GESTATIONAL DIABETES: An Overview

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Brief overview of Insulin

- Insulin is a protein hormone synthesized in beta cells of Islets of Langerhans in Pancreas;
- Metabolic functions enhanced by Insulin include:
  - Uptake of glucose in muscle and adipose tissue,
  - Glycogenesis,
  - Glycolysis,
  - Protein synthesis,
  - Cellular uptake of Potassium and Phosphate ions;
- Insulin stimulates synthesis of: Glycogen, Fats & Proteins,
- Insulin inhibits degradation of: Glycogen, Fat & Proteins

- Insulin regulates uptake of Glucose into tissues with GLUT 4 Transporter, Examples:
  - Muscle cells, Adipose tissue, Connective tissues, White blood cells;
- Insulin DOES NOT regulate Glucose uptake into tissue with GLUT 2 Transporter, Examples:
  - Brain, Liver, Kidneys,
- **BUT** Insulin regulates biosynthesis of Glycogen in Liver cells (Glycogen Synthetase reaction);
- Insulin counter regulatory hormones oppose the actions of Insulin; these hormones include: Glucagon, Epinephrine, Glucocorticoids, Growth hormone;

Brief overview of Glucagon

- Glucagon is produced in Alpha cells in Pancreas
- Glucagon causes increase in blood glucose level;
- Glucagon acts on hepatocytes, stimulating breakdown of Glycogen to Glucose, which is then released in blood;
- Glucagon stimulate breakdown of Fat and conversion of fatty acids to glucose (Gluconeogenesis);
- Secretion of Glucagon is stimulated by low glucose level or by increasing amino acid levels (as arise after a protein-rich meal) in blood,
- Increasing blood glucose reduces release of Glucagon;
- Glucagon is one of the Insulin Counter Regulatory Hormones;

What is the Insulin feedback loop?

Insulin feedback loop is:

- Action of Insulin and Insulin Counter Regulatory Hormones in regulating blood glucose level;
- Homeostatic regulation of blood glucose is the balance between actions of Insulin and Insulin Counter-regulatory Hormones: **INSULIN FEEDBACK LOOP ;**
- Failure of the feedback loop affects regulation of blood glucose;
- Failure of part of the loop causes increase in blood glucose level;
  - Glucose cannot get into cells that use or store it;
  - Excess Glucose may be dumped in urine resulting in "Sweet Urine" (**Diabetes Mellitus**)

DIABETES MELLITUS (DM)

- **What is Diabetes Mellitus (DM)?**
- Precise definition of DM is very difficult;
- Diabetes Mellitus:
  - Disease characterized by derangements in Carbohydrate, Fat and Protein metabolism;
- Diabetes Mellitus:
  - Syndrome characterized by Hyperglycemia due to:
  - An absolute or relative lack of Insulin and/or Insulin Resistance

What are the major types of Diabetes Mellitus?

- **Primary DM** is generally sub-classified into:
- Type I DM: Insulin Dependent Diabetes Mellitus (IDDM);
- Type 2 DM: Non-Insulin Dependent Diabetes Mellitus (NIDDM)

- **Secondary DM**: may be due to:
  - Pancreatic disease,
  - Endocrine disease (Cushing's syndrome),
  - Adrenal diabetes,
  - Drug therapy,
  - Insulin receptor abnormalities,
  - Gestational diabetes,

What are some of the causes of Type 1 DM?

- Type 1 DM, (Juvenile-Onset DM),
- Type 1 DM is **not** limited to juvenile patients;
- Causes of Type 1 DM include the inability to produce Insulin, due to either:
  - Defective Beta cells in Pancreatic Islets,
  - Absent of Beta cells in Pancreatic Islets;
  - Autoimmune process causing destruction of Beta cells in Pancreatic Islets,

- Presence of Islet cell antibodies in Serum may predicts future development of Type 1 DM;
- Islet-cell antibodies act against Glutamic Acid Decarboxylase (GAD);
- Environmental precipitating factors of DM:
  - Viral infections,
  - Dietary factors (presence of anti-metabolites in some foodstuffs);

What are some of the characteristics of Type 1 DM?

- Type 1 DM is usually characterized by:
  - Deficiency in Insulin and consequent Hyperglycemia,
  - Hyperglycemia causes blood glucose level to exceed Renal Threshold of 200mg/dl or 11mmol/L, Resulting in Glucosuria,
- Following sequence of events occur:
  - Sugar is excreted in urine (**Glucosuria**),
  - Water follows the sugar due to osmosis (**Osmotic diuresis**),
  - Large volume of urine is passed out (**Polyuria),**

- Patient becomes thirsty, drinks lots of water (**Polydipsia**),
- There is Lack of Insulin:
  - Thus, Muscles, Adipose tissue, Connective tissues and White Blood Cells cannot utilize Glucose present in blood (**Starvation in the midst of plenty**),
- Patient become hungry and eats a lot (**Polyphagia**),
- Due to continuous lack of Insulin, Glucose cannot enter Muscle and other tissues, thus patient may start to loose weight (Wasting),
- Patient may develop Ketoacidosis (**Why?**)

What are the consequences if Type 1 DM is not controlled?

- **Hyperglycemia**:
  - Partly due to inability of Insulin-dependent tissues to use blood glucose (Starvation in the midst of plenty, (**Why?**)
  - Increased Hepatic Gluconeogenesis,
  - Depressed Glycolysis due low glucose levels in cells;
- **Hyper-Lipoproteinemia (Chylomicrons and VLDL)**:
  - Due to low Lipoprotein Lipase activity in Adipose tissue,
  - Insulin is required for biosynthesis of Lipoprotein Lipase ,
- **Ketoacidosis: Increased production of Ketone bodies**:
  - Acetone,
  - Acetoacetic acid,
  - β-Hydroxybutyric acid;

General occurrence of Type 2 DM

- **Type 2 DM:** accounts for 85% cases of DM in PNG
- Formally called:
  - Non-Insulin Dependent Diabetes Mellitus (NIDDM);
  - Maturity-onset diabetes mellitus,
- Common in middle-age obese individuals,
- Can occur in non-obese middle-age individuals,
- Can occur in any age group;

What are some of the possible causes of Type 2 DM?

- May be due to any of the following:
  - Resistance of peripheral tissues to Insulin, despite normal or high Insulin level in blood,
  - Deficiency or defect in Insulin Receptors in target tissues (Relative Insulin deficiency),
  - Obesity, (may have clinical features of Type 2 DM),
  - Defect in Insulin Receptors is related to increased levels of Tumor Necrosis Factor-α (TNF-α) in Adipocytes,
  - Increase adipose tissue mass causes increase TNF-α, which then blocks Insulin Receptors,

- Diet can control Type 2 DM in Obese patient,
- Obese patients that are motivated to lose weight:
  - Insulin receptors will increase in number,
  - Post-receptor abnormalities will improve, resulting in tissue sensitivity to insulin and Glucose tolerance;
- Defects occurring within Insulin-responsive cells at sites beyond Insulin receptors,
- In non-obese individuals:
  - Type 2 DM may be **cause not only by Insulin Resistance, but also by Impaired Pancreatic β-cell function resulting in Relative Insulin Deficiency;**

What are some consequences of uncontrolled Type 2 DM?

- **Uncontrolled Type 2 DM is characterized by**:
  - Hyperglycemia,
  - Hyper-Triglyceridemia,
- Hyperglycemia causes accumulation of glucose in:
  - Eyes (Lens epithelium, Retinal capillaries),
  - Peripheral Nerve cells (Schwann cells),
  - Kidneys (Papillae, Glomerulus),
- Aldose Reductase and Sorbitol Dehydrogenase in these tissues converts:
- Glucose to Fructose, Dulcitol and Sorbitol;

- Sorbitol accumulates and crystallizes causing damage to tissues by causing them to swell;
- Resulting in conditions such as:
  - Cataract formation in eyes (diabetic cataract),
  - Diabetic Neuropathy and loss of sensation,
  - Retinopathy (damage to retina),
  - Damage to blood vessels (Vascular disease),
  - Damage to kidneys causing renal failure,
  - Damage to Cardiac tissue (Ischemic heart disease),

- Type 2 DM does not cause Ketoacidosis (**WHY?)**

GESTATIONAL DIABETES (GDM)

What is gestational diabetes mellitus (GDM)?

- **GDM** is not easily and clearly defined;
- **GDM**: Carbohydrate Intolerance causing Hyperglycemia of variable severity with onset or first recognition during Pregnancy;
- **GDM:** Condition in which blood glucose level is elevated and other diabetic symptoms may appear during pregnancy in a female who has not previously been diagnosed with DM;
- In these women all diabetic symptoms usually disappear after delivery;

IMPORTANT TO NOTE

- Women with DM before pregnancy do NOT have GDM they have “DM and Pregnancy” such women should be treated accordingly before, during, and after the pregnancy;
- In some women, during early part of pregnancy (e.g. First trimester and first half of second trimester) Fasting and Post-Prandial Glucose levels may be lower than in normal, non–pregnant women;

- In some women, High Fasting or Post-prandial Glucose levels during the First trimester and First half of second trimester of pregnancy may reflect presence of DM before pregnancy;

- Normal Glucose Tolerance during the early part of pregnancy does not rule out the possibility that the patient may develop GDM later;

What group of women can be considered at high risk for developing GDM?

- High Risk Groups for GDM include:
  - Women with history of Glucose Intolerance,
  - Women who previously gave birth to larger for gestational age babies,
  - Older women,
  - Women with High Fasting or Random Blood Glucose Levels

DIAGNOSIS OF DIABETES MELLITUS

Is diagnosis of DM the same as monitoring of DM?

- Diagnosis of DM is not the same as monitoring of DM,
- Diagnosis:
  - To clinically establish a condition in a patient,
- Monitor:
  - To follow progress on a condition already diagnosed,
- Specific Biochemical tests and Guidelines are used for diagnosis of DM,
- Specific Biochemical tests and Guideline are used for monitoring DM,

Some Biochemical tests for diagnosis of DM

Glucosuria (Glycosuria):

- Good first-line screening test for DM,
- Glucose appears in urine when plasma glucose level rises above renal threshold (11mmol/L or 200mg/dL);
- Glucosuria may occur in patients with low renal threshold for glucose;
  - Individuals are said to have Glucosuria without DM,
- Renal threshold increases with age, thus some patients may have DM without Glucosuria,
- **Glucosuria indicates Hyperglycemia over the period of formation of the urine, it does not reflect the exact level of blood glucose at the time of testing;**

Fasting Blood Glucose (FBG):

- FBG is measured after overnight fast (8 to 10hrs),
- FBG is better than RBG for diagnostic purposes,
- FBG above **8.0mmol/L** on **two different occasions** may be diagnostic of DM,
- FBG between **6.0 to 8.0mmol/L** is borderline,
- **(Note: to convert mmol/L to mg/dl multiply by 18.0)**

Random Blood Glucose (RBG):

- RBG: one of major tests required in emergency,
- RBG less than **8.0mmol/L** is usually expected in non-diabetics,
- RBG higher than **11.0mmol/L** in **more than one occasion** indicates that the individual be investigated more thoroughly for DM;
- **Measurement of RBG on Whole blood, Plasma or Capillary blood have different cut-off points;**
- **Table 1: WHO guideline for diagnosis**

Table 1: WHO Guideline for diagnosis of DM

RANDOM GLUCOSE SAMPLE (mmol/L)			
	Diabetes likely	Diabetes uncertain	Diabetes unlikely
Venous plasma	≥ 11.1	5.5 - < 11.1	< 5.5
Venous blood	≥ 10.0	4.4 - < 10.0	< 4.4
Capillary plasma	≥ 12.2	5.5 - < 12.2	< 5.5
Capillary blood	≥ 11.1	4.4 - < 11.1	< 4.4

Two Hours Post-Prandial blood glucose:

- Measure blood glucose level 2-hours after consumption of a meal,
- It is a better indicator that FBG and RBG,
- Individuals with blood glucose above 11.0mmol/L should be investigated more thoroughly for DM;

How is Oral Glucose Tolerance Test (OGTT) performed in a patient, when requested?

- **OGTT is recommended only if RBG and FBG tests cannot be interpreted clearly to justify DM;**
- **OGTT must be carried out under proper clinical supervision;**
- Patient should be sitting comfortably throughout test, should not smoke or exercise and should be on normal diet for at least 3 days prior to the test;
- Patient should be properly briefed before starting the procedure;
- Patient should fast overnight (8 to 10 hrs),

PROCEDURE FOR OGTT:

- Measure FBG and Urine Glucose of patient after an overnight fast;
- Record both results;
- Prepare solution containing **75.0g of Glucose in 300ml water**;
- Patient should drink all the solution within 5 min,
- Measure blood glucose level every 30 min for 2 hrs,
- Measure glucose in urine after 2 hrs,
- Record all the results;

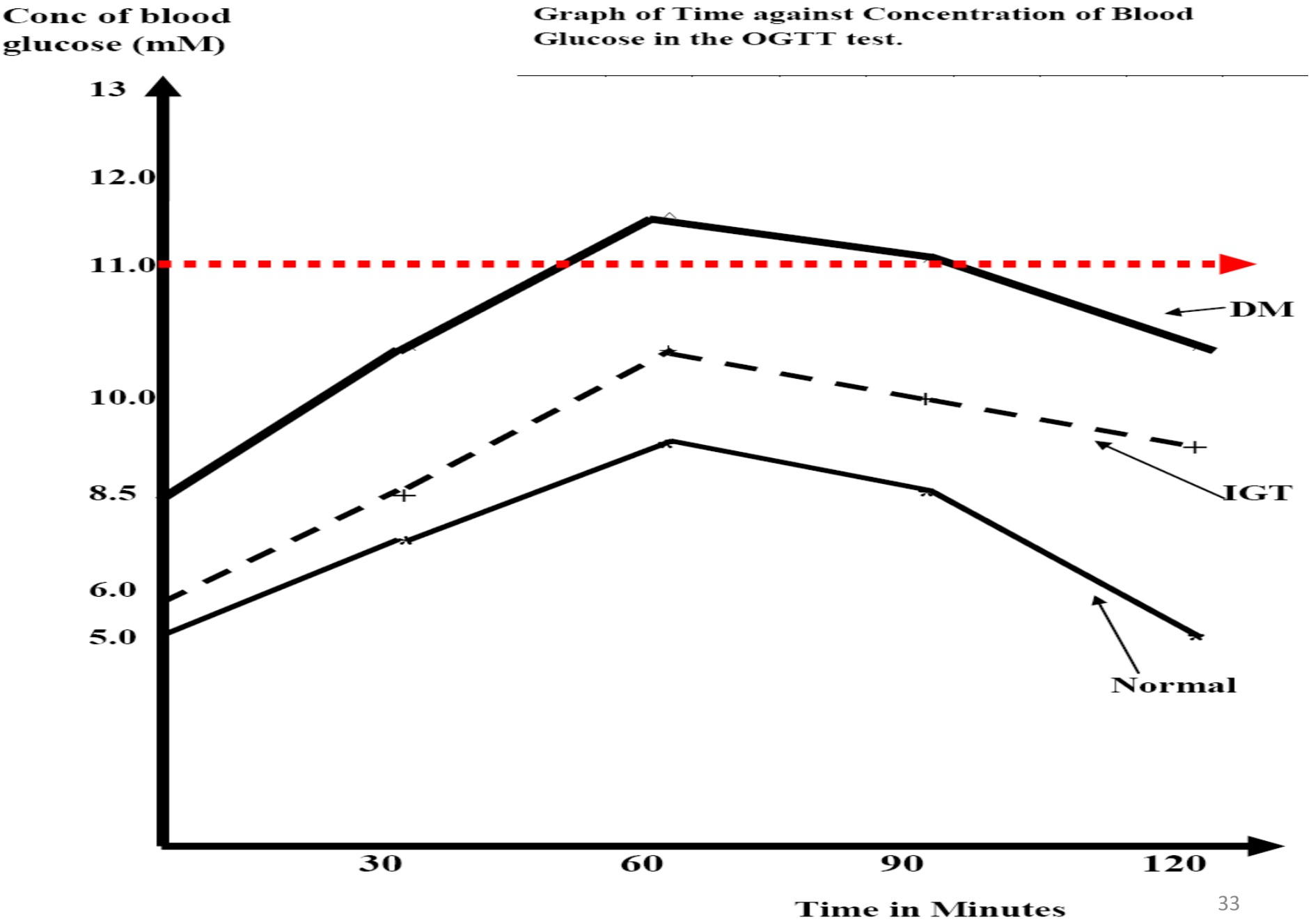
How are OGTT results interpreted?

- WHO Guidelines in **Table 2** may be used, or
- Results used to draw Graph: **Time vs. Blood Glucose**,
- In Asymptomatic patients, OGTT should be interpreted as diagnostic of DM only when:
  - There is an increased 2-hrs Glucose level, and
  - Blood Glucose is equal to or greater than 11.0mmol/L (200.0 mg/dL) at some other point during the test;
- If patient has normal FBG, but the 2hrs value is in the diabetic range, test should be repeated after 6wks;
- Impaired Glucose Tolerance (IGT) is considered abnormal; it is an intermediate stage between normal and DM;
- IGT indicates risk of developing DM;

Table 2: WHO Guidelines for OGTT diagnosis of DM

		DM (mmol/L)	**IGT (mmol/L)**
Venous plasma	Fasting	≥ 7.8	< 7.8
	2hours	≥ 11.1	7.8 - < 11.1
Venous blood	Fasting	≥ 6.7	< 6.7
	2hours	≥ 10.0	6.7 - < 10.0
Capillary plasma	Fasting	≥ 7.8	< 7.8
	2hours	≥ 12.2	8.9 - < 12.2
Capillary blood	Fasting	≥ 6.7	< 6.7
	2hours	≥ 11.1	7.8 - < 11.1

Graph of Time against Concentration of Blood Glucose in the OGTT test.



How can GDM be diagnosed?

- Screening for GDM can be carried out between 24 and 28 weeks of gestation:
- Two or three separate measurements of FBG and RBG should be done on the patient;
- **OGTT is recommended only if RBG and FBG tests cannot be interpreted clearly to justify DM;**
- In such cases to diagnose GDM in the patient the OGTT can be performed under proper clinical supervision;
- ***OGTT should not be carried out in a diabetic patient!!***

- Pregnant women having results that meets the WHO criteria for DM or Impaired Glucose Tolerance (IGT) are classified as having GDM;
- It is recommended that the patient be tested (repeat OGTT) again about six or more weeks after delivery;
- This is to enable reclassification of the patient as having either DM, IGT, or normal glucose tolerance;
- Patient must be put into the high-risk group for DM, regardless of the outcome of the test results;

What are the possible causes of GDM?

- Actual causes of GDM are not fully known, but some Theories have been suggested:
- GDM is related to Insulin Resistance cause by actions of Insulin Counter-Regulatory Hormones produced in the Placenta;
  - Placenta provides Nutrients and other components required for normal fetal growth and development;
- Placenta also releases hormones (**Cortisol, Estrogen, Human Placental Lactogen**) whose metabolic functions are to ensure normal progression of pregnancy;

- High plasma levels of these hormones tend to block the action of Insulin;
- Effects of these hormones are usually more apparent during 20 to 24 weeks of Gestation;
- As pregnancy progresses the placenta produces increase amounts of these hormones, thus increasing their actions against Insulin, which then leads to Insulin resistance;
- Effects of these hormones are more intense from the 20^{th} to 24^{th} week of gestation;

- Normally, pancreas is able to make additional insulin to overcome Insulin Resistance, but when production of Insulin is not enough to overcome the effect of the Placental hormones, Gestational Diabetes results;
- Some women who have GDM may develop Type 2 DM (NIDDM) years later;
- Gestational diabetes and Type 2 DM involve Insulin Resistance
- Lifestyle changes may help prevent DM after Gestational diabetes

What are some of the complications of GDM?

- Imbalance in some biochemical parameters is a common feature of neonates of GDM mothers;
- Examples of such imbalances include:
  - Hypocalcaemia,
  - Low serum Magnesium,
  - Macrosomia (Fat babies),
  - Hypoglycemia;

What is Macrosomia and what causes it?

- **Macrosomia**: baby considerably larger than normal,
- Placenta is major source of nutrients for fetus,
- Maternal Insulin does not cross the placenta, but glucose easily crosses the placenta,
- Hyperglycemia in a mother with GDM will result in Hyperglycemia in Fetus causing the Pancreas in the fetus to produce more insulin in an attempt to clear the extra glucose in circulation,

- Since the fetus is getting more glucose and thus more energy that it needs to grow and develop, the extra glucose will be converted to fat for storage,
- Thus, even when the mother has GDM, the fetus is able to produce all the insulin it needs;
- Combination of high blood glucose levels from the mother and high insulin levels in the fetus results in large deposits of fat in the adipose tissue of fetus;
- This leads to Macrosomia, or excessively “Fat” baby;

Why can Hypoglycemia develop in neonates from GDM mothers?

- Hypoglycemia may occur if the mother's blood glucose level (mother with GDM) have been consistently high, causing the fetus to have a high level of insulin in circulation;
- After delivery, the neonate continues to have high insulin level, but no longer has the high level of glucose from the mother, resulting in the neonate becoming hypoglycemic;

How can a patient with DM be monitored? (Long-term indices of diabetic control)

What is Glycosylated Hemoglobin (HbA_{1c})?

- About 98% of Hb in RBC is HbA_1
- HbA_1 is made up of HbA_{1a}, HbA_{1b}, HbA_{1c}
- HbA_{1c} is highest in amount, and is the component that strongly undergoes Glycosylation with Glucose;
- HbA_1 combines with blood glucose in a non-enzymatic reaction to form Glycosylated Hb (**HbA_{1c}**),
- Amount of HbA_{1c} formed is dependent on amount of Glucose in blood over 120-days life span of RBC;

- HbA_{1c} level reflects the average blood sugar level for the 100- to 120-day period before the test;
- Elevation of HbA_{1c} occurs about 3 weeks after sustained elevation in blood glucose;
- It takes about 4 weeks for HbA_{1c} to decrease after a sustained reduction in blood glucose,
- Measurement of HbA_{1c} is a good Clinical indicator of Glycemic control in a patient on DM medication,
- In healthy person HbA_{1c} is 4% to 6% of total HbA,
- In prolonged Hyperglycemia the level of HbA_{1c} may rise to as much 12% of Total HbA;

What are some of the uses of Test for HbA_{1c}?

- HbA1c is a good index of diabetic control, it is used to complement results from single blood glucose level, or as patient's log of own blood glucose measurements;
- Used to evaluate DM treatment and compliance;
- Use to compare past and new diabetic therapy,
- Used to estimate duration of hyperglycemia in patients with newly diagnosed DM,

What is Microalbuminuria (MAU)?

- **MAU** is increase in urinary albumin that cannot be detected during urinalysis with Albustick, Clinistick, Dipstick or Multistick;
- MAU is urinary albumin level between 25 to 250mg/day,
- MAU is may lead to progressive increase in proteinuria resulting in clinical Albuminuria (Macroalbuminuria) and declining Glomerular Filtration Rate,
- Macroalbuminuria may be associated with renal damage leading to end stage renal failure and increased coronary mortality among diabetic and hypertensive patients;
- For a diabetic patient MAU indicates early (Sub-clinical), reversible renal damage;

What is Hypoglycemia?

- **Hypoglycemia** is a laboratory "diagnosis" that means blood glucose level below 2.2mmol/L (40.0 mg/dl);
- Hypoglycemia may be due to:
  - Endocrine disorders,
  - Liver disease,
  - Inborn errors of metabolism,
  - Gastrointestinal surgery,

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