nutrients, cross the placenta in diminish intensity. The maternal lipid metabolism is consistently and intensely involved during pregnancy to supply the maternal and fetal needs. Other than these three nutrients, vitamins are also necessary for fetal growth and development (Banerjee S, et.al, 2012).

Srilaxmi in her book has explained major prenatal nutrition alterations as decrease in hemoglobin status, serum vitamin C, folic acid and B12, remarkably decrease in
albumin and increase WBC, serum carotene, serum tocopherol, urinary riboflavin, etc (Srilaxmi B, Nutrition Science, pp294-315).

Insulin resistance arises as a combined effect of increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta. Since insulin resistance rapidly diminishes following delivery, it is suggested that the major contributors to this state of resistance could be placental hormones (Herrera E, et al, 2008, Buchanan & Xiang, 2005).

In normal healthy non-diabetic state, pancreatic beta cells in normal physiology increase their insulin secretion to compensate for the insulin resistance of pregnancy and thereby maintaining normal glucose level. Hence, “changes in circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity” (Buchanan TA, et al, 2007).

Robust plasticity of beta-cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy (Herrera E, et al, 2008), however “the cellular mechanisms underlying insulin resistance in normal and diabetic pregnancy” are still unknown (Bonet B, et al 2008).

Insulin resistance is an expected occurrence that ensures adequate fetal glucose supply during a normal pregnancy, particularly near mid-pregnancy, and it progresses through the third trimester (Setji et al., 2005). The insulin resistance during this phase of pregnancy approaches the level seen in patients with type 2 diabetes. This resistance arises from a combination of increased maternal adiposity and insulin desensitizing effects of hormones secreted from the placenta (Banerjee S, et al, 2012).

Pregnant women with GDM on a background of chronic insulin resistance, develop greater insulin resistance than normal pregnant women. Factors like genetic, TNF-α, adrenomedullin (newly identified peptide), adiponectin (adipose tissue hormone), hormonal effects (human placental lactogen, human placental growth hormone, leptin) which cause this resistance.

The mechanisms of GDM development are not properly understood but consist of exacerbation of the β-cell dysfunction in subjects genetically predisposed to β-cell alterations, which favor the development of GDM (Banerjee S, et al, 2012).
A woman with GDM does not demonstrate an adequate secretion of insulin during this state of insulin resistance and hyperglycemia will ensue. Loss of insulin release is a typical marker for beta cell loss seen in GDM (Buchanan & Xiang, 2005; Setji et al., 2005). Beta cell inadequacy during pregnancy can be autoimmune in nature, monogenic, or as a result of insulin resistance. The majority of women with GDM experience beta-cell dysfunction related to the latter factor, namely chronic insulin resistance.

The increased needs for insulin during pregnancy overwhelm the beta-cell functioning of a woman with GDM, and as a result, greater insulin resistance than normal tends to be manifested. Following the pregnancy, these same women continue to have chronic insulin resistance (Buchanan & Xiang, 2005, U. Satyanarayana, et. al, 2006). Yet the predominant pathogenesis factor in GDM is inadequate insulin secretion.

The principal metabolic nutrients in the fetus are glucose and amino acids as explained earlier. Glucose (including its metabolic product lactate) serves as the principal energy substrate in the fetus for maintenance of basal metabolism, energy storage in glycogen and adipose tissue, and energy requirements of protein synthesis and growth. Amino acids, while primarily providing the structural basis for protein synthesis and growth, also serve as oxidative substrates for energy production, especially when glucose is deficient.

Fatty acids also are taken up by the fetus, where they are primarily used for structural components of membranes and for growth of adipose tissue(Herrera E, et. al, 2008). Maternal triacylglycerols do not directly cross the placenta. But the fetus and newborn are benefited from maternal hypertriglyceridemia. Under fasting conditions, the maternal liver uses plasma triacylglycerols as substrates for the production of ketones. These ketones save glucose in maternal tissues as well as cross the placental barrier and are directly metabolized by the fetus (Banerjee S, et.al, 2012).

It has been reported that in normal pregnancy there is an increase of lipid peroxidation products in serum with advancing gestation, which is balanced by an adequate anti-oxidative response(Uotila J, et al, 1991, Curr diabetes report,
2005). But in diabetic pregnancy there is increased oxidative stress leading to increased free radical generation and decreased antioxidant defenses.

2.2.1. Placenta. Placenta is a multi-organ structure serving different functions for the fetus (Banerjee S, et.al, 2012). In uncomplicated maternal diabetes the placenta is heavy, large, and somewhat immature. The extent of placental findings is related to maternal insulin and glucose levels. Sometimes, maternal diabetes is associated with hypertension. Hypertension, per se, can cause vascular damage to the uterus and results in an impairment of blood flow to the placenta causing reduced placental growth and villous hypermaturity (Hod M, et al, 2008).

In mammals, the major determinant of intrauterine growth is the placental nutrient supply, which occurs primarily by diffusion and transporter mediated transport. Also placental factors lead to insulin resistance directly (e.g. hpGH, TNF-α) and indirectly through the increase in appetite and weight gain (Banerjee S, et.al, 2012). There is increasing evidence that oxidative stress arising from increased placental mitochondrial activity and production of reactive oxygen species (ROS), nitric oxide, carbon monoxide, and peroxynitrite is a general underlying mechanism of altered placental function and vascular reactivity (Bonet B, et. al, 2008).


In maternal diabetes mellitus, the human placenta undergoes a number of changes. The extent of these predominantly depends on the quality of maternal glycemic control and hence fetal glycemia. Structural changes are found mostly in the fetal aspect of the placenta (YogeY, et al, 2008).

In gestational diabetics in particular, there is increasing evidence that up-regulation of nutrient transport capacity in the placenta contributes significantly to nutrient supply to and growth of the fetus. Recent studies in vivo provide evidence for
increased delivery of amino acids to the fetus in gestational diabetes (GDM) even when metabolic control is strict. Studies in vitro demonstrate an up-regulation of placental transport systems for certain amino acids in GDM associated with fetal overgrowth (Yoge Y, et.al 2008).

![Figure2.9. Weight gain distribution during pregnancy (in Kg)](image)

### 2.2.2. Fetal nutrition and growth:

About more than two third of fetal growth occurs in the third trimester and the weight of the fetus increases from approximately 1000 g to 3400 g. Multiple factors are responsible for the variability in the fetal growth. Nutrition is the most important factor. In addition ethnic, geographic and socioeconomic are other factors (Banerjee S, et.al, 2012).

Fetal nutrition is the main regulator of fetal growth in late gestation. However the influence of maternal nutrition on fetal growth is also dependent on the relative efficiency of the fetal supply line, the timing and balance of changes in maternal nutrition, and the indirect effects of altered maternal nutrition on fetal endocrine status and substrate balance (Harding JE2001).
A chronic positive energy balance results in maternal adipose tissue accumulation which can be used later for increased fetal demands in late pregnancy and lactation (Banerjee S, et.al, 2012).

There is increasing evidence that maternal nutrition around the time of conception is particularly critical in the regulation of fetal growth. Maternal weight before pregnancy is an important influence on birth size in women, but it is not yet clear to what extent improved maternal nutrition in early pregnancy may influence birth size independent of nutritional status at pregnancy onset (Harding JE2001).

In contrary simple limitation of substrates to growing organs leading to reduction in size of those organs is an inadequate explanation. For example, maternal protein restriction in pigs results in reduced fetal weight and length at mid-gestation at a time when the fetus is extremely small (Pond WG 1991). Similarly, maternal under-nutrition in either early or late gestation in sheep, leading to fetal under nutrition and limited nutrient supply to growing organs (Oliver MH 2000, Harding JE 2001).

Lipids including essential fatty acids and long chain poly unsaturated fatty acids (LCPUFA) cross the placenta with difficulty, necessary for fetal growth and development (S. Banerjee, et.al, 2012). Also in a study by Nolan et.al 1995, they noted that triglyceride if measured between 9-12 weeks of gestation has moderate predictive value for subsequent glucose tolerance in pregnancy. It is also predictive of birth weight ratio corrected for gestational age in GDM subjects.

Fatty acids also stimulate fetal insulin secretion; their concentrations are increased in pregnant diabetics and in their fetuses in late gestation, perhaps contributing to augmented fetal insulin secretion (Catalano P et al, 2004). In contrast sustained hypoglycemia usually diminishes fetal insulin secretion (Bonet B, et.al, 2008).

Fetal growth in late gestation is normally limited by maternal size and her capacity to supply nutrients to her fetus, a phenomenon known as maternal constraint. Thus fetal growth in late gestation is normally regulated by fetal nutrient supply (Gluckman P1992).this principle of nutritional regulation of fetal growth is relatively easily demonstrated in animal species. In pregnant sheep, maternal under-nutrition in late gestation results in prompt slowing of fetal growth, and fetal growth resumes with
maternal re-feeding (a. Harding JE 1997, b. Harding JE, 1997). However such a relationship is more difficult to demonstrate in human pregnancy.

In early pregnancy fetal plasma glucose is equal or higher than maternal Glucose level but at term there is some maternal-fetal glucose gradient. Glucose production of fetus is insignificant and the fetus depends totally upon the glucose uptake by placenta from maternal circulation of which maximum amount is delivered to the fetus (Kalhan SC, et.al, 1979).

There are cases reported regarding women with sever under-nutrition for medical reasons resulting in impaired fetal growth which is at least partially reversed by improving maternal nutrition status (Rivera-Alsina ME 1984, Adami GF 1992). Never the less, in general, relationship between maternal nutrition and fetal growth is difficult to demonstrate in human pregnancy. Hence there is a difficulty in demonstrating a direct relationship between maternal nutrition and fetal nutrition.

Maternal amino-acids are the major source of nitrogen for feto-placental tissue that is transported through placenta like other nutrients (Banerjee S, et.al, 2012). Among all proteins only albumin and Ig.G are transferred to the fetus and provide the major source of nitrogen for both maternal plasma and fetus. Total amino-acid is higher in fetus than mothers (Yudilvich DL, et.al, 1985). In presence of GDM, concentrations of some specific amino-acids like alanine, phenyl alanine, methionine, leucine, isoleucine, proline, etc, are increased in fetal circulation only (Cetin I, et.al, 2005).

In randomized control trials of maternal dietary supplements have shown relatively little effect on birth weight. Supplements with a relatively high proportion of calories provided from protein actually result in reduced mean birth weight (Kramer MS 1999). Similarly, in a relatively well nourished population, the combination of high carbohydrate intake in early pregnancy and low protein intake in late pregnancy was shown to be associated with reduced birth weight, low ponderal index and reduced placental weight (Godfrey KM 1996, Godfrey KM 1997). The proportion of protein and carbohydrate in a woman’s diet in pregnancy have also been shown to influence both the placental size and the blood pressure of the adult off-spring (Campbell DM 1996).
Although it is clear from experimental data that nutrition influences fetal growth in late gestation, the mechanisms by which this occurs, are far from clear. It appears superficially logical to assume that nutrient limitation to the fetus at a given stage of development is likely to inhibit growth of organs that are growing rapidly at that time. This is explained elaborately as fuel mediated teratogenesis by N Freinkel 1980.

Karver TD et al, 1995, in Experiments on fetus of Sheep have shown that sustained, marked, relatively constant hyperglycemia actually decreases both basal and glucose stimulated fetal insulin secretion (GSIS); responsiveness to amino acids such as arginine also is diminished. In contrast, glucose-stimulated insulin secretion is augmented in most gestational diabetic women. In these cases, there is a strong tendency to develop increasingly exaggerated, meal-associated hyperglycemia in late gestation (Catalano P, et al, 2004).

Figure 2.10. Potential long range effects upon the fetus of chronic alterations in concentration of maternal fuel during pregnancy. Fuel mediated teratogenesis as the basis for long range anatomic and functional changes (Freinkel N, 1980)
Studies with fetus of a sheep have shown that the net uptake of glucose by the fetus from the placenta invariably is equal to the fetal glucose utilization rate, independently measured with glucose tracers. Thus, there is no evidence for fetal glucose production under normal conditions (DiGiacomo JE, et al, 1989).

2.2.3. Fetal exposure to diabetic intra uterine environment:

The principal actions of insulin in the human fetus are to increase protein anabolism and, by increasing cellular glucose uptake, to promote lipid formation and deposition in adipose tissue. In this situation, substrate supply (amino acids, glucose, fatty acids and triglycerides, and glycerol) is probably as or more important than insulin itself (Hod M, et al, 2008). One growth-regulating effect of insulin in the fetus is its capacity to enhance glucose utilization, in addition to its independent and direct effects to stimulate protein synthesis via the classical insulin signal transduction cascade and inhibit protein breakdown (Bonet B, et.al, 2008).

Circulating maternal lipids but not glucose correlates with fetal growth at different time points during the third trimester in a population of well controlled GDM pregnancies (Banerjee S, et.al, 2012).

Glucose-stimulated fetal insulin secretion (measured as an acute increase in fetal plasma insulin concentration) increases more than five-fold during the second half of gestation with fetus of a sheep (Aldoretta PW et al, 1998) Similar results appear to occur in human fetuses, derived from studies of human fetal islets in vitro and insulin secretion in preterm infants (Van Asscheb FA et al, 1984) Fetal insulin secretion also can be modified by the degree, duration, and pattern of changes in the fetal plasma glucose concentration (Yoge Y, et al, 2008).

During gestation, the human embryo and fetus are exposed to a metabolic environment that is determined largely by concentrations of nutrients in the maternal circulation (Buchanan 2000a).

Placenta is an important regulator of maternal-fetal nutrient transport. The rate of glucose transport is proportional to maternal circulating glucose level. The transfer of glucose to fetus is facilitated by insulin-independent glucose transport molecules (GLU-1 and GLUT-3), which are present in placenta. Amino acid and ketones are transferred
across the placenta by diffusion. FFA’s are transported down a concentration gradient from mother to fetus. Triglycerides do not appear to cross placenta, however placenta has enzymes capable of hydrolyzing triglycerides into FFA and glycerol (Buchanan2000).

Insulin and glucagons do not appear to cross the placenta under normal condition (Buchanan2000). During diabetic pregnancy, glucose, amino acids and FFAs are transferred from the maternal circulation to the fetus in excess quantity, resulting in an overfed fetus. Raised amniotic fluid insulin concentration, usually observed in diabetic pregnancies is an indicator of fetal compensation for increased nutrient delivery.

The increased release by fetus may lead to neonatal hypoglycemia during first days of extra uterine life (Rosenn and Miodovnik 2000). The evidence is agreed with the idea that exposure to elevated level of maternal nutrients leads to fetal hyperinsulinemia, neonatal hypoglycemia, and macrosomia (Pederson’s hyperglycemia-hypoinsulinemia hypothesis).

The fetal hyperinsulinemia also results in increased tissue fat, liver glycogen content, and total body size (Rosenn and Miodovnik 2000). This might be partly explained by the role of insulin as the major anabolic hormone of the fetus that increases cell size by stimulating protein synthesis and increases glucose uptake and glycogenesis in peripheral tissues (Rosenn and Miodovnik 2000).

Vitamin C plays a role in collagen metabolism and maintaining mechanical strength of the chorioamniotic membranes throughout gestation (Siega-Riz et al, 2003).
2.2.4. Carbohydrate metabolism:

Figure 2.11. Major metabolic alterations in Diabetes (Satyanarayana U, et al. 2006)

The human fetus is almost totally dependent on maternal glucose passing through the placenta, since its own glucose production is minimal (Herrera E, et al., 2008). A maternal–fetal glucose concentration gradient is normally observed at term (Desoye G, et al., 1992). Earlier in gestation, however, plasma glucose levels in the fetus may be equal to, or even higher than those in the mother (Bozetti P, et al., 1988, Nicolini U et al., 1989).

Fetal glucose utilization amounts to 38–43 µmol/kg at a maternal glucose level of 100 mg/dl (Desoye et al., 1992). This value will be higher in the presence of fetal hyperinsulinism, because trans-placental passage of glucose among other factors is directly proportional to the maternal–fetal glucose gradient (Hod M, et al., 2008).

In well-controlled GDM, maternal glucose levels are slightly but not significantly elevated. The umbilical cord glucose levels are elevated as compared to normal control subjects. However, the venous–arterial concentration difference is unchanged (Radaelli T, et al., 2005).

Factors that determine nutrient flux across the placenta, including maternal–fetal concentration gradient, maternal blood flow, placental structure and morphology,

Alterations in glucose metabolism occur significantly, in women who develop gestational diabetes relative to pregnant women with normal glucose tolerance (Catalano PM, et al, 2003).

During normal pregnancy, the body insulin sensitivity is found to be reduced 45-70% below non-pregnant women (Buchanan, 2000b). The insulin sensitivity decreases progressively throughout pregnancy to ensure glucose to be shunted from mother to fetus and meet the need of fetus for growth and development (Buchanan b2000).

A progressive increase in basal and post-prandial insulin concentration is found with advancing pregnancy. This hyper-insulinemia represents the β-cells compensation for pregnancy-induced insulin resistance (Buchanan 2000b, Butte 2000). Although the cause of enhanced insulin secretion is not clearly understood, it might be due to increase in β-cell mass that appears to be of both hypertrophy and hyperplasia. (Buchanan 2000b).

Basal hepatic glucose production is lower in third trimester in healthy pregnancy compared with non-pregnant women, whereas the insulin level is almost doubled. Endogenous glucose production remains sensitive to increased insulin concentration throughout gestation. This is in contrast with the progressive decrease in peripheral insulin sensitivity (Butte 2000). Gluconeogenesis is increased in late gestation. (Butte2000).
Figure 2.12. Normal Hormonal regulation of blood glucose (U Satyanarayana, et. al 2006)

Significant alteration in glucose metabolism has found in women with GDM relative to healthy pregnant women. Studies on metabolic status of women with GDM shows that in late gestation these women have up to 40% lower insulin sensitivity, increased fasting glucose concentration and low suppression of hepatic glucose production during insulin infusion relative to matched normal glucose tolerant pregnant women (Herrera E, and Ortega H, 2008).

The imbalance between insulin resistance and pancreatic β-cells compensation in GDM pregnancy, results in abnormalities in maternal circulation level of carbohydrates, lipids and proteins (Ryan 1985, Catalano 1993, Butte 2000).

2.2.5. Fat metabolism:

Fat accumulation takes place during the first two trimester (Lupe LP, et.al, 1991) most of increase in maternal structure which takes place during pregnancy and increments of maternal fat deposition stop during the third trimester of gestation. This is due to first decrease in lipoprotein lipase (LPL) activity and increase in adipose tissue lipolytic activity (Banerjee S, et.al, 2012).
At delivery of a normal pregnancy the concentrations of cholesterol, triglycerides, total free fatty acids and lipid soluble vitamins are higher in the maternal side than umbilical circulation. However, individual fatty acids in the total plasma compartments such as total saturated fatty acids and arachidonic acid are selectively enriched in the umbilical cord blood. In GDM the mothers have unchanged arachidonic acid and docosahexaenoic acid levels, whereas the concentrations of both fatty acids are lower in their offspring than in normal pregnancies (Herrera E and Ortega H, 2008).

In other words during pregnancy, there is a changed in hepatic and adipose metabolism, which leads to a shift from anabolic to catabolic state in lipid metabolism. This leads to alteration in circulating concentrations of triglycerides, fatty acids, cholesterol, and phospholipids and would promote the use of lipids as maternal energy source while preserving glucose and amino-acids for the fetus (Butte 2000, Catalano 2003).

To state the matter differently alteration of lipid status developped during the last third of gestation and mainly manifested by the increase in tri-acyl-glycerols with smaller rises in phospholipids and cholesterol (Herrera E and Ortega H, 2008). There is an increase in VLDL levels as a result of their enhanced liver production and decreased removal from circulation as a consequence of reduced adipose tissue LPL (lipo protein lipase) activity in biochemical scene (Banerjee S, et.al, 2012).

Two important alteration in lipid metabolism during pregnancy include, stimulation of lipolysis and ketogenesis that is progressive over the course of gestation, and increase in circulating triglycerides concentrations (1.5-2.0 fold above non-pregnant levels by third trimester) (Buchanan 2000b).

The hypertriglycridemia might result from interaction of several factors such as increased circulating free fatty acid concentration and hyperinsulinemia (combined to promote triglyceride synthesis in the liver), increase food intake ( resulting in increased appearance of chylomicrons from the gut) and reduced activity of lipoprotein lipase in adipose tissue (resulting in reduced clearance of triglyceride from circulation)(Buchanan 2000b)
Studies on lipid metabolism during GDM pregnancy indicate that, there is an increase in triglyceride, decrease in HDL-C with mild alteration in free fatty acid (FFA) concentrations throughout gestation. The ability of insulin to suppress FFA is decreased in GDM pregnancy in compare with normal glucose tolerant pregnant women. An increased fat catabolism, which is the risk for fasting ketosis is also reported in diabetic women (Butte 2000, Catalano 2003).

High-fat diets have been associated with the development of glucose abnormalities in pregnancy (Saldana TM et al), and with the recurrence of GDM in future pregnancies (Moses RG et al).

Fat content in the American Diabetic Association’s diet consists of less than 25% of the total caloric intake, whereas the euglycemic diet (refer to appendix) is composed of 40% of the total daily caloric intake. The role of saturated and monounsaturated fats in GDM women is different with respect to the uptake of glucose post-prandially. In a study comparing these two types of fats, 1-h postprandial glucose levels are approximately equal; however, the duration of the elevated glucose levels differ.

In GDM women who consumed mono-unsaturated fat, the glucose levels remained elevated longer and thus insulin dosage had to be adjusted to counteract the maintained elevated glycemia. Conversely, meals consumed containing saturated fat, had a shorter duration of elevated glucose levels, making them preferential with regard to glycemic control of postprandial glucose levels (Hod M, et al, 2008, pg 200).

**2.2.6. Protein metabolism:**

Protein is essential for fetal growth. During first trimester, the level of protein synthesis is similar in non-pregnant and pregnant women. However there is a progressive increase in protein synthesis during pregnancy (15% increase in 2nd trimester and 25% during 3rd trimester) (Duggleby and Jackson 2002). The results from few studies on protein metabolism during GDM pregnancy are contrary. Rate of protein turn over (synthesis and degradation) is reported to be increased or unaltered in GDM (Butte 2000).

Protein content in the ADA diet and euglycemic diet makes up 20% of the total daily caloric intake. Increased satiety has also been correlated with meals that are high in
protein content (Hill AJ, et.al, 1986, Westerterp-Plantenga MS, 2003). Thus, this aspect could help morbidly obese patients manage their overall caloric intake especially when moderate caloric restriction therapy is being used. Low carbohydrate/ high protein diets in normal pregnant women have been explored notably in the Mother well studies running from 1938 to 1977. The Mother well studies suggested a link between increased protein content and low birth weight (Kerr JF, et al, 1978, pp518-534).

There is also pregnancy induced hypoaminoacidemia and diminished amino acid response to protein intake, suggesting an increased uptake of amino acids in the splanchnic compartment (Kalhan 2000). The amount of the circulating amino acids has been related to fetal outcome, particularly to infant birth weight (Kalhan 2000).

“Different mechanisms involved in reduced amino acid levels include: A. the effect of placental hormones on amino acid release from skeletal muscles (during fasting state). B. accelerated uptake of amino acids in response to postprandial hyperinsulinemia C. alterations in the distribution volume of amino acids as a result of intravascular and interstitial volume expansion during pregnancy. D. increased amino acid utilization by the fetus during late pregnancy” (Buchanan 2000b).

It is assumed that leucine represents fixed component of the whole body protein and therefore the rate of appearance of leucine can be used to calculate the rate of protein breakdown or proteolysis. The rate of appearance of leucine per Kg body weight is found to be significantly less in pregnant women than in non-pregnant women. However, the total rate of appearance of leucine is similar in the pregnant and non-pregnant control group (Kalhan 2000).

The decreased insulin sensitivity manifested by a decreased suppression of leucine turnover, during insulin fusion in late gestation is reported in all pregnant women. There is also evidence for an increase in basal leucine turnover in women with GDM compared with matched control group (Catalano 2003).

The pregnant women do not store protein during early pregnancy, when fetus needs are scarce. The increased requirements of late pregnancy must be met by metabolic adjustments that enhance both dietary protein utilization and nitrogen retention in order to satisfy fetal needs (Bnaerjee S, et.al, 2012). The rate of maternal nitrogen retention...
between 20 and 40 weeks of gestation is higher than predicted need (Mojtahedi M, et.al, 2002) so that the mother gains additional protein in her own tissue.

However among the maternal plasma proteins, only IgG and albumin are able to be transported to the fetus in significant amounts. Therefore, maternal amino acids provide by far the major source of nitrogen for both the placenta and the fetus. Total amino acid concentrations are higher in fetal plasma than in the maternal circulation (Herrera E, Ortego H, 2008).

The concentrations of most amino acids in the placenta exceed those in the maternal and fetal circulation, probably due to a high content in the syncytiotrophoblast. High amino acid concentrations are generally associated with a high rate of protein synthesis and are characteristic of rapidly growing tissues (Herrera E, Ortego H, 2008).

In human pregnancies complicated by gestational diabetes the concentrations of some amino acids (methionine, isoleucine, leucine, phenyalalanine, alanine and proline) are selectively increased in the fetal circulation with no apparent change in the maternal circulation. This strongly suggests an altered amino acid metabolism in placenta, fetus or both or a change in maternal-to-fetal amino acid transfer (Yoge Y, et.al, 2008).

2.2.7. Vitamin/mineral metabolism:

Presence of adequate micronutrient and vitamin is essential during pregnancy. During pregnancy major changes also occur in vitamin metabolism. Vitamin A and E are most affected ones. Maternal plasma retinol falls as gestation advances, whereas vitamin E levels increase parallel to the increase in plasma lipids. Trans-placental transfer of these vitamins is limited, but both the fetus and the newborn need them, which will be provided during lactation. (Bnaerjee S, et.al2012)

It is believed that the ascorbic acid is converted to dehydroascorbic acid, before crossing the placenta to enter fetal circulation. There it is reduced back into ascorbic acid and maintain in high concentration on the fetal side of the placenta. Lee BE et, al in 2004 have found that Maternal serum plasma vitamin C during the second trimester of gestation have been correlated with birth weight and length in full term babies.
Pregnant women utilize a defense mechanism, composed of antioxidant enzymes and nutrients including vitamin C, against oxidative stress and free-radical damage. (Bnaerjee S, et.al2012).

Iron deficiency is the most commonly recognized nutritional deficiency in both the developed and developing world. It is estimated that <50 % of women do not have adequate iron stores for pregnancy (Muthayya S, 2009).

Requirements for absorbed iron increase during pregnancy from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester. Average requirement during the entire gestation is approximately 4.4 mg/day. (Muthayya S, 2009). An adequate iron balance during pregnancy implies body iron reserves of >500 mg at conception. The physiologic iron requirements in the second half of gestation cannot be fulfilled solely through dietary iron (Milman N. et.al, 2006).

2.3. Medical nutrition therapy (MNT) in diabetes:

The controversies in GDM management includes how far to manipulate energy intake, dietary composition (Carbohydrate and fat) and gestational weight gain (Banerjee S, et.al, 2012). However treatment strategies must be targeted to prevent over-nutrition of the fetus (Jovanovic L, 2000). Over-nutrition of the fetus leads to macrosomia, and consequently other complications like, still birth, shoulder distocia, insufficient lung maturation due to elective early delivery because of fetal macrosomia.

Also the management of diabetes is aimed at maintaining the glucose levels within normal levels but it is important to prevent hypoglycemia. This is the most important aspect in managing GDM and juvenile diabetes. Dietary counseling should be based on increased consumption of low glycemic index (GI) foods and avoidance of free sugars. Carbohydrate is the main source of calories which affects post prandial glucose levels (Bhaskarachary K, et.al, 2010)


MNT is the cornerstone of treatment for GDM. However, relatively little information is available to allow evidence-based recommendations regarding specific nutritional approaches such as total calories and nutrient distribution to the management of GDM. (API-ICP diabetes guideline, 2007; India diabetes educator project, 2008; Douglas CH, 2009; Daniel H. Cooper, 2007; Alpers DH, et.al, 2008; Irawalinsky,2007 ; ADA,2000; ICMR guidelines for T2DM, 2007; Sadikot SM, 2006; ADA 2008,ADA 2001).

The food plan should be designed to fulfill minimum nutrient requirements for pregnancy and to achieve glycemic goals without inducing weight loss or excessive weight gain. Adequate energy intake that provides appropriate weight gain is recommended during pregnancy. For overweight and obese women with GDM, modest energy and carbohydrate restriction may be appropriate.

Ketonemia from starvation should be avoided (Boyd E, et. al, 1998), however IOM 1990 introduced weight gain as 12.5-18 kg for underweight (<19.8 kg/m²), 11.5-16 kg in normal weight (19.8-26 kg/m²), 7-11.5 kg in over-weight (>26 kg/m²), at least 6 kg in obese subjects (>29 kg/m²) and 16-20.5 kg in twins pregnancy.

In Normal pregnancy, expected weight gain varies based on prenatal BMI. In a report(Metzger BE, et. al, 1998) recommended a relatively small gain during pregnancy of 7 Kg or 15 lb for patients who are obese (BMI 30 kg/m²) and a proportionally greater weight gain (up to 18 kg ) for patients who are underweight (BMI <18.5 kg m²) at the onset of pregnancy . Plotting weekly body weights on a weight gain grid specific to BMI classification is encouraged to facilitate recognition of inadequate or excess weight gain (Metzger BE, et. al, 1998).

Planned physical activity of 30 min/day is recommended for all individuals capable of participating. Advising GDM patient to walk briskly or do arm exercises while seated in a chair for at least 10 min after each meal accomplishes this goal with safety precautions. Regular aerobic exercise with proper warm-up and cool-down has been shown to lower fasting and postprandial glucose concentration in several small studies of
previously sedentary individuals with GDM (Metzger BE, et. al, 1998; Hinnen D, et. al, 2005).

The American College of Obstetrics and Gynecology has published guidelines for safe exercise during pregnancy and also gives guidelines for which women should not be encouraged to exercise (ACOG technical bulletin, Feb 1994) In general, for a healthy pregnancy, moderate regular exercise of a non-standing nature (cycling, swimming) that does not require a lot of balance, when well-hydrated and well-nourished, is encouraged.

Hypertensive women, however, should not exercise, as this may lead to preeclampsia. (Thomas-Doberson D, 1999). Brisk walking, cycling, and swimming are often done safely by pregnant women. Communities often have prenatal exercise programs in pools or gyms. Exercising for 15–20 minutes after a meal may help to keep blood glucose levels within the target range for women with GDM (Thomas-Doberson D, 1999).

The goals of MNT are to provide adequate nutrition for the mother and fetus. Provide sufficient calories for appropriate maternal weight gain, maintain normoglycemia, and avoid ketosis. In general, energy requirement does not increase during the first trimester of pregnancy (Setji TL, et.al, 2005). However women with normal weight, require an additional 30 kcal/kg in their second and third trimester. The principle approach to glycemic control in pregnant women with diabetes is dietary therapy, with the addition of insulin when diet alone is not sufficient. (Langer O, et. al, 2000; Langer O, et. al, 1994; ACOG bulletine 1994; ADA 1998; Metzger BE, et. al, 1998).

In the normal weight GDM women, the recommended daily calories intake is 30 kcal/ kg/ day based on their present pregnant weight. In women with GDM who are overweight (BMI>30 kg/m²) a 33% calorie restriction of their estimate energy needs is recommended. (25 kcal/ kg/ day based on their present pregnant weight). This level of calories restriction is not associated with an elevation of free fatty acids or ketonuria (Srilaxmi, 2007). Antioxidants may be necessary in high risk cases particularly vitamin C and vitamin E which is known to prevent pre-eclampsia and congenital malformations (Chappel LC, et.al, 1999).
In conclusion flat recommendation for pregnancy diabetes will not work and time
to time modifications are to be accomplished on the basis of assessment of metabolic and
physiological changes, taking into account the maternal health and fetal growth (Banerjee

2.4. Nutritional requirements during pregnancy, effects on mother and fetus:

In experimental animals, the relative distribution of embryonic cells to the inner
cell mass (which develops into the fetus) and the troph-ectoderm (which becomes the
placenta) is largely determined by maternal nutrient availability. (Sacks DA, et.al 2004).

Appropriate nutrient intake and weight gain during pregnancy are considered as
two of the most important modifiable behaviors for improved maternal and infant
outcomes, (Institute of medicine (IOM), 1990). The WHO collaborative study on maternal
anthropometry and pregnancy outcomes (WHO, 1995, Kelly et.al 1996), reviewed
information on 110,000 births from 20 countries to determine anthropometric indicators
associated with poor fetal outcomes, such as LBW, IUGR, and pre-term birth. Also with
poor maternal outcomes such as pre-eclampsia, eclampsia, need for assisted delivery, and
post-partum hemorrhage.

Attained maternal weight (pre-pregnancy weight plus pregnancy weight gain) was
the most significant predictor of LBW and IUGR. Low pre-pregnancy weight and BMI,
and weight gain between 20 and 28 weeks of gestation were moderate predictors of pre-
term delivery. And low maternal height (e.g. 146 compared with 160 cm) was a moderate
predictor of caesarean delivery (Merchant KM et.al, 2001).

Women with short stature especially in developing countries with inadequate health
care systems and high prevalence of impaired growth during child hood are also at high
risk of developing LBW or have pre-term delivery, and of obstetric complications during

An analysis of studies in 20 countries (Kelly et al, 1996) showed that in ten
countries many women had pre-pregnancy weight of less than 50 Kg and heights of less
than 150 Cm. these cut-off points were associated with increased risks of maternal
complications. In addition weight below 45 kg or height below 148 cm was associated
with poor fetal outcome.
The association of short stature with increased risk of either delivering a low birth weight infant or requiring special assistance during delivery owing to cephalo-pelvic disproportion (Merchant KM, et.al, 2001) indicates the importance for such women to have adequate prenatal attention and access to appropriate care during labor and delivery.

This also reinforces the recommendations for good nutrition and measures to prevent repeated infections during childhood, which may result in stunting and in pregnancy-related problems at a later age.

Under-nutrition is the relative risks of neural tube defects, congenital malformations whereas pre-term delivery is higher in overweight and obese women (March of Dimes, 2002).

Maternal nutritional status both before and during pregnancy is a well-recognized determinant of birth outcomes (Osrin D, 2000). Only two indicators of maternal nutritional status during pregnancy have shown consistent positive association with infant birth weight: maternal pre-pregnancy weight for height and weight gain during pregnancy (Neggers Y, 1995).

In 1990 the United States institute of medicine established new weight gain recommendations for women during pregnancy using BMI as the preferred way to classify women into pre-pregnancy weight categories. A low pre-pregnancy BMI is considered a marker for minimal tissue nutrient reserves (Schieve LA, 2000). Women with low pre-pregnancy weight for height or BMI are at increased risk for a number of adverse pregnancy outcomes, including pre-term birth and IUGR (Siega-Riz, AM, 1994).

Schieve LA (2000) reported that women with low pre-pregnancy BMI were at increased risk of pre-term delivery only if they failed to gain weight at an adequate rate during pregnancy. Considerable evidence suggests a role for micronutrients in pregnancy outcomes (Seshadri S, 2001, Bendich A, 2001).

Nutrition intervention studies have not provided unequivocal evidence of an association between micronutrient intakes and pregnancy outcomes such as birth weight, IUGR, pre-term delivery and pregnancy induced hypertension (Onis M, 1998, Ramakrishnam U, 1999).
Indications that ‘the balance of macronutrients in the mother’s diet can have important short and long-term effects on the off-spring’ have been reported from the experimental studies in pregnant rats. These have found that maternal diets with a low ratio of protein to carbohydrate and fat alter fetal and placental growth, and result in lifelong elevation of blood pressure in the off spring (Langley-Evans SC 1994).

A follow up study of 40 year old men and women in Aberdeen UK suggested that alterations in the maternal macronutrient balance during pregnancy could have similar adverse effects on the off-spring (Campbell DM 1996).

2.4.1. Energy:

The maternal diet during pregnancy must provide sufficient energy to ensure the delivery of a full-term healthy infant of adequate size and appropriate body composition. The total cost of energy during pregnancy has estimated as around 77000 kcal. In an environment in which food intake cannot be increased, pregnant women have ‘metabolic plasticity’ and adapt in order to conserve energy, presumably for the developing fetus.

In an environment with ample resources an increase in nutrient intake results in a positive energy balance throughout pregnancy. Therefore recommendations for the adequacy of caloric intake are variable and largely dependent on the resources available and the nutritional status of the mother at the start of pregnancy (Banerjee S, et.al, 2012). There is a suggestion of calorie restriction in obese pregnant with minimum 1800 calorie per day (Reader DM, 2007).

In obesity calorie restriction up to 50% is safe but close watch on fetal growth and maternal ketosis should be maintained (Banerjee S, et.al, 2012). Also in general calorie should be distributed in three major meals and 3-4 snacks (Banerjee S, et.al, 2012).

2.4.2. Protein:

The total protein requirement during pregnancy has been estimated to be approximately 925 gm for a woman gaining 12.5 kg weight during gestation and delivering an infant of 3.3 kg. (Hyttten 1980). Protein is not gained at a constant rate, the rate at which protein is deposited increases as pregnancy progresses. Estimates for the first, second, third, and fourth quarters are 0.64, 1.84, 4.76 and 6.10 gm of protein per day, respectively (FAO/WHO/UNU1985).
Results from rodent studies suggest that low protein intake during gestation can result in low birth weight or thinness at birth and subsequently the development of metabolic disturbances in adult life, such as high blood pressure, impaired glucose tolerance and insulin resistance (Lucas A 1998). By contrast there is some evidence that high protein or energy intake during gestation can lead to reduced birth weight (Daenzer M, 2000, Robinson JS, 1994, Rush D, 1989).

However, more recent estimates from longitudinal studies of women in developed countries (e.g. U.K, USA) suggests protein gains in pregnancy may be lower, in the range of 497 to 696 gm for an average weight gain of 12 kg.(FAO/WHO/UNU 2004).

2.4.3. Fats:

An adequate amount of dietary fat is essential for health, particularly for pregnancy and lactation. Essential fatty acids play a major role during pregnancy. They provide the precursors for prostaglandins and leucoterins and are present mainly in highly specialized membranes (retina and synapses) (Srilaxmi, B, 2007).

The consumption of essential fatty acids is deemed important for normal growth and development in infants. The interest in essential fatty acids in relation to pregnancy stems from both epidemiological observations (Oslen SF, 1989, 1990, 1991, 1993, 2006 Harper V, 1991) and intervention studies (Oslen SF and Secher NJ, 1990, Oslen SF, 1992). They showed longer gestation, larger babies and in some cases, reduced numbers of pregnancy complications such as intra-uterine growth retardation (IUGR), pregnancy induced hypertension (PIH), and pre-delivery in association with higher marine fatty acid (long chain PUFA or n-3 fatty acids), fish or fish oil intake.

No dietary reference intakes (DRIs) for total lipids during pregnancy have been established. The amount of fat in the diet should depend on energy requirements for proper weight gain (IOM2002). However pregnant women and those planning a pregnancy need an adequate dietary intake of essential fatty acids and their longer chain derivatives, DHA and arachidonic acid, Which are necessary for the development of the brain and nervous system of the fetus, particularly in late pregnancy.(British national formulary (BNF)1999). The best dietary source of long chain n-3 fatty acids (EPA and DHA) is oil-rich fish (Williamson CS, 2006).
There is a need of prospective clinical trials on ratio of SFA: PUFA: MUFA. Till now suggested ratio is 1:1:1 with oily fish three times per week for ω3 fatty acid source (Lean MEJ, et.al, 1992).

The most vulnerable period of neural development is during embryonic and fetal growth. Essential fatty acids, especially DHA, are required for fetal brain, nervous system and retinal growth in late pregnancy. The maternal plasma concentration of individual fatty acids, and hence the composition of the maternal diet, may have large effects on long-chain PUFA delivery to the fetus. (Drouillet P, 2009).

### 2.4.4. Carbohydrate:

The institute of medicine has established DRIs for carbohydrate intake during pregnancy. The estimated average requirements (EAR) are 135gm/day, and the adequate intake (AI) is 175 gm/day (IOM 2002). The recommended amount of 135 to 175 gm/day is the quantity needed to provide enough calories in the diet, to prevent ketosis, and maintain appropriate blood glucose levels during pregnancy (Mahan LK, 2008).

In another prospective observational study conducted to assess how nutrient intakes of mothers in early and late pregnancy influence placental and fetal growth and concluded that “mother who had high carbohydrate intakes in early pregnancy had babies with lower placental and birth weights” (Borazjani F, 2012).

Post-prandial hyperglycemia is very common during pregnancy and is the risk time for feto-maternal glucose transfer (De-Veciana M et.al, 1995). ADA recommended lowering of carbohydrate up to 40% of total calorie and increase fat up to 40% (Jovanovic L, 1998), Whereas Reader DM in 2007 suggested 35-40% of carbohydrate for total calorie. Besides the total amount of carbohydrate the type of carbohydrate is also matter. Intake of low glycemic index (<55mg) which produces a lower post meal glucose elevation are preferred source (Moses RG et.al, 2009). Also when additional insulin is required low glycemic snacks are necessary between meals to avoid hypoglycemia and weight gain (Banerjee S, et.al, 2012).

Reece EA et.al, (1993) were studied on low, moderate and high fiber diet (20, 40-60, 70-80g per day respectively) in non-insulin required GDM subjects. They demonstrated that high fiber were not associated with a lowering of blood glucose level.
More international studies to assess the effect of low glycemic index diet in GDM women are necessary.

2.5. Antioxidants:

Free radicals influence cellular and molecular biology/physiology and human disease. Nature is sometimes incapable of providing conditions for human body to control the biological production of very active chemical substances, known as free radicals and this can lead to biochemical modifications, cellular damage and even death of the organism. The role of diet on the deleterious effects of oxygen is important. Eventhough vary considerably according to the organism tested, age, physiological status and diet history (Moreira EAM, et.al, 1997).

**Functional foods:** Department of food science and technology, Ohio state university has defined functional foods as “any food or food ingredient that may provide health benefits beyond the traditional nutrients that it contains.” Antioxidants are a group of functional foods.

The term antioxidant describes dietary components that have the ability to protect body cells by binding with free radicals to prevent oxidation in cells and DNA, (Nutrition update, 2008). Thus the USDA definition of antioxidant can be extended in a nutritional context to include “compounds that protect biological systems against the potentially harmful effects of processes or reactions that can cause excessive oxidations (Srilaxmi, 2007).

Antioxidant absorption and utilization vary depending on the particular antioxidants ingested, the characteristics of the food or beverage suppling the antioxidants, and other foods eaten along with it (Nutrition update, 2008). USDA scientists have found that absorption and utilization of antioxidants vary among different food sources (Prior RL, et al, 2007).
Table 2.9: Dietary antioxidants: (srilaxmi, 2007)

<table>
<thead>
<tr>
<th>Nutrient:</th>
<th>Non- nutrients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-carotene- provitamin A</td>
<td>Carotenoids (lycopene, Xanthophylls)</td>
</tr>
<tr>
<td>Ascorbic acid-vitamin C</td>
<td>Lutein, α- and γ- carotenes (cryptoxanthine, zeaxanthine)</td>
</tr>
<tr>
<td>Tocopherols</td>
<td>Flavonoids (quercetin, myrictin, quercetagatin, gossypetin)</td>
</tr>
<tr>
<td>Tocotrienols</td>
<td>Isoflavones</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>Anthocyanins</td>
</tr>
<tr>
<td>Sulphar amino acid</td>
<td>Phenolic compounds (catechin)</td>
</tr>
<tr>
<td>Cysteine and methionine</td>
<td>Phenolic compounds (catechin)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Indoles</td>
</tr>
</tbody>
</table>

Another study revealed that the role of diet on the deleterious effects of oxygen vary considerably according to the organism tested, age, physiological status and diet consumed (Moreira EAM, et.al, 1997)

As U. Satyanarayana, et.al, (2006) has defined “A free radical as a molecule or a molecular species that contains one or more unpaired electrons, and capable of independent existence. It is estimated that about 1-4% of the O2 taken up by the body is converted to free radicals. The common characteristic features of free radicals are: highly reactive, very short half-life can generate new radicals by chain reaction, cause damage to bio molecules, cells and tissues. Free radicals are highly reactive, and are capable of damaging almost all types of bio-molecules (proteins, lipids, carbohydrates, nucleic acid).”

Srilaxmi (2007) believes that the normal functioning of cells is dependent on a proper balance of pro-oxidants and antioxidants. The former promote the release of oxygen to provide energy needed for cell functioning. In this process, different biochemical reactions take place, which continuously produce various free radicals. If these free radicals are not quenched by antioxidants, they cause damage to the cells, proteins, DNA, and RNA (Srilaxmi, 2007). Cumulative tissue injury thus caused by free radicals is now known to underlie the pathogenesis of such diverse conditions as non-
communicable disease like Diabetes, cancer, atherosclerosis, radiation damage and accelerated aging (Srilaxmi, 2007).

In addition U. Satyanarayana, et.al, (2006) showed that free radicals have been implicated in the causation and progress of several diseases such as: cardiovascular disease (CHD), cancer, inflammatory diseases, respiratory diseases, cataract, male infertility, aging process, Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, liver cirrhosis, muscular dystrophy, toxemia of pregnancy, diabetes, etc.

Reactive oxygen species (ROS)-induced mitochondrial abnormalities may have important con-sequences in the pathogenesis of degenerative diseases like DM. Vitamin C is an important antioxidant known to quench ROS. (Sagun KC et al, 2005).

2.5.1. Oxidative stress: harmful effect of free radicals:

Oxidative stress is an imbalance between the production of free radicals and the synthesis of antioxidant defense against them (Chen X et al, 2005) (figure2.13). Oxidation has an effect on major macronutrient such as carbohydrate, protein and lipids (PUFA). In healthy individuals antioxidants supply can be accomplished through a balanced diet with 3 servings of vegetables and 2 servings of fruits. However deficiency may result due to inadequate dietary intake, intestinal disease or accelerated metabolic conditions etc (Chertow MD, 2004).
Oxidative stress is defined as excess pro-oxidants and reduced concentration of antioxidants leading to potential cellular damage (Blumberg J 2004).

Alteration in oxidant antioxidant profile is known to occur in diabetic pregnancy (Carone D, 1993). In addition it has been established that oxidative stress is induced by both the increases in free radicals and the disturbance in the free radical scavenging system in diabetes mellitus (Therond P, et al, 2000, Sinclair AJ, 1993). Similarly there is an evidence suggests that oxidative stress may contribute to the pathogenesis of type 2 diabetes by increasing insulin resistance or impairing insulin secretion(Oberley LW, 1988).

The effect of free radicals in diabetes will be Destruction of islets of pancreas due to the accumulation of free radicals is one of the causes for the pathogenesis of insulin-dependent diabetes mellitus (Satyanarayana U, et. al, 2006).

“Oxidative stress due to the damage brought about by free radicals is also known to influence formation of anomalies in fetuses born to women with diabetes. Factors responsible for these anomalies are not fully understood but there are several reports showing that increased free radical production and antioxidant depletion in diabetic pregnant women might contribute to formation of anomalies”(Eriksson UJ, et al, 1991).
In diabetes, excess oxygen radicals may result from auto oxidation of glucose (Wolff SP, et al, 1991) and increased glycated hemoglobin levels, because of increased glucose levels in body (Eriksson UJ, et al, 1991). There is considerable evidence that antioxidant defense system is depleted and activity of antioxidant enzymes is reduced in diabetes (Tho LL, et al, 1988).

Oxidative stress may be amplified by a continuing cycle of metabolic stress, tissue damage and cell death leading to increased free radical production and compromised free radical scavenger system which further exacerbates the oxidative stress (Baynes JW, 1991). Also it has been seen that increased blood glucose levels induce oxidative stress and decrease antioxidant defenses apparent in diabetes (Thou LL, et al, 1988).

2.5.2. Antioxidants in biological system:

“Antioxidants can be categorized in different groups as follows (Satyanarayana U, et. al, 2006).

2.5.2.1. Antioxidants in relation to lipid peroxidation: which comprising of two subgroups, 1. Preventive antioxidants that will block the initial production of free radicals (e.g. catalase, glutathione peroxidase). 2. Chain breaking antioxidants that inhibits the preoperative phase of lipid peroxidation (e.g. superoxide dismutase (SOD), vitamin E, uric acid) (Satyanarayana U, et. al, 2006).

2.5.2.2. Antioxidants according to their location: Including three sub-groups, Plasma antioxidants e.g. β-carotene, ascorbic acid, bilirubin, uric acid, ceruloplasmin, transferin, cell membrane antioxidants e.g. α-tocopherol, Intracellular antioxidants e.g. superoxide dismutase, catalase, glutathione peroxidase (Satyanarayana U, et. al, 2006).

2.5.2.3. Nutrient and metabolic antioxidants: Nutrient antioxidants are Comprising of tocopherols (Vitamin E), ascorbic acid (vitamin C), carotenoids (vitamin A precurser), selenium, whereas there are many metabolic antioxidants of biological importance. A selected few of them are listed below with a short explanation of their roles (Satyanarayana U, et. al, 2006).

Gluthatione: reduced glutathione (GSH) plays a key role in the biological antioxidant enzyme system. GSH and H2O2 are the twin substrates for gluthathione
peroxidase. The reduced glutatione (GSH) gets regenerated from the oxidized glutatione (GS-SG) through the participation of glutatione reductase NADPH. It is suggested that the ability to synthesize GSH decreases as age advances, and this has been implicated in certain diseases e.g. cataract. **Uric acid**: a powerful scavenger of singlet oxygen (\(^1\)O\(_2\)) and OH radicals. **Ceruluplasmin**: inhibits iron and copper dependent lipid peroxidation. **Transferrin**: binds to iron and prevents iron-cataysed free radical formation. **Albumin**: can scavenge the free radicals formed on its surface.

**Bilirubin**: protects the albumin bound free fatty acids from peroxidation. **Haptoglobin**: binds to free hemoglobin and prevents the acceleration of lipid peroxidation (Satyanarayana U, et. al, 2006)

### 2.5.3. Biomarkers according to oxidative stress: (Chen X, et al, 2005)

#### 2.5.3.1. Markers of DNA oxidation and damage: 8hydroxydeoxyguanosine (8 OH-dG), is an ROS induced modification of purine residue of DNA, it is a sensitive index of oxidative DNA damage and frequently used biomarker of oxidative stress. (Chen X, et al, 2005)

#### 2.5.3.2. Markers of lipid peroxidation: lipid peroxide results from the oxidative degradation of poly unsaturated fatty acids (PUFA). As Davi G et al, (1999) explained, 8 isoprostaglandin F2\(\alpha\) (8 iso PGF 2 \(\alpha\)) considered to be an accurate marker of endogenous lipid peroxidation and it can measured from plasma, urine, placenta. Another product of the peroxidation chain reaction of PUFA is **MDA**. To assay MDA, serum, plasma, blood erythrocyte and urine can be used. Arikan S et.al in 2001 cited that conventional assay to measure lipid peroxidation is TBA (Thiobarbituric acid) which involves adding TBA to the sample and calorimetrically measuring resultant reactive substances (TBARS) (Chen X, et al, 2005). Indicates that pregnant women with either GDM or type one diabetes have increased maternal product of lipid peroxidation, which is positively correlated with glycemic level.

#### 2.5.3.3. Markers of protein damage: protein carbonyl groups results from free radical induced protein oxidation and tissue cells and plasma levels of them are a relatively stable marker of oxidative damage (Chen X, et al, 2005).
2.5.3.4. Markers of antioxidant status: SOD, GPx, catalase, selenium (Chen X, et al, 2005).

Table 2.10: Compounds with established or proposed antioxidant activity in vivo (Garrow J.S, et al, 2000)

<table>
<thead>
<tr>
<th>Primary antioxidant</th>
<th>secondary antioxidant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E*</td>
<td>Copper*</td>
</tr>
<tr>
<td>Vitamin C*</td>
<td>Glutathione reductase</td>
</tr>
<tr>
<td>Carotenoids*</td>
<td>Ascorbate reductase</td>
</tr>
<tr>
<td>Falvonoids*</td>
<td>Glucose-6-phosphate</td>
</tr>
<tr>
<td>Dehydrogenase</td>
<td>Ceruloplasmin</td>
</tr>
<tr>
<td>Polyamines</td>
<td>Transferin</td>
</tr>
<tr>
<td>Melatoin</td>
<td>Metallothionein</td>
</tr>
<tr>
<td>Oestrogen</td>
<td>Albumin</td>
</tr>
<tr>
<td>Ubiquinone</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Lipoic acid</td>
<td>N-Acetylcysteine</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td></td>
</tr>
<tr>
<td>catalase</td>
<td></td>
</tr>
</tbody>
</table>

*Needed in the diet. Endogenous but possibly also needed in the diet (all the other compounds are endogenous)

Primary antioxidants delay or inhibit the initiation step of oxidation, while the secondary antioxidants slow down the oxidation by removing the substrate or by quenching free oxygen radicals (Okubena O, 2011).

Table 2.11: Factors that increase free-radical formation: (Srilaxmi, 2007)

<table>
<thead>
<tr>
<th>Body factors:</th>
<th>Environmental factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy metabolism</td>
<td>Air pollution</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Asbestos</td>
</tr>
<tr>
<td>Exercise</td>
<td>High level of vitamin C</td>
</tr>
<tr>
<td>Acute disease</td>
<td>High level of oxygen</td>
</tr>
<tr>
<td>Immune response</td>
<td>Radioactive emissions</td>
</tr>
<tr>
<td></td>
<td>(e.g. Radon gas)</td>
</tr>
<tr>
<td>Injury</td>
<td>Some herbicides</td>
</tr>
<tr>
<td>Obesity</td>
<td>Tobacco, smoke</td>
</tr>
<tr>
<td>Other diseases</td>
<td>Trace minerals (Iron, copper)</td>
</tr>
<tr>
<td>Other metabolic reactions</td>
<td>Ultraviolet light rays</td>
</tr>
<tr>
<td>Xenobiotics</td>
<td></td>
</tr>
</tbody>
</table>
2.5.4. Studies in antioxidant and disease context:
Different researches in area of different antioxidant level and risk of GDM has been performed.

The antioxidants which were more matter of concern in most recent studies with their association with gestational diabetes were Vitamin C, vitamin E, SOD, MDA. Even though yet need more exploration with larger studies in different parts of the world to confirm present findings and starting a strategy of prevention according to their confirming or ruling out results.

However very scarce data are available on other antioxidants regarding their role during pregnancy, e.g. LPO, GSH, GST, GPx, TBARS, TAS, AOPP, MPO, LHP, β-tocotrienol.

Various studies in this context in India were carried out in Manipal, Chennai, Delhi, and Allah Abad. Among them only three studies vitamin C was matter of interest.

Toesco V et al, (2002 and 2004), has quoted that instead of quantifying the concentration of a specific antioxidant “total antioxidant capacity” (TAC) has been greatly practiced for oxygen radical absorbance capacity or capacity of plasma sample to restrain an oxidative reaction. However TAC does not always include all of the major antioxidants.

Toesco et al in their study in 2004 proposed that substances contributing to TAC are comprised of vitamin A, vitamin C, vitamin E, Uric acid and thiols. The exact pro-oxidant and antioxidant status in gestational diabetes is still not clear.

(In brief all following studies has been present in tabular formats in table2.12).

Chaudrhi L, et al, (2003), suggest increased oxidative stress and decreased detoxification or free radical scavenging capacity in pregnancy complicated by diabetes. Also there are reports suggesting that increased free radical production and antioxidant depletion in diabetic pregnant female may contribute to this risk(Eriksson UJ et al, 1991).

There are considerable evidences that antioxidant defense system is depleted and activity of antioxidant enzymes is reduced in diabetes (Tho LL, et al, 1988). Normal pregnancy is also associated with increased oxidative stress causing increase in
lipoperoxidation products but this lipid peroxidation is balanced by adequate antioxidant responses (Uotila J et al, 1991).

Another study in early diabetic pregnancy found no evidence of greater lipid peroxidation as compared to normal pregnant women and total antioxidant capacity was also reported to be similar in both the groups (Bates JH et.al, 1997).

2.5.5. Vitamin C:

Association of plasma vitamin C and consequent contrarvertial reports are found in literature risk of GDM.

Like vitamin E, vitamin C also does not have a significant effect on fasting blood glucose levels and insulin concentrations (Akbar S et.al, 2011). However a 6 week vitamin C supplementation study with a dose of 1000mg/day suggested that vitamin C help reduce fasting and post prandial oxidative stress and may help in preventing diabetes related complications (Mazloom Z, 2011). But this study was conducted with 30 subjects and hence a study with more number of subjects is needed to establish its benefits.

It is suggested that 100 mg/ day suggested that vitamin C helps reduce fasting and post prandial oxidative stress (For ES, et al, 1999, NIN 2009).Regarding bioavailability of vitamin C 70-90% usual dietary intakes of vitamin C (30-180mg/day) is absorbed and however absorption falls to about 50 % or less increasing doses above 1 g/day.

The bioavailability of the vitamin from food and supplements are not significantly different (Institute of medicine 2000).however natural sources would provide other health benefits like fiber, other micronutrients and antioxidants. Supplementation may be suggested in people with lesser intake of food rich in vitamin C. also people with diabetes may lose vitamin C due to ployuria (Chertow MD, 2004) and hence may benefit from supplementation.

In a study by Carol S. Johnston et.al in USA 1998, they found that lower paternal plasma vitamin C leads to GDM. Zhang Cuilin et.al (2004) and Suprapaneni KM et.al, from India 2008 found same results.

In a recent research (2010) by Mohd S. et.al, in India they discover that plasma vitamin C is lower in normal pregnancy in compare with non-pregnant controls. Similarly plasma vitamin C is lower in GDM pregnant in compare with normal pregnant controls.
In an interesting study in UK during 1999 by Andrew R et al, they found that plasma level of vitamin C is lower in South Asian races and the level is higher in non-smoker, supplement taker, vegetarian population.

In contrast with above studies, Grissa O, et.al (2007) in a recent study in Tunisia, found that the plasma vitamin C level of GDM mothers as well as in their macrosomic babies, had no changes in compare with their normal controls and their babies respectively. A year later in India this finding strengthen but only about GDM mothers by Dey P. et.al (2008).

To come to conclusion, larger studies mostly in form of clinical trials, is suggested to finalize controversies. But since there are more evidence available in lower plasma vitamin C and GDM, supplementation of vitamin C in addition to introducing and encouraging intake of rich sources of vitamin C is recommended.

![Figure 2.14. Factors which determine the body pool size of a vitamin (Seymour L, and Halpern MD, 2005)](image)

**2.5.5.1. Chemistry of vitamin C (ascorbic acid):**

Ascorbic acid is a hexose (6 carbons) derivative and closely resembles mono-saccharaides in structure. The acidic property of vitamin C is due to enolic hydroxyl groups. (Satyanarayana U, et.al 2006). Vitamin C is susceptible to oxidation because it is
a reducing agent that functions in the body as antioxidant. (Srilaxmi B, 2006, Mahan LK, 2008).

Most mammals can synthesise vitamin C from glucose but a few including humans lack the liver enzyme gulonolactone-oxidase, which is required to catalyse one step of this process. It is the lack of this enzyme that forces humans to depend on supplies of vitamin C from their food (Srilaxmi B, 2006).

**2.5.5.2. Biochemical functions of vitamin C:**

Most of the functions of vitamin C are related to its property to undergo reversible oxidation reduction i.e., inter-conversion of ascorbic acid and dehydro-ascorbic acid: collagen formation, bone formation, iron and hemoglobin metabolism, tryptophan metabolism, tyrosine metabolism, folic acid metabolism, peptide hormone synthesis, synthesis of corticosteroid hormones, sparing action of other vitamins, immunological function, preventive action on cataract, preventive action on chronic diseases, i.e. cancer, cataract, diabetes, and coronary heart disease. (Satyanarayana S, et.al 2006).

Other functions of vitamin C in brief are comprised of: collagen formation, carnitine synthesis, neurotransmitter synthesis, activation of many peptide hormones and hormone releasing factor, drug detoxification, general antioxidant and iron metabolism (Mahan KL, 2008). Vitamin C also aids Calcium absorption by preventing the incorporation of calcium into insoluble complexes; vitamin C converts inactive form of folic acid into its active form di-hydrofolic acid and terta-hydrofolic acid and also stabilizes the active form. Vitamin C alleviates allergic reactions, enhances immune functions, stimulates formation of bile and facilitates the release of some steroid hormones. Vitamin C also is necessary for the conversion of cholesterol to bile acids and has been reported to be involved in the detoxification of many chemical carcinogens. (Mahan KL, 2008, srilaxmi 2007). Also vitamin C is crucial for iron absorption (Rao S, et al, 2001).

Metabolic functions of ascorbic acid are not completely understood. With consideration to the above statements other functions of vitamin C are as follows: formation of nore epinephrine from dopamine and subsequently to serotonin enhances microsomal drug metabolism, wound healing, leucocyte functions, and as an excellent
antioxidant, scavenging free radicals. The half life in the body is 10-20 days (Halpers D et al, 2002).

2.5.5.3. **Recommended dietary allowance (RDA) for vitamin C:** About 60-70 mg vitamin C intake per day will meet the adult requirement. Additional intakes (20-40% increase) are recommended for women during pregnancy and lactation (Satyanarayana U, et.al 2006). Also the efficiency of enteric absorption of the ascorbic acid is high (80-90%) at low intake but declines markedly at intakes greater than about 1g/day (Mahan KL, et.al2008).

The absorption of ascorbic acid is carrier-mediated, active and sodium dependent. Two sodium-dependent vitamin C co-transporters have been cloned, SVCT1, SVCT2 (Wilson JX, 2005). SVCT1 is found in kidney, intestine and liver; SVCT2 is in choroid plexus and pigmented epithelium of the retina.

The efficiency of ascorbic acid absorption decreases with a daily intake above 180 mg. In such cases, 55% to 90% of the ingested vitamin appears in the urine, the stool contains the rest, with the proportion increasing as the oral dose increase. Ascorbic acid is catabolized to oxalate and accounts for 20-30% of urinary oxalate under normal conditions (Halpers D, et al, 2002).

2.5.5.4. **Dietary sources of vitamin C:**

Plasma vitamin C concentrations in people who regularly consume vitamin C supplements are 60–70% higher than those who do not take supplements (75–80 and 45–50µmol/L, respectively (Byerley LO and Kirksey A 1985) A daily intake of 500–1000 mg is necessary to maintain plasma vitamin C concentrations at 75–80µmol/L. (Handbook of vitamins pp529-554).

Ascorbic acid is widely distributed in foods in high concentrations, especially in green vegetables and citrus fruits. However the content is quite variable from one food to another, and within each type, even for foods from the same region and source, depending on species and degree of ripeness (Vanderslice JT, et al, 1991). Ascorbic acid content of foods is available in the appendix.

Citrus fruits (orange, lime), gooseberry (amla), guava, green vegetables, (cabbage, spinach), tomatoes, potatoes (particularly skin), are rich in ascorbic acid. High content of
vitamin C is found adrenal gland and gonads. (Satyanarayana U, et.al 2006). In the third national health and nutrition examination survey (NHANES III), vitamin C intake for adults was only 70-80 mg per day (Ausman LM, 1999).

With the ingestion of 60 mg of vitamin C per day (the previous RDA), wide fluctuations in plasma vitamin C were associated with small changes in the amount consumed. Saturation did not occur until intake levels were at 1000 mg per day. (Halpers D, et al, 2002).

Of all the vitamins, ascorbic acid is the most susceptible to destruction by atmospheric oxidation, one of the characteristic properties of this vitamin is its intense reducing action and hence it’s oxidized rapidly in air. It is for this reason that when vegetables become dry and stale or cut and exposed to air most of the vitamin C originally present is destroyed. However, when dry pulses and beans are allowed to germinate, vitamin C is formed in the grain and the growing sprout, about 85% being present in the former and 15% in the latter part.

Sprouted green grams contain about 3 times more vitamin C than sprouted Bengal gram. 17-20 mg vitamin C is produced during germination per 100 gm of pulses. Often only 50% of the content of the raw food survives processing and cooking (Halpers D, et al, 2002).

2.5.5.5. Intake of rich vitamin C foods during pregnancy/ assessment of plasma vitamin C:

In general, plasma or serum ascorbic levels reflect intake even though Plasma levels may not always reflect intake. Levels of ascorbate maybe reduced in patients with chronic inflammatory diseases, cigarette smokers, persons experiencing acute emotional or environmental stress, and women taking contraceptives, diabetics and elderly (older than 65 years of age). They should be encouraged to increase their vitamin C intake, most likely via a supplement, because 5-10 servings of fruits/vegetables are needed to fulfill their increased requirements. (Halpers D, et al, 2002).

Levels < 23µmol per L, indicate deficient intake or absorption. Seasonal changes occur, with the highest levels seen in summer, when large amounts of fresh fruits and vegetables are consumed. Levels are very high in first 3 days of life. When intake
decreased, deficiency develops within 3 to 5 months. Severe infections and acute illness can lower serum levels in the absence of deficiency. Levels should be measured in patients at risk, including those with a poor diet (elderly, alcohol or drug abuses, patients with chronic disease or cancer), patients on dialysis and smokers (Halpers D, et al, 2002).

Fruit and vegetable intakes have frequently been inversely related to the risk of chronic diseases (WHO 2004). Fruits and vegetables are important source of antioxidant and consumption has been positively correlated with serum vitamin C and carotenoids (Zino S1997, Ness AR1999, Palli D 1999). Vitamin C and β-carotene are known to be powerful antioxidant nutrients. Via their antioxidant functions of protecting organisms against free radical damage, vitamin C and β-carotene may play a helpful role in the prevention of the diseases initiated or promoted by oxygen radicals, such as cardiovascular diseases and cancers (Hercberg S 1998).

One of the relevant nutritional factors during pregnancy is the intake of specific micronutrients such as folate, vitamin C, and carotenoids. These are plentiful in fruits and vegetables and have been associated with increased birth size within the full birth weight and birth length range in developed countries, where under-nutrition is uncommon (Mathio F1999, Laglou P 2005).

Till date, to our knowledge, just two studies, in distinct populations of pregnant women, have determined the association of the intake of fruits and vegetables with birth size. After adjusting for covariates, both found a small significant increase in birth weight with higher consumption of fruits and vegetables. One study was from general population in Denmark and the other was from rural area in India. (Mikkelson 2006, Rao S 2001).

Also Vitamin C was related to GDM but there is scarce information in this regard available.

2.5.6. Other plasma antioxidants:
In a study in Finland by Montonen J et al 2004, found that vitamin E intake (α, β, gama, and δ tocopherol) prevents glycemic status disturbance and consequently gestational diabetes. This finding were confirmed in other ways by other studies in years later, in 2007, 2008 and 2010, by Grissa O. et.al in Tunisia, Suprapaneni KM et.al and Mohd S. et.al from India respectively.
Grissa O, et.al (2007), found out the level of plasma vitamin E is lower in GDM mothers as well as their macrosomic babies.

Two different studies, with two different conclusions in Sweden (2011), and India (2003), by Lopez C and chawdhari L. et.al, respectively, have been performed. In first study they found that **Catalase** (an antioxidant enzyme) had a protective effect against GDM while in Indian study they found no catalase plasma level change.

In same study in Sweden 2011, they found LPO as a risk factor for GDM.

Prasenjit Dey et.al 2008 in an Indian study found that Glutathione (**GSH**) and Glutathione S transfrase (**GST**) levels are higher in GDM mothers. Other high plasma antioxidant levels in GDM mothers were Glutathione peroxidase (**GPx**) (Suropaneni KM et.al, 2008, India), Thiobarbituric acid reactive substances (**TBARS**) (Grissa O et.al, 2007, Tunisia) and malonaldehyde (**MDA**). The last antioxidant higher level in GDM was approved in several studies by chaudhari L. et.al (2003) and Suprapaneni KM et.al 2008, both in India.

While Mohd S, et.al (2010) found GDM mothers had higher MDA levels in compare with their normal pregnant controls, and also normal pregnant had higher MDA in compare with non-pregnant matches. Karacay O, et.al (2010) from Turkey found high level of MDA not only in GDM mothers but also during preeclampsia.

There is a need of more studies on these antioxidants to confirm the above primary studies’ findings and afterwards decide about alternate protective strategies by this antioxidant for GDM.

In a recent study (2010) in Turkey by Karaccay O., et.al they found lower level of TAS in GDM and preeclampsia where as higher level of advanced oxidation protein products (**AOPP**) and no changes in myeloperoxidase (**MPO**) and lipid hydroperoxide (**LHP**) in both situations.

**β- tocotrienol** was only studied in Finland in 2004 by Jukkamonto Nenpaukrekt et.al and they discovered lower level of **β- tocotrienol** in GDM mothers.

Three recent studies were carries out in India and Tunisia to estimate **SOD** level. But there are controverses, maybe due to different methods or different geographical area of research.
Grissa O, et.al 2007 (Tunisia) found same conclusion with Chaudhari L et.al (2003, India) in which the SOD level were lower in GDM mothers. In a more recent study, these findings were ruled out by obtaining the opposite result.

Yet there is a need for more studies with larger sample size, and also the other factors may increase SOD level to overcome controversy and confirm a final result to place a correct action to prevent GDM.

Nenpoukrekat J et.al in a study in Finland (2004) found lower level of plasma β-cryptoxanthin (a carotenoid) in GDM mothers. Whereas Grissa O et.al 2007 discovered that there is no change in plasma vitamin A level of GDM mothers as well as their macrosomic babies. A recent study in 2010 by Mohd S.et.al in India showed lower level of plasma vitamin A in GDM mothers in compare with their normal matches. In addition lower level of plasma vitamin A in normal pregnant subjects in compare with their normal non-pregnant matches.

As above discussed findings it may be suggested clinical trial studies by supplementation of different antioxidants during pregnancy (considering their side effects for dosage adjustment).
Table 2.12: Summary of methods in different studies of antioxidants effects

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Title of the article</th>
<th>Authors/Journal/year</th>
<th>Sample size/population</th>
<th>Type of study</th>
<th>objectives</th>
<th>Antioxidants studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxidative stress and antioxidant status in patients with late-onset GDM</td>
<td>Lopez C. et al, Acta diabeto, 2011</td>
<td>53 GDM, 25 normal pregnant, Stockholm, Sweden</td>
<td>Case control</td>
<td>To evaluate the relationship between maternal levels of markers of oxidative stress in women with late onset of GDM</td>
<td>LPO, SOD, GPX, GST, catalase</td>
<td>Catalase might have a protective effect against GDM development while LPO may be a risk factor for the disease</td>
</tr>
<tr>
<td>2</td>
<td>Antioxidants and lipid peroxidation in gestational diabetes, a preliminary study</td>
<td>Dey P, et.al, Indian J of physiol pharmacol, 2008</td>
<td>18 GDM, 18 normal pregnant, Manipal, India</td>
<td>Case control</td>
<td>To estimate antioxidant maternal plasma and cord blood level in GDM</td>
<td>GSH, SOD, TBARS, total GST, Cp, vitamin C and E, protein thiols</td>
<td>In GDM cases significant increase in GSH, GST and protein thiols and significant decrease in SOD, no change in vitamin C</td>
</tr>
<tr>
<td>3</td>
<td>Antioxidant Enzymes And Vitamins In Gestational Diabetes.</td>
<td>Surapaneni K M, et.al, J of Clinical and Diagnostic Research, 2008</td>
<td>20 GDM, 20 normal pregnant, Chennai, India</td>
<td>Case control</td>
<td>To estimate pro-oxidant and antioxidant status of GDM patients</td>
<td>Erythrocyte vitamin C, plasma vitamin E, Catalase, SOD, GPx, MDA, GSH</td>
<td>Increase in SOD, GPx, MDA, GSH, decrease in plasma vitamin C, vitamin E, catalase in GDM group</td>
</tr>
<tr>
<td>4</td>
<td>Dietary antioxidant intake and risk of T2DM</td>
<td>Montonen J, et.al, Diabet care 2004</td>
<td>2285 men, 2019 women 40-69 years of age, Finland cohort 23 year follow up, 164 male 219 female got DM</td>
<td>Case control</td>
<td>To clarify ability of antioxidant intake to predict risk of T2DM</td>
<td>Intake of dietary antioxidants in last year( vitamin C, 4tocopherol, 4tocotrienols, 6carotenoids)</td>
<td>Significant risk reduction by vitamin E and β cryptoxanthin (carotenoid), inverse relation of α, Y(γama), δ tocopherol and βtocotrienol, no association of plasma vitamin C and T2DM</td>
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<td>Sr. No</td>
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<td>5.</td>
<td>Vitamin C Status of an Outpatient Population</td>
<td>Johnston CS, et.al, J of American college of nutrition, 1998</td>
<td>144 male, 350 female, Arizona USA</td>
<td>Cross sectional</td>
<td>To determine the prevalence of vitamin C deficiency, or depletion in an outpatient population</td>
<td>Plasma vitamin C</td>
<td>Diabetes had lower plasma vitamin C, high rates of vitamin C deficiency and depletion were evident among generally healthy, middle class patients visiting a health care facility for routine health or, gynecological, and pregnancy exams.</td>
</tr>
<tr>
<td>6.</td>
<td>Plasma vitamin C levels in men and women from different ethnic backgrounds, living in England</td>
<td>Ness AR, et al, Int J of Epidem, 1999</td>
<td>455 men, 563 women 40-59 years age, UK</td>
<td>Cross sectional</td>
<td>To compare plasma vitamin C level of men and women of different ethnic background in UK</td>
<td>Fasting plasma vitamin C</td>
<td>Fasting plasma vitamin C were significantly higher in women, vegetarian, supplement takers and non-smokers, dietary vitamin C intake differences significantly in different ethnic groups, especially south Asians which may contribute to their higher risk for CHD.</td>
</tr>
<tr>
<td>7.</td>
<td>Antioxidant status and circulating lipids are altered in human gestational diabetes and macrosomia</td>
<td>Grissa O, et.al, J of laboratory an clinical medicine, 2007</td>
<td>59 GDM, 60 normal pregnant, 19-42 years, Tunisia</td>
<td>Case control</td>
<td>To investigate modulation of antioxidant status and circulating lipids in GDM and normal pregnant and their babies</td>
<td>Vitamin A, C, E, SOD, TBARS</td>
<td>In GDM cases reduction of SOD, Vitamin E, increase of TBARS and vitamin C, no change in vitamin A, in macrosomic babies reduction of vitamin E no change in vitamin A, C</td>
</tr>
<tr>
<td>Sr. No</td>
<td>Title of the article</td>
<td>Authors/Journal/year</td>
<td>Sample size/population</td>
<td>Type of study</td>
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<td>8.</td>
<td>Vitamin E: maternal concentrations are associated with fetal growth</td>
<td>Scholl TO, et.al, Am J clin Nutr, 2006</td>
<td>1231, USAUSA</td>
<td>Cohort, follow up</td>
<td>To measure the effect of vitamin E isomers on fetal growth</td>
<td>α tocopherol</td>
<td>Early and late circulating concentrations of tocopherol is positively associated with fetal growth.</td>
</tr>
<tr>
<td>9.</td>
<td>Antioxidant Vitamins and Lipoperoxidation in Non-pregnant, Pregnant, and Gestational Diabetic Women: Erythrocytes Osmotic Fragility Profiles</td>
<td>Mohd S., et.al, J Clin Med Res 2010</td>
<td>23GDM, 23 normal pregnant, 23non GDM, India</td>
<td>Case control</td>
<td>To evaluate oxidative stress during the development of GDM and to evaluate antioxidant capability in non-pregnant pregnant and GDM</td>
<td>MDA, Vitamin A,C,E</td>
<td>Increase in MDA, decrease in plasma vitamin C and vitamin A in pregnant and especially GDM, vitamin E decline in GDM</td>
</tr>
<tr>
<td>10.</td>
<td>Lipid peroxidation and antioxidant enzymes in Gestational diabetics</td>
<td>Chaudhari L, et.al, Indian J Physiol Pharmacol 2003</td>
<td>20 GDM, 20 normal pregnant, Delhi, India</td>
<td>Case control</td>
<td>To add a new insight to antioxidant status of GDM</td>
<td>MD, SOD, catalase</td>
<td>Reduction of SOD and increase of MDA in GDM and no change in catalase</td>
</tr>
<tr>
<td>11.</td>
<td>A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24–36 weeks of gestation</td>
<td>Karacay,O, et.al, Diabetes 2010</td>
<td>27 GDM, 27 preeclampsia, 29 normal pregnant</td>
<td>Case control</td>
<td>To assess the plasma and serum maternal total antioxidant status</td>
<td>MDA, AOPPs (protein oxidation markers), MPO, LHP</td>
<td>Reduction of TAS and increasing of MDA and AOPP in GDM and preeclampsia, no change in MPO and LHP</td>
</tr>
<tr>
<td>12.</td>
<td>Maternal Plasma Ascorbic Acid (Vitamin C) and Risk of GDM</td>
<td>CuiLin.Z, et.al, Epidemiology 2004</td>
<td>755 pregnant average 13 weeks of gestation, USA</td>
<td>Prospective cohort</td>
<td>To study the association of maternal plasma vitamin C and intake with risk of GDM</td>
<td>Dietary and plasma vitamin C</td>
<td>33 (4%) diagnosed with GDM, lower plasma vitamin C 3.1 fold higher risk of GDM, lower vitamin C intake, 1.8 fold higher risk of GDM</td>
</tr>
</tbody>
</table>

2.5.7. High oxygen radical absorbance capacity foods (HORAC):

The antioxidant potential of a dietary component is often expressed as the Oxygen Radical Absorbance Capacity (ORAC). The ORAC is an in vitro measure that has
biological relevance to in vivo oxidation; however, it does not fully account for how well an antioxidant is absorbed or utilized (nutrition update, 2008).

Although the human body has developed a number of systems to eliminate free radicals such as reactive oxygen species from the body, it is not 100% efficient (Young, IS et.al, 2001). Diets rich in fruits and vegetables are considered to be an excellent source of antioxidants (Kaur C, et.al 2001). Some minerals and vitamins have a role as dietary antioxidants. As explained above, these include carotenoids (vitamin A precursor), vitamin C (ascorbic acid), vitamin E and its isomers (tocopherols and tocotrienols), α-lipoic acid and selenium.

2.6. Physical activity, smoking, stress:

The major metabolic benefits of exercise are related to its ability to enhance insulin sensitivity (Fagen C et al, 1995). Regular exercise sessions, rather than sporadic exercise, are effecting in regulating blood glucose levels (Peterson JL, et al, 1990).

The role of exercise in women with GDM has been controversial in the past because maternal exercise on a bicycle ergo meter has been associated with fetal bradycardia. Subsequent small studies have shown small transient increases in fetal heart rate after maternal exercise. There was no fetal complication in either study (Racy L, et. al, 2007). Based on the potential benefits of exercise in women with GDM, the ADA recommends starting or continuing a program of moderate exercise in women without medical or obstetrical contraindications (ADA, 2004).

In developing countries like India, women are responsible for a wide range of household work and childcare duties, as well as work outside the home. These women are the women at risk for a poor birth outcome (Launer LJ 1990).

Even though exercise is recommended during pregnancy especially for GDM, there are some contraindications for exercise during pregnancy: such as risk for premature labor, vaginal bleeding, placenta previa, anemia, cardiac disease, thyroid disease, hypertension, IUGR, mal-presentation in the last trimester, excessive obesity, extreme under-weight, etc (Artal R 1990).

Earlier studies regarding recreational activity during pregnancy and GDM have suggested a protective role of recreational physical activity. However case-control study

American College of Obstetricians and Gynecologists (ACOG) 2002, guidelines for physical activity in pregnancy recommend 30 minutes of moderate physical activity on most days for pregnant women, with no contraindications to physical activity in pregnancy. Therefore, women with ≥10MET hrs/week in sports/exercise activities of moderate intensity or greater were considered to have met the physical activity guidelines. (MET-hours/week means measure of average energy expenditure, and 10 MET hours per week = 2.5 hours per week x 4 (the minimum MET for moderate physical activity).


In a case-control study, Dempsey et al, 2004, found that participating in any recreational activities during the first 20 weeks of pregnancy reduced gestational diabetes risk by 48 percent.

For insulin-resistant persons, regular exercise improves glucose tolerance and insulin sensitivity through tissue adaptations. Exercise training has been shown to increase expression of GLUT4 in skeletal muscle, reduce insulin secretion by the pancreas, and decreases the liver’s glucose production (Alcazar O, et al, 2007), although underlying mechanism of preventing of gestational diabetes by regular physical activity has not been elucidated.

Evidence available sofar about effects of physical activity during pregnancy on gestational diabetes is suggestive but inconclusive.
Another factor to be considered is smoking. The infants born to women who smoke during pregnancy are lighter (approximately 200g) as compared to those women who do not smoke and are at increased risk of being SGA (Banerjee S, et.al, 2012).