Austin Endocrinology and Diabetes Case Reports

Open Access

Austin Publishing Group

Review Article

Gestational Diabetes Mellitus: Current Perspectives

Sheela P[1], Lakshmi VB[1], Sharadha M[2], Ramaiah A[3], Nallari P[4] and Jyothy A[1]*

[1]Institute of Genetics and Hospital for Genetic Diseases, Osmania University, India

[2]Department of Biochemistry, Modern Government Maternity Hospital, India

[3]Department of Gynaecology, Modern Government Maternity Hospital, India

[4]Department of Genetics, University College of Science, Osmania University, India

***Corresponding author:** Akka Jyothy, Former Director, Emeritus Professor, Institute of Genetics and Hospital for Genetic Diseases, Osmania University, India

Received: November 21, 2016; **Accepted:** December 14, 2016; **Published:** December 16, 2016

Abstract

GDM is a multifactorial disorder which is increasing globally because of the lifestyle and genetic predisposition as GDM and T2DM clusters in the family. Though mothers return to normal glycemic states after delivery it is associated with increased short and long term maternal and fetal complications. There is no cure yet been found; however it can be managed by lifestyle modifications and thereby maintaining desired glycemic levels. As screening based on risk factors leave many of the women undiagnosed, universal screening has to be recommended and medical nutrition therapy should be necessarily individualized to reduce and prevent further complications both in mother and fetus. In this review we highlight the key factors responsible for the development of GDM which are usually overlooked such as depression, smoking, stress, calorie intake, age at menarche, vitamin and trace mineral deficiencies, lack of physical activity besides the genetic factors. Recent research into genetics causing GDM has led to identifying genes specific to GDM. This review is an overview of pathophysiology, role of ethnicity, risk factors, genetics, screening, diagnosis and treatment that leads to GDM based on the recent literature.

Keywords: GDM; T2DM; Risk factors; Insulin resistance; Hyperglycemia and genetics

Abbreviations

GDM: Gestational Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; OGTT: Oral Glucose Tolerance Test; FBS: Fasting Blood Sugar; BMI: Body Mass Index; POP: Persistent Organic Pollutants; PCOD: Poly Cystic Ovarian Disease; HIP: Hyperglycaemia in Pregnancy; HPL: Human Placental Lactogen; PM2.5: Particulate Matter 2.5; WHO: World Health Organization; ADA: American Diabetes Association; IADPSG: International Association of Diabetes and Pregnancy Study Group; DIPSI: Diabetes in Pregnancy Study Group India; IDF: International Diabetes Federation; NIH: National Institute of Health; NICE: National Institute for Health and Care Excellence; HAPO: Hyperglycemia and Adverse Pregnancy Outcome; ACOG: American College of Obstetricians and Gynecologists; IGT: Impaired Glucose Tolerance

Introduction

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance causing hyperglycemia with onset or first recognition during pregnancy at any trimester. It is a multifactorial and polygenic disorder characterized by insulin resistance and pancreatic beta cell dysfunction. This metabolic condition remains for a time period i.e., till the delivery of the baby, having both short and long term complications. Most of the cases can be treated by diet, exercise and upon persistent high glycemic index insulin therapy will be given. Most women with GDM will return to normal glucose tolerance after delivery, a significant number may continue to be hyperglycemic after delivery. There are many genes identified by genome wide association studies that are associated significantly with GDM that play a role in the pathogenesis of GDM. The absence of universally validated guidelines for screening and diagnosis, following selective screening strategy, lack of awareness of the consequences of GDM, all together lead to increasing prevalence rates worldwide. Controversies still exists regarding the amount of glucose load given during OGTT, duration of the test after the glucose load is given (2hr or 3hr), cutoff values and also 1 or 2 high values necessary for diagnosis [1]. It is said that women with GDM have a 40-60% chance of developing T2DM in future within 5-10 years after pregnancy [2].

Prevalence of GDM is high in Asian countries compared to other countries [3]. In Scotland prevalence was found to be 1.9% [4] a 9-fold increase in the prevalence of GDM was observed from 1981 to 2012. In Europe GDM is present in about 2-6% [5]. Prevalence varies among racial and ethnic groups depending on different diagnostic criteria used. In India GDM prevalence ranges from around 5% to 18% [6-8] 34.9% in Punjab and 41.9% in Uttar Pradesh [9]. In South India, the prevalence has been increased from 1% in 1998 to 16.55% in 2004 [10].

Screening

A screening test can be performed on either a selective or a universal basis. It is believed that screening on the basis of risk factors seems to be inefficient as most of the women were missed and ended up with GDM later in pregnancy. Identifying GDM by factors like family history of T2DM, previous history of diabetes, adverse obstetrics outcomes will miss to identify one half of women having GDM.

Women who are tested positive for screening test will go for a diagnostic test. Screening and diagnosis are usually performed during second trimester, between 24 and 28 weeks because the diabetogenic effect of pregnancy hormones increases during this period. There is lack of international consensus regarding timing of screening and methods to be used and the optimal cut-off points for diagnosis of GDM.

Citation: Sheela P, Lakshmi VB, Sharadha M, Ramaiah A, Nallari P and Jyothy A. Gestational Diabetes Mellitus: Current Perspectives. Austin Endocrinol Diabetes Case Rep. 2016; 1(1): 1005.

According to ADA low risk group with age < 25 years, BMI ≤ 25kg/m^2, not a member of high risk ethnic group, no previous history of glucose intolerance, adverse obstetric outcomes, no known history of diabetes in first degree relatives, do not need to be screened [11].

The recommendations given by IADPSG which was approved by ADA based on Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study is to screen on the first prenatal visit, fasting plasma glucose, HbA1C or random plasma glucose should be performed in all women visiting antenatal OPD. If there are no abnormal values diagnostic of overt diabetes and fasting plasma glucose ≥ 92mg/dl it is diagnosed as GDM, if it is < 92mg/dl at the first antenatal visit a 2-hour 75g OGTT should be repeated at 24-28 weeks of gestation [12].

Diagnosis

According to WHO criteria, OGTT should be performed to diagnose GDM, where 75g anhydrous glucose load is given to the women after overnight fasting. Fasting blood glucose and values after 2-hours after glucose load is given are measured. If the values are diagnostic for overt diabetes mellitus or Impaired Glucose Tolerance (IGT) it is considered to be GDM. If the 2-hours plasma glucose is ≥ 140mg/dl diagnosed as GDM.

According to DIPSI criteria, OGTT is performed irrespective of the last meal. It is a single step procedure, where 75g anhydrous glucose water of 250-300ml is given to the pregnant women visiting antenatal OPD and 2-hour venous plasma glucose was measured. If the 2-hour plasma glucose is more than or equal to 140mg/dl it is considered as GDM. A value of ≥ 200mg/dl as DM and ≥ 120mg/dl as decreased gestational glucose tolerance.

According to IADPSG criteria, OGTT is performed by giving a 75g of glucose load in a fasting state. To diagnose GDM any one of the following cut-off values should be met. Fasting blood Glucose (FBG) ≥ 92mg/dl, 1-hour ≥ 180mg/dl and 2-hour ≥ 153mg/dl. Except NIH, the IADPSG criteria was endorsed by WHO (2013) and ADA stating that it needed more evidence for adoption. Considering the NIH report, ADA has recommended two options either one step IADPSG or the two step procedure.

ADA recommends selective screening of high risk GDM women and ACOG guidelines suggests universal screening. ADA has proposed two methods to diagnose GDM at 24-28 weeks in women not having pre-existing diabetes. The two methods are 1) One step procedure and 2) Two step procedure. In One Step Procedure OGTT is performed giving 75g of anhydrous glucose water after an overnight fast of ≥ 8hours. If fasting blood glucose is ≥ 92mg/dl, 1-hour blood glucose value is ≥ 180mg/dl and 2-hour blood glucose is ≥ 153mg/dl it is diagnosed as GDM.

In Two Step Procedure, Step one include 50 gram OGTT is performed irrespective of last meal. If 1-hour Plasma Glucose is ≥ 140mg/dl, 100g glucose OGTT is done. In step two, if FBS value is ≥ 95mg/dl or FBS ≥ 105mg/dl, 1-hour blood glucose is ≥ 180mg/dl or ≥ 190mg/dl, 2-hour blood glucose is ≥ 155mg/dl or ≥ 165mg/dl and 3-hour blood glucose is ≥ 140mg/dl or ≥ 145mg/dl it is diagnosed as GDM.

Complications of GDM

GDM carries significant short-term and long-term consequences for both mother and offspring. Studies have shown that women with GDM are seven times more likely to develop diabetes, nearly 50% of GDM women will develop T2D within 10 years by this we can say that GDM is a window for predicting future T2D. It is associated with adverse perinatal outcomes [13], and also increases long term cardiometabolic risk in both mother and child. It not only increases the risk of T2D in the later life both in mother and baby [14-17] it is said to be a very strong risk factor for cardiovascular and metabolic diseases in later life [18].

Maternal complications

The adverse maternal complications include hypertension, hydramnios, pre-eclampsia, urinary tract infection, increased caesarean deliveries and future T2DM. Caesarean delivery is one of the most common and important complications of GDM. One meta-analysis showed overweight, obese and severely obese pregnant women have 2.14, 3.56 and 8.56 fold higher risk of GDM respectively compared to pregnant women with normal weight [19]. Some studies also showed that children born to mothers with GDM have two to eight fold risk of becoming obese, diabetic and impaired insulin sensitivity and secretion compared to non diabetic mothers. Progression of women with history of GDM to T2D can be prevented by lifestyle modifications. Follow-up assessments of glycaemic levels postpartum will prevent progression of GDM to diabetes.

Fetal complications

Fetal complications include neonatal hyperbilirubinaemia, respiratory distress, hypoglycaemia, syndrome [20] and metabolic abnormalities, childhood and adolescent obesity. The high glucose levels in mother results in macrosomia as the glucose crosses the placenta, therefore glucose levels in the fetus continuously increases and stimulate insulin secretion. Fetal pancreas will start responding to this hyperglycemia at 11th or 12th week of gestation [21]. The fetus gradually becomes hyperinsulinemic, thus the fetus subsequently becomes larger leading to macrosomia i.e. birth weight of ≥ 4500grams which is one of the most common complications. This leads to shoulder dystocia, brachial plexus injuries, clavicular fractures in normal deliveries leading to c-section [22] and birth trauma. Babies born to obese women with GDM have a higher risk of developing macrosomia when compared to non obese women with GDM.

Feto - Placental Unit and Its Role in GDM

The process of insulin resistance usually starts between 20 and 24 weeks of pregnancy. It is mainly due to maternal adiposity and the antagonizing effects of the pregnancy associated hormones like bound and free cortisol, estrogen, progesterone, prolactin, and HPL that are produced during pregnancy rise in the maternal circulation [23,24] leading to increasing insulin resistance in the peripheral tissues as gestational age progresses. After parturition and delivery of the baby, placental hormones will not be produced as the placenta is also delivered so insulin resistance subsides (or decreases), which strongly suggests that placental hormones are major contributors of GDM [25].

HPL is known to stimulate lipolysis, which leads to an increase

in free fatty acids to provide a different fuel to the mother other than glucose and amino acids and to spare fuel for the fetus. The rise in the free fatty acid levels interferes with the proper function of insulin as it is said to antagonise insulin in pregnancy. It stimulates insulin like growth factor production and control intermediary metabolism that results in the increase in glucose and amino acids to the developing fetus [26]. It is known to induce insulin secretion in the fetus and decreases the peripheral glucose uptake in the mother [27]. There is a 10-fold increase in the maternal HPL concentration in second trimester, elevated levels are seen with hypoglycemia and decreased with hyperglycemia.

Normally in pregnancy i.e., in non diabetic pregnant women progressive insulin resistance begins near mid pregnancy and progresses through the third trimester. Estrogen and progesterone increase and promote pancreatic ß-cell hyperplasia and increase insulin secretion which compensates the insulin resistance during the first and second phase insulin release .It is said that insulin sensitivity falls by ~ 50% in late pregnancy [28]. In normal pregnancy, increase in the cortisol is considered to be the main hormone that cause increase in the insulin resistance and it is said to have the highest diabetogenic effect and has peak effect at 26 weeks of gestation and progesterone peaks at 32 weeks gestation. Some others believe that estrogen and progesterone are the major hormones that influence beta cell function early in pregnancy and insulin resistance in the late pregnancy [23].

The post-insulin receptor events cause the insulin resistance to increase in the degree, which is the effect of pregnancy hormones. GDM is also caused due to b-cell dysfunction it may be due to one of three major categories autoimmunity, monogenic and most commonly due to insulin resistance [25]. Women who could not secrete additional insulin to compensate this insulin resistance develop GDM.

Risk Factors for GDM

There is an increased necessity to identify modifiable risk factors to prevent GDM. Several risk factors have been associated with GDM like increased maternal age, high BMI (BMI above 30kg/m^2) obesity, previous macrosomic baby weighing ≥ 4500g, previous history of GDM, family history of T2DM, ethnicity, previous history of PCOD, acanthosis nigricans and history of hypertension or hypercholesterolaemia, clinical manifestations associated with insulin resistance like PCOD and acanthosis nigricans. According to the IDF 2009 Guide and the current recommendations of ACOG, macrosomia is a major risk factor for GDM [29].

Modifiable risk factors

Early lifestyle modifications in pregnancies at risk for GDM might reduce the risk of T2DM in mother, risk of diabetes and obesity in child.

Diet

Calorie intake: A recent large prospective cohort study found potato consumption to be significantly associated with risk of GDM. In a study by Bao, substitution of potatoes with vegetables, legumes, or whole grain foods was associated with a significant lower risk of GDM [30]. A number of epidemiological studies have shown that high potato consumption increases fasting plasma glucose, insulin resistance and also an increased risk of T2DM. In a recent study by Barbieiri et al, the quality of dietary fat in pregnancy was found to be strongly associated with GDM although these findings need to confirmed [31]. Researchers identified diet rich in saturated fats as a risk factor [32].

Vitamins: Deficit of vitamin D was another risk factor for GDM [33,34].The active form of vitamin D (1,25(OH)2D3) binds to the vitamin D receptor on the pancreatic beta-cell and regulates glucose levels by modulating insulin secretion [35,36]. As the vitamin D deficiency and insufficiency is increasing worldwide the appropriate supplementation during pregnancy is on debate [37]. In a meta-analysis study of 20 observational studies indicated a consistent strong evidence for the association between vitamin D deficiency and increased risk of GDM [38].

Trace minerals: In a meta-analysis of a prospective cohort study and case-control study by Shimin, higher ferritin levels were significantly associated with greater risk of GDM and there is no definitive proof that iron and serum transferrin has relation to GDM [39].

Though association of serum selenium level with GDM is controversial an association was found in a study suggesting a low level of serum selenium was seen in non-Caucasian GDM women when compared with normal pregnant women [40].

Lifestyle

Physical activity: There are studies that have reported a positive association between physical activity and improved insulin sensitivity [41,42] during pregnancy it has been associated with improved maternal and neonatal outcomes [43].

In a study by Gibson, gestational weight gain before 24 weeks was a risk factor for GDM in overweight and obese patients but it was not found to be same in patients with a normal BMI or who were underweight before pregnancy [44].

BMI: Body Mass Index (BMI) is one of the major risk factors that is significantly associated with GDM. In Pacific Islands GDM women were shown to have high pre-pregnancy BMI (34.5 ± 8.0kg/m^2) than South East Asia (23.7 ± 4.8kg/m^2) [45]. According to a study by Shah data suggested that African-Americans are at increased risk of developing GDM (OR: 5.1) compared to US Caucasians, Hispanics and Asians when BMI > 25kg/m^2 was used as screening tool [46]. Despite of having BMI below normal range Asian women were diagnosed with GDM [47].

Smoking: Heavy smoking during pregnancy that is ≥25 cigarettes per day was found to be associated with increased risk of developing GDM in daughters in adulthood as the fetus is exposed to maternal smoking and in another study in China passive smoking during pregnancy is also associated with increased GDM risk independently and synergistically with pre-pregnancy obesity [48] while in some other study in Scotland, smoking was not found to be associated with GDM and confirmed that GDM prevalence was low and needed further investigations [4].

Stress: Stress is other important risk factors for GDM which is

usually neglected. Stress exposure and psychological stress responses were identified to be associated with FBS during pregnancy. Pregnancy-related major life events were found to be significantly associated with FBS [49].

Depression: Development of GDM is also affected by history of depression and depression during antepartum period. Byrn and Penckofer, 2015 support this finding in a recent cross-sectional study that suggests women with GDM to be 3.79 times more likely to have a history of depression (p=0.04) as compared to non GDM women [50]. Women with low income (poor), less educated, high maternal age, obese and who experienced depression have increased risk of GDM.

Environment toxicants /pollutants

A cohort study in Massachusetts found that young women who were having greater exposure to PM2.5 in second trimester are associated with higher risk of GDM though all the women in the study did not show association [51]. According to Smarr findings, maternal preconception exposure to POPs (Persistent Organic Pollutants) may increase the risk of developing GDM [52].

Non-modifiable risk factors

Family History: Having family history of T2DM (First Degree Relative with Diabetes Mellitus) and having mother or father or both diabetic were shown to be significantly independent risk factors for Hyperglycaemia in Pregnancy (HIP). In a prospective study family history of diabetes and personal history of GDM showed a statistically significant correlation with GDM [53].

Ethnicity: Ethnicities of women have been considered as a risk factor for GDM. In a study by Hollander there was a twofold increased risk found in obese Hispanic women compared to African American and Caucasian women [54]. In a study by Shin in 2013, the adjusted percentages of GDM deliveries attributable to overweight and obesity were 17.8%, 41.2%, 44.2%, 51.2%, 57.8% among Asians/ Pacific Islander, Whites, Hispanic, Blacks and American Indian women respectively [47].

Menarche: Few studies suggested that earlier menarche was significantly associated with an increased risk of GDM which is largely mediated through prepregnancy excessive body adiposity [55] and these findings were in agreement with other recent several large cohort studies [56-61] which showed earlier menarche was significantly associated with an increased risk of T2D in middle to old aged adults. In a prospective cohort study by Chen, early menarche was significantly associated with an increased risk of GDM which was largely mediated through pre-pregnancy excessive body adiposity [55]. While in a previous study age at menarche was not shown to be associated with GDM risk but women with longer menstrual cycles and overweight had 4-5-fold increased risk of GDM compared with women who had normal cycle length and were non-obese [62].

Genetics of GDM

Meta-analysis showed that the T allele of rs7903146 TCF7L2 was significantly associated with increased risk of GDM in the Asian population and did not identify any significant association of T allele of rs4402960 IGF2BP2 with the increased risk of GDM. The G allele of rs10830963 MTNR1B gene to be significantly associated with increased risk of GDM. Studies found that risk allele was significantly associated with increased risk of GDM in Asian populations and Caucasian populations. Subjects with high mean pre-pregnancy BMI ($\geq$ 25kg/m^2) were significantly associated with the risk variant and GDM. The T allele of rs1801278 IRS1gene was significantly associated with the increased risk of GDM. The G allele of rs1801282 PPARG gene was not significantly associated with the increased risk of GDM. Studies concerning ethnicity showed the risk allele was significantly associated with decreased risk of GDM in Asian populations and not in Caucasian populations. It was shown that there is no significant association between rs1800629 variant of TNF-α and GDM.

Transcription factor 7-like 2(TCF7L2) gene is the most studied gene and is having a positive association with T2DM by 1.7 times. Studies have proposed that it plays a role in insulin secretion, and its suppression reduces insulin secretion [63]. TCF7L2 gene polymorphisms were having strong association with risk of GDM [64].

Glucokinase (GCK) is involved in glucose metabolism alteration/ mutations in this gene leads to impairment of glucose metabolism in beta cells which in turn reduces the production of insulin. In a study by Shaat et al among Scandinavian women GCK rs1799884 polymorphism was associated with GDM [65].

PPAR is a transcription factor that regulates glucose homeostasis, lipid metabolism, and inflammation [66]. PPAR gene polymorphisms are positively associated with Korean women [67].

CDKAL1 rs5945326 polymorphism was reported to be associated with GDM in Korean population [68]. The rs10830963 polymorphism of MTNR1B gene is associated with GDM in different populations however further studies are needed for validation [69]. Polymorphisms in the ADRB3 gene predispose pregnant women to GDM [70].

In a recent genome wide association study HKDC1 (Hexokinase Domain Containing 1) gene which affects glucose metabolism showed a strong correlation with 2-hr plasma glucose. The minor alleles of rs10762264 and rs4746822 of gene showed a significant association and conferred 1.24 and 1.34 times increased risk, respectively [71].

In a recent study by Lowe, BACE2 and HKDC1 were shown to have unique association with maternal metabolic quantitative traits [72].

The variants rs7903146, rs12255372 (TCF7L2), rs1799884, rs4607517 (GCK), rs5219 (E23K, KCNJ11), rs7754840, rs7756992(CDKAL1), rs4402960, rs1470579 (IGF2BP2), rs10830963, rs10830962, rs1387153 (MTNR1B), rs1801278 (Gly972Arg, IRS1), rs2237892, rs2237895 (KCNQ1), rs2383208, rs10811661 (CDKN2A/2B), rs391300 (SRR), rs1111875, rs5015480, rs7923837 (HHEX), rs13266634 (SLC30A8) and rs7501939 (TCF2) were significantly associated with a higher risk of GDM.

Therapeutic Strategies

There is evidence that screening and treating GDM reduced perinatal morbidity and improved post-delivery outcomes [73]. Initially GDM is managed by dietary modification, also called as medical nutrition therapy is effective in reducing the perinatal complications and also in achieving desired glycemic control [74].

Regular moderate exercise was for 30 minutes was recommended [75] this helps in reducing insulin resistance. Dietary advice which is the frontline therapy along with lifestyle modifications improves overall health, reduces weight which improves the neonatal outcomes. ADA and NICE have recommended moderate exercise to reduce the risk and maintain normal glycemic levels. Taking metformin orally is second non-insulin treatment which controls the glycemic levels without increasing the risk of maternal hypoglycemia with satisfying neonatal outcomes [76]. Women with BMI <19.8kg/m^2, BMI 19.8–29.9kg/m^2 and BMI ≥ 30kg/m^2 should consume 35–40Kcal/kg/day, 30–32Kcal/kg/day and 24–25 Kcal/kg/day is suggested. Women with FBG > 95mg/dl should be given pharmacological therapy. If the FBG on 3-hr OGTT is below 110mg/dl between 11-33 weeks of gestation without sulfa allergy glyburide administration is recommended. If this criteria is not met by the women insulin can be recommended. Glyburide do not cross the placenta, it acts by increasing insulin secretion and diminishing insulin resistance. If the desired glycemic levels are not achieved insulin therapy is recommended. Insulin dosage is given according to body weight, 0.7-1.0 Units/kg. As gestational age advances insulin dosage also increases. It improves the insulin sensitivity by activating adenosine monophosphate kinase.

In a recent retrospective cohort study by Silva et al among Brazilians states that mothers treated with metformin were having more chances to have neonates adequate for gestational age and those treated with insulin were less likely to have preterm child. When women were treated with metformin and insulin there were more chance for newborn to be large for gestational age and low chance to have preterm [77].

Conclusion

GDM is a genetic metabolic disorder which shares same genetic susceptibility with T2DM, so this made it difficult to identify specific markers responsible for GDM. It is important to evaluate the specific risk factors to give personalized treatment and to improve perinatal outcomes. Postnatal counseling should be individualized for women with GDM to prevent future diabetes risk. Pre-pregnancy weight gain is a modifiable risk factor which when managed can reduce the risk of GDM and T2DM. Dietary changes can help in managing GDM but it is necessary to maintain throughout the life. Obesity has been increasing with change in the lifestyle and has become a major health issue which is one of the risk factors for GDM. Evidence show that early diagnosis and intervention can reduce the risk for mother and baby and even reduce adverse perinatal outcomes [78]. To reduce maternal and neonatal complications it is a prerequisite to diagnose in the early stages of gestation besides preconceptional management, antenatal management and postpartum follow-up. It is very important to do follow-up in order to know the health status of the women postpartum as some women continue to have abnormal glycemic levels. As a treatment option Metformin is an effective drug and cost effective for women with GDM with and without insulin supplementation.

Universal screening should be recommended as selective screening would leave some women undiagnosed. Selective screening based on risk factors using WHO criteria missed 40% of the cases in Srilanka [79].

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Austin Endocrinol Diabetes Case Rep - Volume 1 Issue 1 - 2016
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Citation: Sheela P, Lakshmi VB, Sharadha M, Ramaiah A, Nallari P and Jyothy A. Gestational Diabetes Mellitus: Current Perspectives. Austin Endocrinol Diabetes Case Rep. 2016; 1(1): 1005.