



## A BRIEF ACCOUNT OF GESTATIONAL DIABETES MELLIUS (GDM): FETOPLACENTAL IMPAIRMENT AND DEVELOPMENTAL PROGRAMMING OF DISEASE IN OFFSPRING

### Pharmacy

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### ABSTRACT

Gestational diabetes mellitus(GDM) has serious ramifications on the offspring such as Hypoxemia, Visceromegaly, Perinatal mortality, Hyper bilirubinemia, Obesity, Hyperglycemia, reduced immune function and cognitive function. Gestational diabetes is known to effect placental metabolism, growth, and development. The maternal and fetal hyperglycaemia have an impact on the production of placental proteins. Concerns regarding these denouements are escalating rapidly in the developing countries, there is a need of deeper understanding pertaining to the pathophysiological, therapeutic and preventive measures of GDM. Lack of awareness among the patients is also responsible for fetal abnormalities caused by GDM. In this review we have given a brief account of Fetal Developmental Trajectory, Intrauterine exposure to gestational diabetes, Placental impairment and Modifications in materno-placental oxygen supply. At the end, we have noted the impact of Embryonic Amino Acid Metabolism during Early Pregnancy.

### KEYWORDS

Hypoxemia, Visceromegaly, Perinatal mortality, Hyper bilirubinemia, Hyperglycemia.

### INTRODUCTION:

Gestational diabetes mellitus(GDM) is defined as any degree of impaired glucose tolerance of with onset or first recognition during pregnancy<sup>1</sup>.

- Many are denovo pregnancy induced
- Some are type 2 (35-40%)
- 10% have antibodies

Difficult to distinguish pregestational Type 2 DM and denovo GDM<sup>2</sup>

- Fasting hyperglycemia
- blood glucose greater than 180 mg/dL on OGT
- *Acanthosis nigricans*
- HbA1C > 5.3%
- a systolic BP > 110 mm Hg
- BMI > 30 kg/m<sup>2</sup>
- Fetal anomalies

Causes for Type 1

- Lean
- Diabetic ketoacidosis (DKA) during pregnancy
- Severe hyperglycemia with large doses of insulin

### FUEL METABOLISM IN PREGNANCY:

- Goal is uninterrupted nutrient supply to fetus
- The metabolic goals of pregnancy are
  - 1) in early pregnancy to develop anabolic stores to meet metabolic demands in late pregnancy
  - 2) in late pregnancy to provide fuels for fetal growth and energy needs<sup>3</sup>.

### GLUCOSE METABOLISM IN PREGNANCY:

- Early pregnancy
  - E2/PRL stimulates b cells –Insulin sensitivity same and peripheral glucose utilisation – 10% fall in BG levels
- Late pregnancy
  - Fetoplacental unit extracts glucose and aminoacids, fat is used mainly for fuel metabolism<sup>4</sup>
  - Insulin sensitivity decreases progressively upto 50-80% during the third trimester<sup>5</sup>

- variety of hormones secreted by the placenta, especially hPL and placental growth hormone variant, cortisol, PRL, E2 and Prog<sup>6</sup>

### Glucose metabolism in pregnancy

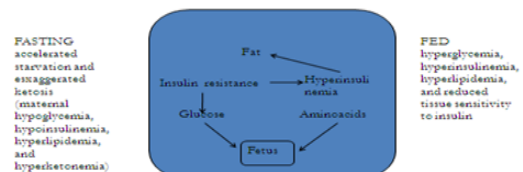


Figure 1: Glucose metabolism in pregnancy

- 24-hour insulin requirement before conception is approximately 0.8 units / kg.
- In the first trimester, the insulin requirement rises to 0.7 units / kg of the pregnant weight – more unstable glycemia with a tendency to low fasting plasma glucose and high postprandial excursions and the occurrence of nocturnal hypoglycemia
- By the second trimester, the insulin requirement is 0.8 units per kilogram. From 24th month onwards steady increase in insulin requirement and glycemia stabilises
- By third trimester the insulin requirement is 0.9 - 1.0 unit / kg pregnant weight per day
- Last month – may be a decrease in insulin and hypoglycemias esp. nocturnal

### RISK INVOLVED IN THE DEVELOPMENT OF GDM:



Figure 2: Gestational Diabetes Risk factors

**PATHOPHYSIOLOGY OF GDM:**

- GDM is characterized by hyperinsulinaemia and insulin resistance resulting in abnormal carbohydrate intolerance.
- In first trimester and early second trimester, increased insulin sensitivity occurs due to relatively higher levels of estrogen.
- In late second and early third trimesters, increased insulin resistance and reduced sensitivity due to a number of antagonistic hormones especially, placental lactogen, leptin, progesterone, prolactin, cortisol and adiponection<sup>7</sup>

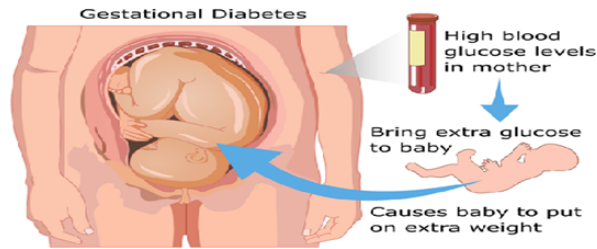


Figure 3: Gestational Diabetes Mellitus

**EFFECT OF DIABETES DURING PREGNANCY:**

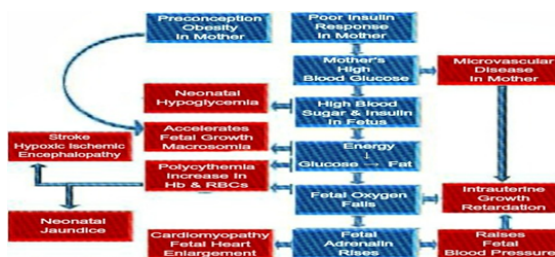


Figure 4: Effect of Diabetes During Pregnancy

**SCREENING OF GDM:**

It is done in two steps which involves clinical risk assessment and blood glucose screening.<sup>8</sup>

**Step-1: Clinical Risk Assessment**

1. High risk patient: at first antepartum visit or as soon as possible thereafter blood glucose screening is done, and repeated at 24-48 weeks if not already diagnosed by that time
2. Average risk patient: between 24-48 week gestation blood glucose screening is done.
3. Low risk patient: blood screening is not required.<sup>8</sup>

**Step-2: Blood Glucose Screening**

Glucose cut off value:  $\geq 140\text{mg/dl}$  (80% sensitivity for GDM) or  $\geq 130\text{mg/dl}$  (90% sensitivity for GDM).<sup>8</sup>

**DIAGNOSIS OF GDM:**

In the first trimester women diagnosed with diabetes are classified as preexisting pregestational diabetes i.e, type 2 diabetes, type 1 diabetes (rare) or monogenetic diabetes. Diabetes which is first diagnosed during second or third trimester is not clearly pre-existing type 1 or 2 diabetes.<sup>9</sup>

The currently recommended criteria by American diabeticcassociation is based on O'sullivan's criteria.<sup>8</sup> According to "classification and diagnosis of diabetes : standards of medical care in diabetes-2018" gestational diabetes mellitus diagnosis can be done with either of two strategies.<sup>9</sup>

**1. One-step strategy :**

In women who are not previously diagnosed with diabetes, perform a 75g oral glucose tolerance test (OGTT), at 24-48 weeks of gestation when patient is on fasting and at 1st hour and 2nd hour, with plasma glucose measurement. After an overnight fasting of minimum 8 hours the test should be done in the morning. The patient is considered as diabetic when the following values are met or exceeded.<sup>9</sup>

- Fasting: 92mg/dl,
- 1hour: 180mg/dl,
- 2hour: 153mg/dl

This strategy increases the incidence of GDM from the range of 5-6% to 15-20%, since only one abnormal value is sufficient to make diagnosis instead of two values. The increase in this incidence rate has substantial impact on costs, medical infrastructure needs and potential to check previous pregnancies considered as normal<sup>9</sup>

**2. Two-step strategy:**

**STEP-1:** Perform a 50-g glucose load test (GLT) (nonfasting) in women not diagnosed with diabetes previously, at 24-48 weeks of gestation, with plasma glucose measurement at 1hour. if plasma glucose level is  $\geq 130\text{mg/dl}$ ,  $135$  or  $140\text{mg/dl}$  measured at 1 hour after the load, then proceed to a 100-g OGTT.

**STEP-2:** When the patient is fasting 100-g OGTT should be done. The diagnosis is made when at least two of the following values are met or exceeded.<sup>9</sup>

- Fasting: 105mg/dl
- 1hour: 190mg/dl
- 2hour: 165mg/dl
- 3hour: 145mg/dl

**FETAL DEVELOPMENTAL TRAJECTORY:**

A wide range of gestational events can alter the fetal developmental trajectory (Figure 5). These include maternal nutritional deficit/excess, environmental exposure to endocrine-disrupting chemicals (EDCs), disease states, lifestyle choices, substance abuse, and medical interventions during pregnancy. Although some of these insults lead to alterations that are manifested immediately after birth such as spina bifida associated with folate deficiency or congenital limb malformations due to thalidomide medication for morning sickness<sup>20</sup>, a host of adult onset manifestations such as coronary and metabolic diseases may not be apparent until adulthood.

Although a wide variety of perinatal insults during critical windows of differentiation alter the developmental trajectory of the fetus/offspring, there are often many commonalities in the phenotypic outcomes. Most of these insults result in placental alterations, intrauterine growth restriction (IUGR), and catch-up growth culminating in adult diseases. For example, offspring born to women with gestational undernutrition or excess androgen exposure<sup>19,22,23</sup> are reported to undergo IUGR, to be born small for their gestational age, and to manifest adult reproductive and metabolic abnormalities.

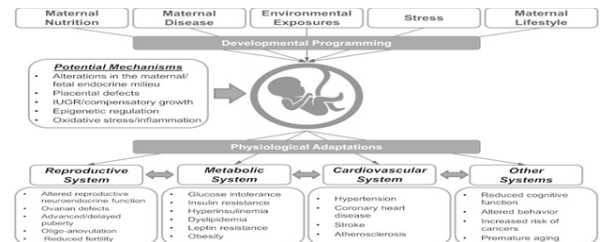


Figure5: Impact of perinatal insults in programming adult pathologies in the offspring. Exposure of the foetus/offspring to different insults during critical periods of development may lead to adaptations that prove to be detrimental and associated with adult defects in several organ systems.

**INTRAUTERINE EXPOSURE DURING GDM:**

The Bakers hypothesis postulates that there is development of adult disease when there is alteration in intrauterine environment and in nutrition provided to fetal and infant. Based on several data it is confirmed that infants born small at birth are at increased risk of having hypertension, stroke, type 2 diabetes and obesity. Permanent changes occur during fetal development allowing adaptation to survive in a suboptimal intra uterine environment so that these developmental adaptations will contribute for the development of pathogenesis of multiple chronic diseases in later life. Similarly, women with pre-gestation diabetes or GDM pose increase risk of developing chronic disease in infant. By this, fetal intra-uterine exposure to undernourishment or diabetes will have increased risk of disease development in later life.<sup>10</sup>

It is hypothesized that dysfunctional stem and progenitor cells are involved in disease pathogenesis. There are numerous functional deficits of cord blood endothelial colony-forming cells (ECFC's)

which are exposed to GDM in utero. The mechanism for fetal adaptation include epigenetic modification which will lead to gene expression abruptly and subsequent cellular dysfunction. Based on several studies it is concluded that during fetal exposure to GDM genetic changes are induced in ECFC's which will result in cellular dysfunction and improper gene expression.<sup>10</sup>This intrauterine programming can occur at any level like gene, cellular, tissue, organ, and system levels resulting in long lasting functional and structural changes.<sup>11</sup>

#### PLACENTAL IMPAIRMENT DURING GDM:

Normally placenta serves as a natural selective barrier between blood circulations of mother and fetus. Due to adverse intrauterine conditions in GDM it acts as target for maternal and fetal metabolic alterations. When diabetes is developed in early pregnancy structure of placenta is affected whereas later disturbances in glucose metabolism is known to effect placental function<sup>12</sup>

Placental villi will undergo angiogenesis and vascularisation during second half of pregnancy. Early onset of diabetes is mainly related to the placental development disorders like villous immaturity and alteration in villous branching.<sup>12</sup>

In diabetic pregnancy, macroscopically placenta is enlarged, become thickened and plethoric and have increased placental to fetal weight ratio. Histological changes in placenta includes villous edema, fibrin deposits in syncytiotrophoblast, and hyperplasia of cytotrophoblast.<sup>12</sup>In general there are higher number of transversal interconnection between villous branches and higher total length volume and there is also higher surface area of villous capillaries of a GDM placenta.<sup>12</sup>

Typical feature of placenta exposed to hyperglycemic environment is increased angiogenesis of fetoplacental vessel and there is lower concentration of adherence proteins and tight junctional protein. There is also fetoplacental vessel leakiness to macromolecules that are larger than albumin.<sup>12</sup>

In fetus metabolic and hormonal changes are directly stimulated by maternal hyperglycemia fetal metabolism is accelerated by higher levels of insulin and subsequently enhance oxygen demand in fetus. Thus, increased oxygen consumption and placental abnormalities leads to chronic fetal hypoxia which will lead to increase erythropoiesis by erythropoietin (EPO) secretion. Vasoconstriction of placental vessel is induced by synthesis of reactive oxygen species and transient dysregulation of NO and activate the generation of pro-inflammatory cytokines. In GDM placenta there is enhance transport of cholesterol and triglycerides.<sup>12</sup>

#### MODIFICATION IN MATERNO-PLACENTAL OXYGEN SUPPLY:

In gestational diabetes the placental structure is altered. Due to hyperproliferation and hypervascularization, the surface and exchange areas are enlarged. The mechanisms underlying this phenomenon are unclear but the role of hyperglycemia associated with other maternal factors cannot be excluded.<sup>13</sup>

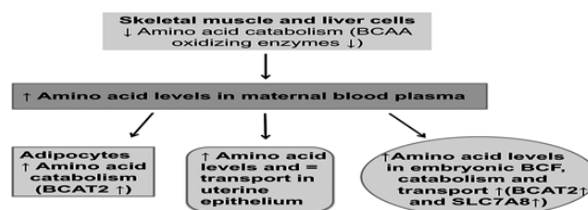
The maternal-placental oxygen supply is reduced and in addition to this the fetal oxygen demand is increased.<sup>14</sup>This could be explained by aerobic metabolism which is stimulated by fetal hyperinsulinemia. The resulting low oxygen levels in the fetus upregulate the transcription synthesis of proangiogenic factors such as leptin, vascular endothelial growth factor (VEGF) or fibroblast growth factors 2 (FGF2). These factors promote endothelial cell proliferation. GDM is characterized by enhanced vascularization.

The diabetic environment have profound effects on placental development and function, especially during the first trimester. During this time the placental structures are formed and the placenta is more sensitive to modifications. In the initial weeks of pregnancy, the blastocyst implants into the uterine wall, surrounded by the trophoblast cells. The cytotrophoblasts (CTB) are a progenitor stem cells that continuously proliferate and differentiate into one of the two cell lineages, 1) villous CTBs which fuse to form syncytiotrophoblast which ensures placental endocrine, protective, and transport functions and 2) Extravillous trophoblasts responsible for performing anchorage of the chronic villi into the uterine wall and for actively regulating the remodeling of uterine spiral arteries to optimize the supply of oxygen and nutrients to the placenta and the fetus. Extravillous trophoblasts are

actively involved in the placentation. Many pregnancy-related complications that generally appear in late gestation (such as preeclampsia, fetal growth restriction, and preterm labor) seem to be caused by abnormalities in the placentation process, in particular inadequate trophoblast invasion and spiral artery remodeling.

The maternal and fetal hyperglycemias are likely to have an impact on the production of various placental proteins. More recently, it has been shown that placental expression and activity of the matrix metalloproteinases as MMP14 and MMP15 are elevated in diabetes especially in type 1 diabetes induced by maternal hyperinsulinemia and TNF- $\alpha$ . MMP14 and MMP15 are proteases which are involved in tissue remodeling processes associated with invasion, angiogenesis and proliferation. The active form of placental MMP14 is elevated in diabetes. It is possible that hypoxic situations in the villous placental structure may be implicated as a cause of increased MMP14 activity.<sup>15</sup>

#### EMBRYONIC AMINO ACID METABOLISM DURING EARLY PREGNANCY:



**Figure 6: Schematic model of amino acid catabolism in maternal tissues and embryos in a diabetic pregnancy<sup>16</sup>.**

Maternal diabetes leads to reduced Branched Chain Amino Acid (BCAA) catabolism in skeletal muscle and liver and to increased BCAA catabolism in adipose tissue. As a result of the reduced catabolism in muscle tissue the maternal blood plasma BCAA levels are enhanced<sup>17</sup>. This might influence the BCAA levels in uterine secretions as BCAA are transferred via SLC7A8 (Solute Carrier Family 7 Member 8 is a Protein Coding gene) to the uterine lumen and to embryos. BCAA accumulate in the blastocyst cavity fluid (BCF) and can be used as a source for embryonic metabolism and protein synthesis, increasing the embryonic BCAA supply<sup>18</sup>.

#### ABBREVIATIONS:

Branched Chain Amino Acid (BCAA)

Branched-Chain Amino Acid Aminotransferase (BCA2)

#### CONCLUSION:

- Gestational diabetes is a common problem in India
- Risk stratification and screening is essential in all Indian pregnant women
- Tight glycemic targets are required for optimal maternal and fetal outcome
- Patient education is essential to meet these targets
- Long term follow up of the mother and baby is essential

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