IJPSR (2012), Vol. 3, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 June, 2012; received in revised form 22 September, 2012; accepted 27 September, 2012

VARIANTS OF ORAL GLUCOSE TOLERANCE TEST (OGTT) CURVE IN GESTATIONAL DIABETES MELLITUS (GDM)

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Keywords:
Oral Glucose Tolerance Test, Gestational Diabetes Mellitus, Carpenter and Coustan Criteria

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QUICK RESPONSE CODE

IJPSR:
ICV- 4.57

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www.ijpsr.com

ABSTRACT

Objective: Gestational diabetes mellitus is defined as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy, whether or not insulin is used and regardless of whether diabetes persists after pregnancy. There is evidence that asymptomatic hyperglycemia during pregnancy leads to important morbidity in the mother and foetus. Hence, early detection and treatment of GDM will definitely reduce the complications and bring down the morbidity.

Methods: Test was performed using 100 gm oral glucose. Blood samples were taken at 1hr, 2hr and 3hr as per standard protocol. Blood glucose was measured by glucose oxidase enzymatic method and all the values were tabulated and plotted on a graph. Interpretation was done using Carpenter and Coustan Criteria.

Results: Out of the 96 women, 15 women were diagnosed as GDM. 5 out of them showed atypical pattern in OGTT curve. Similar such patterns were also seen in 5 normal subjects.

Conclusion: In GDM with mild to moderate elevation in fasting plasma glucose, fasting plasma insulin is elevated in parallel. The presence of IGT in pregnancy is predictive of poor pregnancy outcomes. High 2nd hour glucose could be a marker of poor health.

INTRODUCTION: Diabetes mellitus is a chronic disorder characterized by raised blood sugar level which is due to impaired insulin secretion or resistance or both. Around 180 million people worldwide have diabetes according to World Health Organization [1]. This number is likely to be more than double by 2030.

India has largest number of people with diabetes in the world with an estimate of 31.7 million in 2000. This number is predicted to increase to 79.4 million by 2030. Gestational diabetes mellitus is defined as "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy, whether or not insulin is used and regardless of whether diabetes persists after pregnancy" [2, 3].

Normal pregnancy is associated with increased insulin resistance especially in the late second and third trimesters and euglycemia is maintained by increased insulin secretion, while GDM develops in those women who failed to augment insulin sufficiently [4, 5]. There are different studies on GDM occurring in 1-14% of pregnancies depending on population studies and diagnostic tests employed [3, 6, 7, 8].

Asymptomatic hyperglycemia during pregnancy leads to important morbidity in the mother and feotus and hence early detection and treatment of GDM will definitely reduce the complications and bring down the morbidity [5]. OGTT is the preferred test for diagnosis and treatment in GDM [9]. OGTT was interpreted using Carpenter and Coustan criteria recommended by 4th International Workshop Conference on GDM [3, 10, 11]. It labels 50% more subjects as GDM when compared to NDDG (National Diabetes Data Group) criteria. Studies have shown that these additional cases diagnosed by Carpenter and Coustan criteria have risk of perinatal morbidity similar to those of women diagnosed with NDDG criteria [10, 11].

The objective of the study was to analyze the pattern of OGTT curve. We plotted all the values of OGTT on the graph and compared with Carpenter and Coustan criteria.

MATERIALS AND METHODS: The pregnant women who are at high risk were sent to our lab for OGTT by the Department of Obstetrics and Gynaecology, KLE'S Dr. Prabhakar Kore Charitable Hospital, Belgaum. A total of 96 pregnant women who are free from other diseases were enrolled for OGTT from January to May 2009. As per the standard protocol, OGTT was performed with 100 g of glucose at 24-28 weeks of gestation. They had not taken any medication known to affect glucose tolerance, insulin sensitivity and insulin secretion.

After 10 hr overnight fast and 3 days of unrestricted diet and physical activity, the women were tested in the morning. Initially fasting plasma glucose was measured and then 100 g of glucose dissolved in 300 ml of water was ingested over 5 min. Blood samples were taken at 1hr, 2hr and 3hr for testing. Blood glucose was measured by glucose oxidase enzymatic method and all the values were tabulated and plotted on a graph.

RESULTS: From 96 pregnant women, 15 women were diagnosed as gestational diabetes. 8 cases were below 25 years of age whereas 7 cases were above 25 years of age. All cases of GDM had one or more of the following complications in previous pregnancies: bad obstetrics history, perinatal complication, poly-hydramnios, pregnancy induced hypertension, and fetal anomalies. 6 cases had blood pressure on higher side. Of these 15 women of GDM, 9 women were having high fasting glucose level and 2 women had high glucose level after 2nd hour and 2 women showed high 3rd hour glucose level. **Table 1** depicts the values of OGTT in women diagnosed with GDM. Values are expressed in mg/dL.

TABLE 1: OGTT VALUES OF WOMEN WITH GDM

Subjects	0hr	1hr	2hr	3hr
13	96	100	180	79
16	98	140	158	124
20	100	133	168	150
22	106	160	184	208
23	132	208	180	160
26	144	184	224	192
27	104	144	168	128
38	240	320	400	392
40	92	200	184	128
42	110	168	224	100
71	83	118	192	150
78	130	165	160	144
79	100	140	224	240
88	86	162	172	180
94	123	200	173	170

Figure 1 is the criteria of Carpenter and Coustan and GDM is diagnosed when any two values are met or elevated. **Figure 2** shows the atypical response of subjects with GDM to OGTT. There is increase in the blood glucose level seen at both 2nd and 3rd hour when compared to Carpenter and Coustan criteria with respect to the subject 22, 79 and 88. Subjects 13 and 42 diagnosed as GDM show sudden drop in the blood glucose level at 3rd hour which is below their fasting level when compared to Carpenter and Coustan criteria. We even found atypical OGTT curve in normal pregnant women.

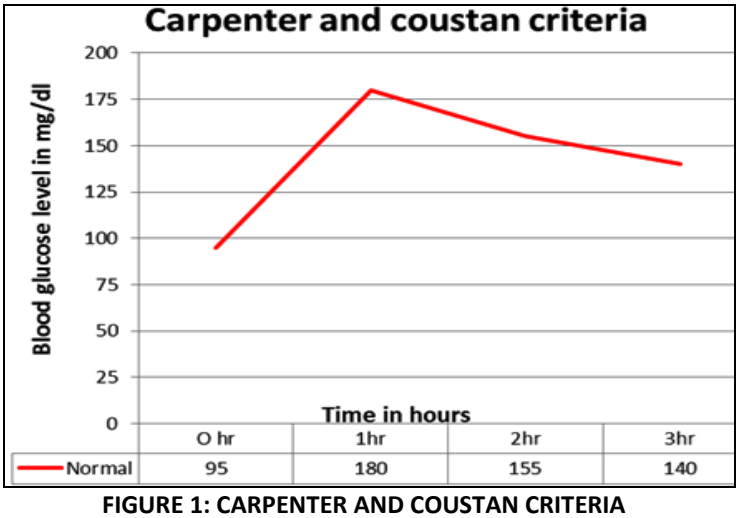
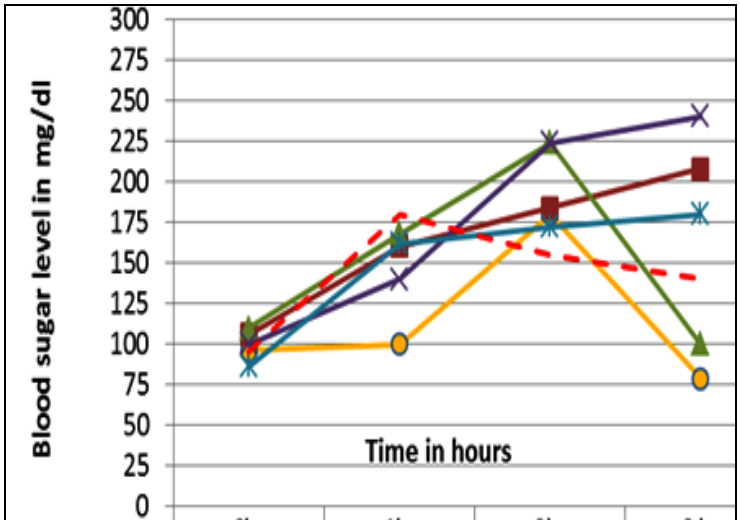


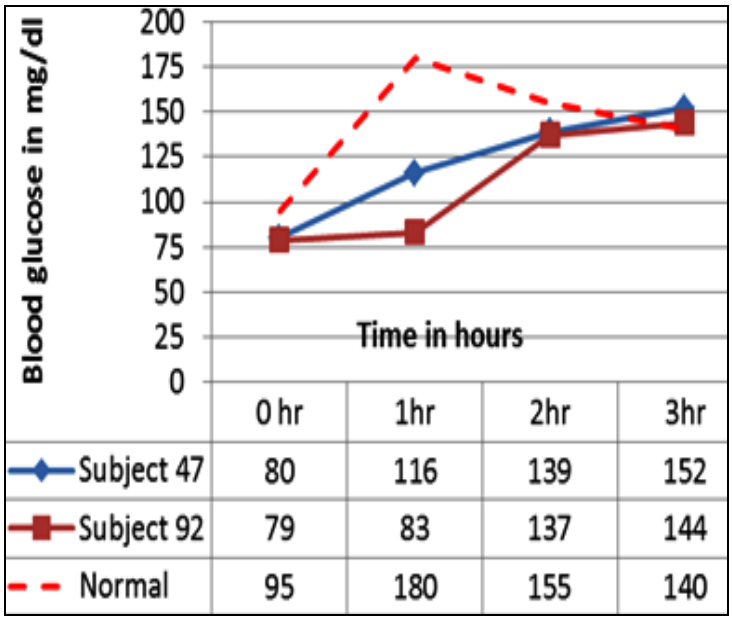
FIGURE 1: CARPENTER AND COUSTAN CRITERIA



	0hr	1hr	2hr	3 hr
Subject 13	96	100	180	79
Subject 22	106	160	184	208
Subject 42	110	168	224	100
Subject 79	100	140	224	240
Subject 88	86	162	172	180
Normal	95	180	155	140

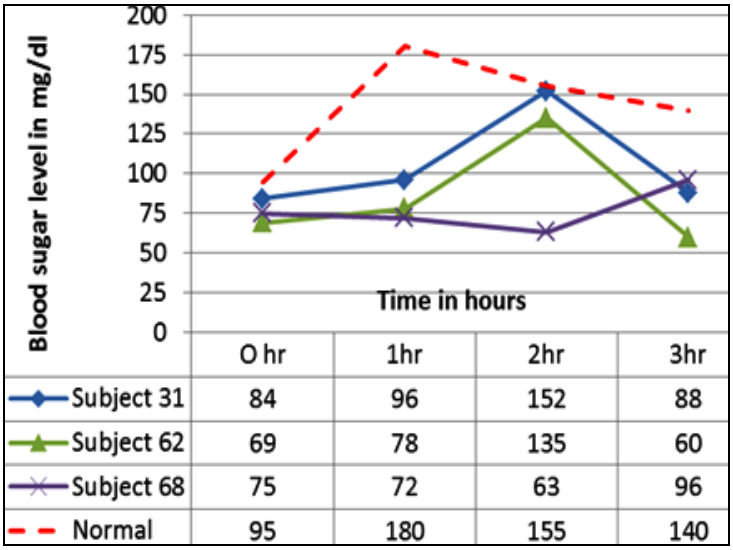
FIGURE 2: SUBJECTS DIAGNOSED AS GDM HAVING ATYPICAL OGTT CURVE

There was steep rise in blood glucose level at 2nd and 3rd hour in two normal subjects 47 and 92 as shown in **Figure 3**. In **Figure 4**, we found one subject 68 showing hypoglycemic pattern of OGTT curve while two subjects 31 and 62 showed rise in blood glucose level at 2nd hour and fall suddenly at 3rd hour below their fasting level.



	0 hr	1hr	2hr	3hr
Subject 47	80	116	139	152
Subject 92	79	83	137	144
Normal	95	180	155	140

FIGURE 3: NORMAL PREGNANT WOMEN 47 AND 92 SHOW ATYPICAL OGTT CURVE



	O hr	1hr	2hr	3hr
Subject 31	84	96	152	88
Subject 62	69	78	135	60
Subject 68	75	72	63	96
Normal	95	180	155	140

FIGURE 4: NORMAL PREGNANT WOMEN 68 SHOW HYPOGLYCEMIC PATTERN OF OGTT CURVE

Subjects 31 and 62 show atypical pattern of OGTT curve.

DISCUSSION: In the present study, we plotted OGTT values on the graph and compared with Carpenter and Coustan criteria as shown in Figure 1. Regular and atypical responses to OGTT were found in both GDM women and normal pregnant women. An attempt was made to understand for the behavioral pattern of both insulin secretion and glucose metabolism. The shape of the plasma glucose curve during an OGTT in non-diabetic individuals is related to the glucose tolerance, beta-cell function and insulin sensitivity [12, 13].

The maintenance of plasma glucose levels within the narrow range and its regulation largely depends on i) the ability of the pancreatic β-cells to secrete insulin both acutely and in a sustained fashion; ii) insulin sensitivity or the ability of insulin to promote uptake of glucose into peripheral tissues; iii) the ability of glucose to enter cells [9]. In healthy individuals insulin is secreted in a pulsatile fashion.

The main stimulus for insulin secretion is increased glucose concentration. Pancreatic β-cells can sense increased glucose concentration in blood.[4] Insulin is released in two phases: First, the rapid release of stored insulin begins immediately within 2 minutes. The second phase depends on continuing insulin synthesis and release lasts until normoglycemia has been restored, usually within 60-120 minutes [14].

Pregnancy is a state of physiologic insulin resistance occurring in maternal tissues in order to satisfy the nutritional demands of the fetus [2]. Increased level of estrogen and progesterone lead to beta cell hyperplasia and increased insulin response to a glucose load in early pregnancy. In second half of pregnancy the human placental lactogen and other contra insulin hormones synthesized by placenta are responsible for diabetogenic state of pregnancy. This is characterized by increased rate and amount of insulin release with decreased insulin sensitivity at cellular level [15, 16].

Normally there is 30% increase in basal insulin production at full term pregnancy. Diabetes will be detected for the first time if the pregnant women have limited pancreatic reserve or inadequate endogenous insulin production. GDM is associated with 56% decrease in insulin sensitivity as compared to 44% decline in normal pregnancy [14]. In GDM with mild to moderate elevation in fasting plasma glucose, fasting plasma insulin is elevated in parallel. However, first phase insulin response as well as subsequent insulin release is generally attenuated in women with GDM, when adjusted for their level of insulin resistance [10].

But there is drop in insulin secretion in second phase thus giving rise to increase in plasma glucose level which is typically observed in Figure 2. Patients with history of GDM have a high risk of progression to type-2 diabetes suggesting that the insulin resistance of pregnancy provides a "stress test" that unmasks women at high risk for development of type-2 diabetes.[10,17] Women with GDM are at high risk for subsequent diabetes.

GDM is a state of insulin resistance and these patients can maintain normal glucose tolerance if their pancreatic beta cells secrete enough insulin to overcome this defect as occurs in impaired glucose tolerance.[18] This group has >50% increased risk of developing diabetes mellitus in future [17, 19, 20]. This pattern is observed in Figure 3. Though in some apparently normal people, there is only small increase in glucose levels, which may scarcely exceed the usual normal fasting levels, this pattern is most commonly seen in hypothyroidism, hypoadrenalism, hypo-pituitarism and idiopathic steatorrhoea. In these cases flat curves of OGTT are frequently obtained.

In figure 4 there was one normal subject showing hypoglycemic pattern with glucose levels going lower than the fasting which cannot be explained. This occurs in hyperinsulinism [21].

Another type of tolerance curve is the "lag" type. This is seen in some apparently normal people who are found to have a tolerance curve in which the blood glucose returns to normal limits in the usual time, but which shows a somewhat exaggerated rise. This type of curve has been termed a lag curve on the assumption that the greater rise in blood glucose is due to a delay in the insulin mechanism coming into action.

It is more probably due to an increased rate of absorption of glucose from the intestine, following rapid emptying of the stomach seen also after partial gastrectomy. These patients exhibit hypoglycemic symptoms due to rapid fall in blood glucose below the fasting levels [21].

In Figure 4, the subjects have blood glucose peaking at the 2nd hour in contrast to the above lag type curve were blood glucose peaks immediately in the first hour. It is possible that as long as β-cells secrete enough insulin to maintain euglycemia, consequences of elevated blood glucose are avoided, regardless of the amount of insulin necessary to maintain glucose homeostasis [22]. High 2nd hour glucose could be a marker of poor health. As elevated glucose indicates poor insulin secretion; this may cause further complications due to hyperglycemia.

Hence, OGTT curve provides an index of insulin secretion; it can also define insulin sensitivity and secretory defects in individuals with IGT. Thus the shape of the curve may be a useful metabolic screening parameter in assessing glucose tolerance.

The intention is to assess whether it is possible to identify more pre-diabetic subjects before they fall into the criteria of WHO and ADA with the help of OGTT curves.

Future studies on large samples are required to know the prevalence of these variant forms of OGTT curves and their significance in pregnancy outcome and future risk of diabetes mellitus.

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How to cite this article:
Gowda S, Desai PB, Kagwad VS, Shetty SJ and Ilakal MB: Variants of Oral Glucose Tolerance Test (OGTT) Curve in Gestational Diabetes Mellitus (GDM). *Int J Pharm Sci Res*. 3(10); 3966-3970.