INTRODUCTION

Gestational diabetes mellitus (GDM) is defined by the World Health Organization (WHO) as a carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.(1)

Large studies have found that GDM occurs in 2.2-8.8% of pregnancies, depending on the ethnic mix of the population and the criteria used for diagnosis.(2)

Prevalence of GDM is increasing all over the world.(3) Risk factors for the development of GDM include obesity, older age, family history, previous history of GDM, poor obstetric outcomes, ethnicity, polycystic ovary syndrome and more recently noted hypertension**.** (4)

GDM carries considerable health risks for both the fetus and the mother, for the infants; they include an increased risk of macrosomia, birth injuries such as (shoulder dystocia, bone fracture and nerve palsies), hypoglycemia and hyperbilirubinaemia**.** (5)

Women with GDM are at increased risk of developing preeclampsia with an increased chance of need for induction of labour and caesarean section, gestational diabetes is also a strong risk factor for later development of type 2 diabetes**.** (6)

Preeclampsia has been frequently reported as a complication of gestational diabetes but the relation between these two conditions is not well understood. Several studies suggest underlying common pathophysiology, including insulin resistance, chronic inflammation and endothelial dysfunction**.** There are common risk factors, such as elevated body mass index and advanced age have been noted for each of the two conditions**.** (7)

Uric acid is the end product of purine catabolism catalysed by the enzyme xanthine oxidase/dehydrogenase**.** (8)

In non-pregnant women, uric acid is associated with insulin resistance and is an independent risk factor for development type 2 diabetes within 10 years**.** (9)

In pregnancy, uric acid is correlated with insulin resistance in women with gestational hypertension and is higher at 24-28 weeks gestation in women diagnosed with GDM compared to women without diabetes**.** (10)

Two mechanisms have been hypothesized by which uric acid can cause insulin resistance, the first proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cell. In animals, insulin action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependant on nitric oxide thus, decreases in nitric oxide lead to decreased glucose uptake and the development of insulin resistance**.** (11)

Another mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice. [12]

AIM OF THE WORK

The aim of the present study is to test the hypothesis that increased uric acid levels, measured in the first trimester of pregnancy, are associated with the subsequent development of GDM.

Chapter (1)

GESTATIONAL DIABETES MELLITUS

Definition

Gestational diabetes mellitus (GDM), a common medical complication of pregnancy, is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy". The definition has applied whether or not insulin is used for treatment or hyperglycemia persists after pregnancy. The possibility that unrecognized glucose intolerance antedated the pregnancy is not excluded. [13,14]

However, in 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, including the American Diabetes Association (ADA), recommended that women found to have diabetes at their initial prenatal visit, using standard criteria, receive a diagnosis of overt, rather than gestational diabetes.[15]

The rationale for this change is that more and more women have personal risk factors, such as obesity, for diabetes, and are therefore being screened early in pregnancy. Women diagnosed in the first trimester likely had pre-existing diabetes unrecognized prior to pregnancy rather than impaired glucose tolerance due to pregnancy-

related hormonal changes, which are most pronounced later in gestation.

Prevalence

It affects between 2-14% of pregnancies. [16] Gestational diabetes mellitus (GDM) is one of the most common medical disorders found in pregnancy. The prevalence of GDM ultimately reflects the background rate of type 2 diabetes. There has also been an increase in the rate of GDM over the last generation, possibly related to community lifestyle factors as well as better case ascertainment. [17]

Pathophysiology

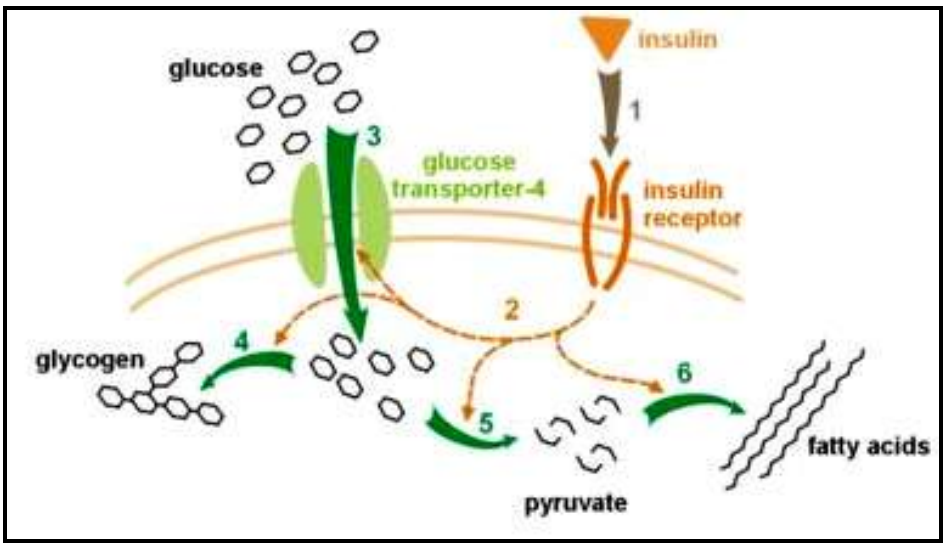

Figure (1): Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1) on the cell membrane which in turn starts many protein activation cascades (2). These include: translocation of GluT-4 (glucose transporter-4) to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signaling pathway behind the insulin receptor. [18]

Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the blood stream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5-2.5 times more insulin is produced than in a normal pregnancy. [18]

Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which progresses thereafter to levels seen in non-pregnant patients with type 2 diabetes. It is thought to secure glucose supply to the growing fetus. Women with GDM have an insulin resistance they cannot compensate with increased production in the β-cells of the pancreas. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Cortisol and progesterone are the main culprits, but human placental lactogen, prolactin and estradiol contribute too. [18]

It is unclear why some patients are unable to balance insulin needs and develop GDM, however a number of explanations have been given, similar to those in type 2 diabetes: autoimmunity, single gene mutations, obesity, and other mechanisms. [19]

Because glucose travels across the placenta (through diffusion facilitated by GLUT3 carriers), the fetus is exposed to higher glucose levels. This leads to increased fetal levels of insulin (insulin itself cannot cross the placenta). The growth-stimulating effects of insulin can lead to excessive growth and a large body (macrosomia). After birth, the high glucose environment disappears, leaving these newborns with ongoing high insulin production and susceptibility to low blood glucose levels (hypoglycemia). [20]

Risk factors of GDM

Classical risk factors for developing gestational diabetes are the following: [21]

- A previous diagnosis of gestational diabetes or prediabetes, impaired glucose tolerance, or impaired fasting glycaemia.
- A family history revealing a first degree relative with type 2 diabetes.

- Maternal age - a woman's risk factor increases as she gets older (especially for women over 35 years of age).
- Ethnic background (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from the Indian subcontinent).
- Body Mass Index (BMI) is another risk factor where BMI=weight (kg)/height (m^2). Being overweight (BMI = 25-29.9kg/m^2), obese (BMI= 30-34.9kg/m^2) or morbidly obese(BMI= 35-40kg/m^2) increases the risk of developing GDM by 2.1, 3.6 and 8.6 respectively.[22]
- A previous pregnancy which resulted in a child with a high birth weight (>90th percentile, or >4000g).
- Previous poor obstetric history as unexplained fetal loss.

In addition to this, statistics show a double risk of GDM in smokers.[23] Polycystic ovarian syndrome is also a risk factor [21], although relevant evidence remains controversial. [24] Some studies have looked at more controversial potential risk factors, such as short stature. [25]

About 40-60% of women with GDM have no demonstrable risk factor; for this reason many advocate to screen all women. [26] Typically women with gestational diabetes exhibit no symptoms (another reason for universal screening), but some women may demonstrate increased

thirst, increased urination, fatigue, nausea and vomiting, bladder infection, yeast infections and blurred vision.

Classification

Diabetes is now classified based on the pathogenic processes involved.[27] Absolute insulin deficiency characterizes *type 1 diabetes*, whereas defective insulin secretion or insulin resistance characterizes *type 2 diabetes* (Table 1). [28] The terms insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM) are no longer used. Age is also no longer used in classification, because pancreatic B-cell destruction can begin at any age. Most commonly, its onset is before age 30, but in 5 to 10 percent of affected individuals, onset is after age 30 years. Type 2 diabetes, although most typical with increasing age, also develops in obese adolescents.

Table (1): Etiological Classification of Diabetes Mellitus [28]

I. Type 1: B-Cell destruction, usually absolute insulin deficiency
A. Immune-mediated
B. Idiopathic
II. Type 2: Ranges from predominantly insulin resistance to predominantly an insulin secretory defect with insulin resistance
III. Other types
A. Genetic mutations of B-cell function
B. Genetic defects in insulin action
C. Genetic syndromes e.g., Down, Klinefelter, Turner
D. Diseases of the exocrine pancreas—e.g., pancreatitis, cystic fibrosis
E. Endocrinopathies—e.g., Cushing syndrome, pheochro-mocytoma, others
F. Drug or chemical induced—e.g., glucocorticosteroids, thiazides, -adrenergic agonists, others
G. Infections—congenital rubella, cytomegalovirus, coxsackievirus
IV. Gestational diabetes (GDM)

Classification of Diabetes Complicating Pregnancy

The White classification, named after Priscilla White [29] who pioneered in research on the effect of diabetes types on perinatal outcome, is widely used to assess maternal and fetal risk. It distinguishes between gestational diabetes (type A) and diabetes that existed prior

to pregnancy (pregestational diabetes). These two groups are further subdivided according to their associated risks and management. [30]

There are 2 subtypes of gestational diabetes (diabetes which began during pregnancy):

- Type A1: abnormal oral glucose tolerance test (OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels.
- Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required.

The second group of diabetes which existed prior to pregnancy is also split up into several subtypes.

Table (2): Classification of DM complicating pregnanc [31]

Class	Onset	Fasting Plasma Glucose	2-hours Postprandial Glucose	Therapy
A_1	Gestational	< 105mg/dL	< 120mg/dL	Diet
A_2	Gestational	> 105mg/dL	> 120mg/dL	Insulin
Class	**Age of Onset in Years**	**Duration in Years**	**Vascular Disease**	**Therapy**
B	Over 20	< 10	None	Insulin
C	10 to 19	10 to 19	None	Insulin
D	Before 10	> 20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Heart	Insulin

Screening

Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied.[32] No specific cause has been identified, but it is believed that the hormones produced during pregnancy increase a woman's resistance to insulin, resulting in impaired glucose tolerance.

The recent point-counterpoint [33,34] comprehensively debated is in regards to whether screening for GDM should be selective (i.e., using risk factors) or universal (i.e., using blood tests). In the United States, most obstetricians prefer universal screening with a screening glucose tolerance test.[35] In the United Kingdom, obstetric units often rely on risk factors and a random blood glucose test.[20,36]

The American Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada recommend routine screening unless the patient is low risk (this means the woman must be younger than 25 years and have a body mass index less than 27, with no personal, ethnic or family risk factors).[337,38] The Canadian Diabetes Association and the American College of Obstetricians and Gynecologists recommend universal screening.[39] The U.S. Preventive Services Task Force of garwal MM, Dhatt GS, und that there is insufficient evidence to recommend for or against routine screening.[40]

Holt et al. acknowledge the cost-effectiveness of the American Diabetes Association (ADA) criteria, which are similar to our recommendation of offering all women a glucose test.[41] They have understated the importance of the article by **Landon et al.** which showed that active management of gestational diabetes mellitus (GDM) not only led to significant reductions in neonatal size/fat mass (which may predict future diabetes/obesity in the

offspring), but also significant reductions in shoulder dystocia (1.5 vs. 4.0%), cesarean delivery (26.9 vs. 33.8%), and preeclampsia/ gestational hypertension (8.6 vs. 13.6%). These findings make screening for GDM even more cost-effective**.** [42]

Screening Timing:

The American Diabetes Association, the American College of Obstetricians and Gynecologists, and the World Health Organization recommend screening most pregnant women for gestational diabetes between 24 and 28 weeks' gestation and screening high-risk pregnant women (for example, those with a personal history of gestational diabetes or marked obesity) at the first antenatal visit**.** [43]

The International Association of Diabetes and Pregnancy Study Groups has recently recommended screening "as early as possible"**.**[44] The NICE recommendations advise screening at 16–18 weeks, which is not early and potentially allows the growing fetus to be exposed to significant hyperglycemia for many weeks. Because of the risks of GDM to the mother and neonate, screening and diagnosis are warranted. Current screening and diagnostic strategies, based on the 2004 ADA position statement on GDM [37]**,** are outlined in (Table 3)**.**