

# REVIEW OF LITERATURE

## **\*\*CLASSIFICATION DURING PREGNANCY\*\***

Following table gives a classification, recommended by the American college of obstetricians and gynaecologists in 1980. This was replaced in 1994 because according to the American college of obstetricians and gynaecologists “ a single classification based on the presence or absence of maternal metabolic control and the presence or absence of maternal diabetic vasculopathy is more helpful.” In the 1986 classification, women diagnosed to have gestational diabetes are subdivided according to their degree of glycosuria specifically; those with fasting hyperglycemia are placed into class A2. Approximately 15% of women with gestational diabetes will exhibit fasting hyperglycemia women in classes B to H corresponding to the white classification have overt diabetes antedating pregnancy. The white system emphasizes that end organ derangements, especially involving eyes, kidneys and heart have significant effects on pregnancy outcomes.

## CLASSIFICATION OF GDM.

| <i>Class</i> | <i>Onset</i>             | <i>Fasting Plasma Glucose</i> | <i>2-hour postprandial glucose</i> | <i>Therapy</i> |
|--------------|--------------------------|-------------------------------|------------------------------------|----------------|
| A1           | Gestational              | <105 mg/dl                    | <120 mg/dl                         | Diet           |
| A2           | Gestational              | >105 mg/dl                    | >120 mg/dl                         | Insulin        |
| <i>Class</i> | <i>Age of Onset (yr)</i> | <i>Duration (yr)</i>          | <i>Vascular Disease</i>            | <i>Therapy</i> |
| 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        |

## **\*\*DIAGNOSIS OF OVERT DIABETES DURING PREGNANCY\*\***

The woman with high plasma glucose levels, glucosuria, and ketoacidosis presents no problem in diagnosis. Similarly, woman with random plasma glucose level greater than 200 mg/dl plus classical signs and symptoms such polydipsia, polyuria and unexplained weight loss or fasting glucose of 126 mg/dl or higher should be considered to have overt diabetes. The new diagnostic cut off value for overt diabetes of fasting plasma glucose of 126 mg/dl or higher is based on data that indicate the risk of retinopathy rising dramatically at that fasting level.

The likelihood of impaired carbohydrate metabolism is increased in women who have a strong family history of diabetes, have given birth to large infants, demonstrate persistent glucosuria or have unexplained foetal losses.

## **\*\*EFFECTS OF GDM ON FETUS\*\***

Screening for GDM is imperative not only for the short-term improvements in obstetric outcomes but also the more important medium and long-term benefits. Major risk factors for developing GDM include maternal age, family history or diabetes, history of GDM in prior pregnancy and increased progravid BMI. In high-risk populations such as Hispanic American women, about 40% women with GDM develop diabetes within six years, which rises to 70% among those with impaired glucose tolerance after birth.

Detecting GDM identifies women at risk of future non-insulin dependent GDM. The concept that diabetes begets diabetes through an intrauterine effect on foetal pancreas, additional to any genetic effect is strongly supported by animal and human epidemiological studies.

In a high risk, population with a 5% prevalence of GDM, up to half the infants above the 90th birth weight percentiles theoretically could be from a diabetic pregnancy. In such populations, both high and low birth weights are associated with a increased risk of diabetes in later life.

By contrast when the prevalence of GDM is low at most only 5 to 10% of all infants above the 90th percentile could be the result of maternal diabetes. As it is ethically difficult to mount randomised trials with sufficient power to test whether GDM treatment reduces perinatal morbidity, prospective studies in populations have used surrogate markers such as macrosomia, need for caesarean section and foetal hypoglycemia. None of these end points are specific for diabetes and are influenced by the practice of individual obstetrician, maternal age, obesity and parity.

Maternal hyperglycemia is the cause of a diabetic fetopathy syndrome of Pederson. Evidence on ultrasound of increased visual fat and enlargement of the liver, spleen and heart is available as early as 28 weeks of gestation. These accelerated growth patterns can be corrected with diet or insulin.

Schmidt et al (2001) evaluated the American Diabetes Association (ADA) and WHO diagnostic criteria for GDM against pregnancy outcomes on 4,977 women. After adjustment for effects of age, obesity and other risk factors, GDM by ADA criteria predicted an increased risk of macrosomia, preeclampsia and perinatal death. Similarly, GDM by WHO criteria predicted a higher risk of the same outcomes.

Data are rather convincing for an association with hypertensive disorders in pregnancy. Careful monitoring of blood pressure, weight gain and urinary protein excretion is recommended.

The risk of foetal abnormalities appears to be limited to infants whose mothers had fasting BG levels of >120 mg/dl. (American Diabetes Association 1990)

Historically stillbirth was an important complication, as a result maternal antepartum surveillance is strongly recommended in patients with such history.

Macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, and polycythemia have been reported with varying frequency. Macrosomia and its attendant complications of labour and delivery constitute one of the most frequent and serious type of morbidity with approximately 20-30% infants of GDM mothers being affected.

It is estimated that GDM recurs in 30-60% of subsequent pregnancies. Factors predictive of recurrent GDM include obesity, multiparity, early diagnosis of GDM in previous pregnancy, need for

insulin during previous pregnancy, macrosomia, advancing maternal age and increase in prepregnancy weight between initial and subsequent pregnancies.

Adverse maternal effects include an increased frequency of hypertension and need for caesarean delivery.

### **MACROSOMIA:**

The perinatal focal point is avoidance of difficult delivery due to macrosomia, with concomitant birth trauma due to shoulder dystocia except for the brain most foetal organs are affected by macrosomia.

Macrosomia infants of diabetic mothers were anthropometrically different from other large for age infants. Specifically, those whose mothers had diabetes had excessive fat deposition on the shoulders and trunk.

Magee and co-workers (1993) reported that 4% of infants of women with gestational diabetes required intravenous glucose therapy for hypoglycemia.

Insulin and insulin like growth factors I and II have a role in the regulation of foetal growth. Insulin is secreted by foetal pancreatic B cells primarily during the second half, and is believed to stimulate somatic growth and adiposity. These growth factors are produced by all foetal organs and are potent stimulator of cell differentiation and division.

Maternal obesity is an independent and more important risk factor for large infants in women with gestational diabetes than is glucose intolerance. Johnson reported that 8% of 588 women who weighed more than 250 pounds had gestational diabetes compared with <1% of women who weighed <200 pounds. London found that the risk of gestational diabetes was increased with truncal obesity.

### **CONGENITAL MALFORMATIONS:**

There is increased incidence of congenital malformation amongst the offspring of mothers with established diabetes varying from 27% to 11.9%.

The results from the UK survey of diabetic pregnancy reported an incidence of 5.7% amongst 664 mothers with established diabetes.

Specific abnormalities are cardiac and neural tube defects and caudal regression syndrome. (Absence or hypoplasia of caudal structures)

There is an association between malformation rate and poor diabetic control i.e. rate of 7% in 363 class B to F diabetics whose diabetes had been well controlled before pregnancy compared to a rate of 14% in 284 women with diabetes of similar severity who had been poorly controlled. According to Leslie` malformation rate was higher amongst the offspring of mothers with established diabetes who had a higher than normal glycosylated haemoglobin in early pregnancy.

### **SPONTANEOUS MISCARRIAGE:**

Uncontrolled studies had suggested an increased incidence of miscarriage amongst women known to have diabetes before pregnancy, possibly related to poor diabetic control during embryogenesis as determined by glycosylated haemoglobin measurement at 8-9 weeks.

### **PERINATAL MORTALITY IN ESTABLISHED DIABETES:**

PNMR amongst women with established diabetes has always been higher than that for population as whole.

#### **CAUSE OF DEATH**

| <b>Year</b> | <b>No. of Patients</b> | <b>Perinatal deaths/ 1000</b> | <b>Obstetric</b> | <b>Diabetic</b> | <b>Congenital malformations</b> | <b>Respiratory distress</b> | <b>Unknown</b> |
|-------------|------------------------|-------------------------------|------------------|-----------------|---------------------------------|-----------------------------|----------------|
| 1951-60     | 318                    | 72(226)                       | 26               | 5               | 6                               | 17                          | 18             |
| 1961-70     | 389                    | 39(100)                       | 9                | 2               | 5                               | 8                           | 15             |
| 1971-80     | 352                    | 13(37)                        | 3                | 1               | 6                               | 1                           | 2              |
| 1981-90     | 390                    | 7(18)                         | 0                | 0               | 4                               | 0                           | 3              |

### **UNEXPLAINED FETAL DEATH IN UTERO:**

Unexplained foetal deaths in utero still accounted in 51% of the perinatal mortality.

### **ABNORMALITIES OF GROWTH:**

IDDM is associated with an increased incidence of infants who are both large and small for gestational age, both conditions being associated with increased perinatal morbidity.

### **CAESAREAN SECTION**

|            |     | Elective | Intrapartum (%) | <38 weeks (%) | PNM / 1000 |
|------------|-----|----------|-----------------|---------------|------------|
| UK Survey  | 664 | 43       | 15              | 51            | 61         |
| NMH Dublin | 285 | 19       | 7               | 18            | 45         |

### **RESPIRATORY DYSFUNCTION:**

Foetal hyperinsulinism reduces pulmonary phospholipid production, particularly phosphatidyl-glycerol leading to surfactant deficiency.

### **POLYCYTHEMIA AND JAUNDICE:**

### **HYPOCALCEMIA & HYPOMAGNESEMIA:**

### **HYPERTROPIC CARDIOMYOPATHY:**

## **\*\*ETIOLOGY AND PATHOGENESIS\*\***

Progressive insulin resistance that begins near mid-pregnancy and progresses through the 3rd trimester to levels that approximate the insulin resistance seen in individuals with type 2 diabetes mellitus normally attends pregnancy. The insulin resistance appears to result from a combination of increased maternal adiposity and the insulin desensitizing effects of normal products of placenta. The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones.

Pancreatic beta cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy. As a result, changes in the circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity. Robust plasticity of beta cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy.

Studies conducted during late pregnancy, when insulin requirements are high and differ only slightly between normal and gestational diabetic women, consistently reveal reduced insulin responses to nutrients in women with GDM. Studies conducted before or after pregnancy, when women with prior

GDM are usually more insulin resistant than normal women, often reveal insulin responses that are similar in the 2 groups or reduced slightly in women with prior GDM. However, when insulin levels and responses are expressed relative to each individual's degree of insulin resistance, a large defect in pancreatic beta cell function is a consistent finding in women with prior GDM.

#### Potential causes of inadequate beta cell function

- (a) Auto-immune.
- (b) Monogenic.
- (c) Occurring on a background of insulin resistance.

#### **(A) AUTOIMMUNE:**

Autoimmune diabetes and GDM type 1 diabetes results from autoimmune destruction of pancreatic beta cells. It Accounts for approximately 5-10% of diabetes in the general populations.

Type 1 diabetes is characterized by circulating immune markers directed against pancreatic islets (anti-islet cells antibodies) or beta cell antigen (such as glutamic acid decarboxylase- GAD). A small minority (<10%) of women with GDM have the same markers present in their circulation. these women have inadequate insulin secretion resulting from autoimmune damage to and destruction of pancreatic beta cell. Patients with anti-islet cell or antiGAD often, but not invariably, are lean, and they can rapidly develop overt diabetes after pregnancy.

## **(B) MONOGENIC DIABETES AND GDM:**

Monogenic diabetes melitus has been identified outside of pregnancy in 2 general forms.

- (1) Some patients have mutations in autosomes (autosomal dominant inheritance pattern), commonly referred to as maturity onset diabetes of young [MODY], with genetic subtypes denoted as MODY1, MODY2, etc.
- (2) Others have mutations in mitochondrial DNA, often with distinct clinical syndromes such as deafness.

In both instances, onset tends to occur at an early age relative to other forms of nonimmune diabetes (e.g. type 2 diabetes), and patients tend not to be obese or insulin resistant.

Both features point to abnormalities in the regulation of beta cell mass and/or function.

Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes coding for

- (1) Glucokinase (MODY 2)
- (2) Hepatocyte nuclear factor 1a (MODY 3)
- (3) Insulin promoter factor 1 (MODY 4)

Together, these monogenic forms of GDM account for <10% of GDM cases.

## **(C) INSULIN RESISTANCE, BETA CELL DYSFUNCTION AND GESTATIONAL DIABETES:**

The majority of women with GDM appear to have beta cell dysfunction that occurs on a background of chronic insulin resistance. Pregnancy normally includes quite marked insulin resistance. This physiological insulin resistance also occurs on a background of chronic insulin resistance to which the insulin resistance of pregnancy is additive. As a result, pregnant women with GDM tend to have even greater insulin resistance than normal pregnant women.

Differences in whole-body insulin sensitivity tend to be small in third trimester, owing to the marked effects of pregnancy itself on insulin resistance.

Sequential measurements of insulin sensitivity performed in the same women before pregnancy, early in the second trimester and in the third trimester have documented insulin resistance in both lean and obese women who go on to develop GDM.

Women with GDM tend to be obese, so mechanisms promoting obesity and/or linking obesity to insulin resistance are likely to play a role. Small studies have revealed increased circulating levels of **leptin** and inflammatory markers e.g. TNF-alpha, c-reactive protein and decreased levels of adiponectin in women with GDM. Increased content of fat in liver and muscle has also been reported in women with previous GDM.

Defects in the binding of insulin to its receptor in skeletal muscle do not appear to be involved in the exaggerated insulin resistance of GDM. Alterations in insulin signaling pathway, abnormal subcellular localization of GLUT 4 transporters, increased expression of membrane glycoprotein PC-1 and reduced insulin mediated glucose transport have been found in skeletal muscle or fat cells of women with GDM. Whether any of these defects is primary or result of more fundamental defects in insulin action is currently unknown.

It has long been thought that GDM develops in women who cannot increase their insulin secretion when faced with the increased insulin needs imposed by late pregnancy. Longitudinal studies of lean and obese women before pregnancy at the beginning of the second trimester, and in the third trimester also reveal an increase in insulin secretion in association with the acquired insulin resistance of pregnancy. However, the increase is less than that which occurs in normal pregnant women despite somewhat greater insulin in individual with GDM.

Very little is known about the genetics of GDM in women with chronic insulin resistance. The few studies that have been done have compared allele frequencies of candidate genes in women with and without GDM, with no selection for specific phenotypic subtypes of GDM.

Variants that differed in frequency between control and GDM subjects were found in genes coding for

- (1) Islet-specific promoter of glucokinase, known to be important for glucose sensing by beta cells.
- (2) Calpain-10, a gene associated with type 2 diabetes.
- (3) Sulfonylurea receptor 1, which is involved in glucose stimulated insulin secretion.
- (4) The beta 3 adenoreceptor, which may regulate body composition.

**\*\*CARBOHYDRATE & LIPID METABOLISM IN  
NORMAL PREGNANCY & IN GESTATIONAL  
DIABETES MELTUS\*\***

Changes in carbohydrate and lipid metabolism occur during pregnancy to ensure a continuous supply of nutrients to the growing fetus despite intermittent maternal food intake. These metabolic changes are progressive and may be accentuated in women who develop GDM.

**(A) CARBOHYDRATE METABOLISM DURING  
NORMAL PREGNANCY:**

In normal pregnancy, glucose metabolism is characterized by a lower fasting plasma and elevated postprandial values. These changes occur as early as 10 weeks. They continue to decrease and only in third trimester, carbohydrate levels stabilize. In first few weeks of pregnancy, maternal carbohydrate metabolism is affected by a rise in maternal levels of estrogen and progesterone, which stimulate pancreatic beta cells causing hyperplasia of the cells and increase in insulin secretion. At the same time there is an increase in the tissue storage of glycogen, decrease in the production of hepatic glucose, an increase in peripheral utilization of glucose and decrease in maternal fasting levels of plasma glucose.

During the later half of pregnancy carbohydrate metabolism is stressed by the rising levels of human chorionic somatotropin (hCS), prolactin, cortisol, glucagon. These hormones cause decrease glucose tolerance, insulin resistance, decreased stores of hepatic glycogen and

increase in production of hepatic glucose. The physiological effect is to ensue a constant supply of glucose, lipids and amino acids to the fetus.

During early pregnancy, glucose tolerance is normal or slightly improved and peripheral sensitivity to insulin and hepatic basal glucose production is normal.

Insulin responses to oral glucose are also greater in the first part of pregnancy. These observations are consistent with a 120% increase at 12-14 weeks of gestation in the first phase of insulin response; which refers to the change in insulin concentration relative to the elevation in glucose concentration from 0 to 5 min. after intravenous glucose administration.

The second phase of insulin response, which refers to the rate of insulin release relative to the glucose concentration 5 to 60 min. after intravenous glucose administration is not significantly different in early pregnancy from pregravid state.

Insulin action in late normal pregnancy is 50-70% lower than that of normal nonpregnant women.

By the third trimester, basal and 24-hour mean insulin concentrations may double.

The first and second phases of insulin release are 3 to 3.5 fold greater in late pregnancy.

Obese pregnant women also develop peripheral and hepatic insulin resistance during the third trimester.

Insulin resistance serves to shunt ingested nutrients to the fetus after feeding.

## **(B) CARBOHYDRATE METABOLISM IN WOMEN HAVING GESTATIONAL DIABETES:**

Gestational diabetes mellitus is accompanied by alterations in fasting, post prandial, and integrated 24-hour plasma concentrations of amino acids, glucose and lipids.

These changes include a 3-fold increase in plasma triacylglycerol concentrations, during the third trimester of pregnancy, elevation of plasma fatty acids, delayed postprandial clearance of fatty acids, and elevation of the branched chain amino acids.

Only quantitative differences in insulin secretion have been observed between women with GDM and normal pregnant women. Evidence supports the view that GDM is related to a pronounced peripheral resistance to insulin.

Basal endogenous glucose production increases similarly in patients with GDM and in control subjects throughout gestation. An increase in first phase insulin response is observed in control subjects and in patients with GDM with advancing pregnancy; however the increase is greater in control subjects. In late pregnancy, insulin suppression of

hepatic glucose production is less in patients with GDM (80%) than in control subjects (96%).

### **(C) LIPID METABOLISM DURING NORMAL PREGNANCY AND IN GDM:**

After an initial decrease in the first 8 weeks of pregnancy, there is a steady increase in triacylglycerols, fatty acids, cholesterol, lipoproteins and phospholipids. The higher concentrations of estrogen and insulin resistance are thought to be responsible for the hypertriglyceridemia of pregnancy.

Changes in lipid metabolism promote the accumulation of maternal fat stores in early and midpregnancy and enhanced fat mobilization in late pregnancy. In early pregnancy, increased estrogen, progesterone and insulin favour lipid deposition and inhibit lipolysis.

GDM induces a state of dyslipidemia consistent with the insulin resistance. During pregnancy women with GDM do have higher serum triacylglycerol concentrations but lower Ldl-cholesterol concentrations than do normal pregnant women.

## **\*\*DIABETOGENIC HORMONES OF PLACENTA\*\***

The major diabetogenic hormones of the placenta are human placental lactogen (hPL), estrogen and progesterone. Also, serum maternal cortisol levels (both bound and free) are increased. At the elevated levels seen during gestation, prolactin has a diabetogenic effect.

### **(1) HUMAN PLACENTAL LACTOGEN:**

The strongest insulin antagonist of pregnancy is hpl, or human chorionic somatotropin (hcs). This placental hormone appears in increasing concentration beginning at the end of 10th week of gestation. By 20 weeks of gestation, plasma hpl levels are increased 300 fold, and by term, the turnover rate is about 1000 mg/day.

The mechanism of action whereby hpl raises plasma glucose levels is unclear, but probably originates from its growth hormone-like properties.

It promotes free acid production by stimulating lipolysis. Lipolysis and free fatty acids also promote peripheral resistance to insulin.

### **(2) ESTROGEN:**

The primary placental estrogen is estradiol. The estrogen has weak anti-insulin action and thus produces modest insulin resistance. Although

estradiol is elevated to pregnancy levels by the 8th gestational week, the insulin requirement rises by only 15% above nonpregnant ranges, usually because of diminished food intake from first trimester nausea.

### **(3) PROGESTERONE:**

When progesterone is administered to normal non-pregnant fasting women, serum insulin concentration rises and glucose remains unchanged.

### **(4) PROLACTIN:**

Rising estrogen levels trigger the rise in pituitary prolactin early in pregnancy. Prolactin's structure is similar to growth hormone, and at concentration reached by the second trimester (7200 ng/ml). Prolactin can affect glucose metabolism. Although no studies have examined prolactin alone as an insulin antagonist, there is indirect evidence that suppression of prolactin in gestational diabetic women with large doses of pyridoxine improves glucose tolerance.

### **(5) CORTISOL:**

Most of the marked rise of serum cortisol during pregnancy can be attributed to the increase of cortisol-binding globulin induced by estrogen. However, free cortisol levels also are increased. Thus, rising cortisol levels may unmask diabetes in a predisposed individual.

## **\*\*MATERNAL EFFECTS OF GDM\*\***

Diabetes and pregnancy interact significantly such that maternal welfare can be seriously jeopardized, with the positive exception of diabetic retinopathy. However, the long-term course of diabetes is not affected by pregnancy.

Maternal deaths have become rare in women with diabetes, although mortality is increased 10-fold, most often as a result of ketoacidosis, underlying hypertension, pre-eclampsia and pyelonephritis.

### **(1) DIABETIC NEPHROPATHY:**

Diabetic nephropathy is the leading cause of end-stage renal disease in the United States (American Diabetes Association, 1996). The incidence of renal failure is nearly 30% with type 1 diabetes and ranges from 4-20% in those with type 2 diabetes. Subclinical diabetic nephropathy increase abruptly when HbA1 values exceed 10%.

The natural history of clinically detectable nephropathy in type 1 diabetes begins with microalbuminemia- 30 to 300 mg of albumin per 24 hours. This may manifest as early as 5 years after the onset of diabetes. After another 5 to 10 years, overt proteinuria- more than 300 mg of albumin per 24 hours- develops in patients destined to have end-stage renal disease. Hypertension invariably develops during this period and renal failure ensues typically in the next 5 to 10 years.

Chronic hypertension with diabetic nephropathy increased the risk of pre-eclampsia to 60%. Plasma creatinine values of 1.5 mg/dl or greater and protein excretion of 3 gm per 24 hours or greater before 20 weeks of gestation were predictive for pre-eclampsia.

## **(2) DIABETIC RETINOPATHY:**

Retinal vascular disease is a highly specific complication of both type 1 and type 2 diabetes.

The prevalence of retinopathy is related to duration of diabetes. After 20 years of diabetes, nearly all patients with type 1 diabetes have some degree of retinopathy and more than 60% of patients with type 2 diabetes have degree of retinopathy.

The first and most common visible lesions are small microaneurysms followed by blot hemorrhages when erythrocytes escape from the aneurysms. These areas leak serous fluid that forms hard exudates. These features are termed benign or background or nonproliferative retinopathy. With increasingly severe retinopathy, the abnormal vessels of background eye disease become occluded, leading to retinal ischemia with infarctions that appear as cotton wool exudates. These are considered pre-proliferative retinopathy. In response to ischemia, there is neovascularization on the retinal surface and out into the vitreous cavity, and these obscure the vision when there is hemorrhage.

Laser coagulation before these vessels hemorrhages reduces by half the rate of progression of visual loss and blindness and is indicated during pregnancy for affected women.

### **(3) DIABETIC NEUROPATHY:**

Although uncommon, some pregnant women will demonstrate peripheral symmetrical sensorimotor neuropathy due to diabetes.

Another form, diabetic gastropathy, is very troublesome in pregnancy because it causes nausea and vomiting, nutritional problems and difficulty with glucose control.

### **(4) PRE-ECLAMPSIA:**

Hypertension induced or exacerbated by pregnancy is the major complication that most often forces pre-term delivery in diabetic women. The perinatal mortality rate is increased 20-fold for pre-eclamptic diabetic women compared with those who are normotensive. Especial risk factors for the pre-eclampsia include any vascular complications, pre-existing proteinuria and/or chronic hypertension.

### **(5) KETOACIDOSIS:**

Although ketoacidosis affects only about 1% of diabetic pregnancies, it remains one of the most serious complications. Diabetic ketoacidosis may occur as a result of hyperemesis gravidarum, the use of

beta-sympathomimetic agents for tocolysis, and use of corticosteroids to induce fetal lung maturation.

## **(6) INFECTION:**

Approximately 80% of insulin-dependant diabetics develop at least one episode of infection during pregnancy compared with 25% in non-diabetic women.

Common infection includes candida vulvo-vaginitis, urinary tract infections, puerperal pelvic infections and respiratory tract infections.

**\*\*MANAGEMENT OF DIABETIC WOMEN**  
**DURING PREGNANCY\*\***

**(A) PRECOCEPTIONAL MANAGEMENT:**

Diabetic women planning to get pregnant should be advised strongly to control their blood sugar level and to present early for ANC booking. Tight control will reduce the incidence of congenital abnormalities due to uncontrolled diabetes melitus in the first trimester of pregnancy.

Non-insulin dependant DM should be change from oral hypoglycemic agents to insulin.

Folic acid supplementation 0.4 mg daily.

Assess complications that may be associated with DM (nephropathy and retinopathy).

In addition, to improving diabetic control, the opportunity may be taken to give general advise regarding the importance of being as healthy as possible at the start of pregnancy- stopping smoking, reducing alcohol intake, and achieving an ideal body weight.

Furthermore, contraceptive or fertility advice may be required and rubella immunity status can be checked.

The American Diabetic Association has defined optimal preconceptional glucose levels of 70 to 100 mg/dl and postprandial values of less than 140 mg/dl and less than 120 mg/dl at 1 and 2 hours, respectively.

Hemoglobin A1 or A1c measurement, which expresses an average of circulating glucose for the past 4 to 8 weeks, is useful to assess early metabolic control. Optimal preconceptional glycosylated hemoglobin values have been defined as those within or near the upper limit of normal for a specific laboratory or within three standard deviation of normal mean. The most significant risk for malformations is with levels exceeding 10%.

## **INSULIN REQUIREMENTS IN PREGESTATIONAL DIABETES:**

If appropriate prepregnancy counselling has been given and near euglycemia has been achieved before conception and if the prepregnancy insulin regimen incorporates two or more insulin injection a day, it may be suitable to achieve the near euglycemia necessary for a pregnancy.

A split/mixed regimen (NPH and regular or lispro insulin) given in the morning and evening is ideal. Using 3 injection of regular or lispro insulin before each meal gives a patient more flexibility in regard to eating and exercise. Pre-prandial regular or lispro insulin can be particularly helpful during the first trimester, when nausea and anorexia (morning sickness) are common. Controlling the fasting blood glucose concentration requires evening NPH insulin.

Adjusting insulin doses is simpler with self-monitoring of blood glucose (SMBG) four times a day because each component of the insulin regimen affects only one SMBG value. Monitoring before breakfast and 1 to 2 hours postprandial is recommended.

Insulin requirement increase during pregnancy because of the increased concentration of circulating anti-insulin hormones. Constant insulin adjustment is necessary to keep up with the increasing insulin requirement of pregnancy. The insulin dose is increased from 0.7 U/kg/day in the first trimester to 0.8 U/kg/day at the week 18, 0.9 U/kg/day at week 26 and 1.0 U/kg/day at week 36 in women who maintained within 15% of ideal body weight.

Rarely a pregestational type 2 diabetic women may require a very high dose of insulin even up to 200 U/day in divided doses.

## **(B) ANTENATAL MANAGEMENT:**

- \* Screening for DM during pregnancy.
- \* Urine test for glucose at each antenatal visit.
- \* Random blood sugar.

All pregnant women should be offered a timed random blood sugar.

The test is done at the initial antenatal visit and if normal repeat at 28 weeks.

The test is done when glycosuria 1+ or more during antenatal visits.

The screening test is done at any time irrespective of fasting or food intake.

\*2-hour glucose tolerance test (OGTT) should be performed if

- => Random blood sugar is more than 105 mg/dl (>6 mmol/L) in the fasting state or 2 hour after food intake.
- => More than 126 mg/dl (>7 mmol/L) within 2 hours of food intake.
- => The patient is at high risk of developing IGT or DM during pregnancy.

- (1) Strong family history of DM.
- (2) Overweight >120% of ideal body weight.
- (3) Previous large baby >4 kg.
- (4) Previous history of abnormal glucose tolerance
- (5) Congenital anomalies
- (6) Factors developing during pregnancy such as polyhydramnios, large fetus for gestational age
- (7) Classical symptoms of diabetes as polydipsia and polyuria.

#### **TREATMENT BY DIET ALONE:**

Dieting has not only decreased postprandial hyperglycemia, but also fasting concentrations. The effect of diet is to make insulin more efficient.

If the women's fasting plasma glucose is <105 mg/dl, then a trial of dietary therapy is possible. The general recommendations of British Diabetic Association are that 50% of energy should be obtained from carbohydrate and this should also apply to pregnancy.

The total calories in the diet should be between 1800 and 2000 daily. In the obese this should be restricted further so that these women put on little or no weight.

The breakfast meal must be small and the carbohydrate portion of the meal is designed to avoid postprandial hyperglycemia and preprandial starvation ketosis.

### **Diet calculation for women 80% to 120% of ideal body weight**

| <b>Time</b> | <b>Meal</b> | <b>Fraction (kcal/kg)</b> | <b>% of daily carbohydrates</b> |
|-------------|-------------|---------------------------|---------------------------------|
| 8:00 AM     | Breakfast   | 2\18                      | 10                              |
| 10:30 AM    | Snack       | 1\18                      | 5                               |
| 12:00 PM    | Lunch       | 5\18                      | 30                              |
| 3:00 PM     | Snack       | 2\18                      | 10                              |
| 5:00 PM     | Dinner      | 5\18                      | 30                              |
| 8:00 PM     | Snack       | 2\18                      | 10                              |
| 11:00 PM    | Snack       | 1\18                      | 5                               |

Kilocalories x weight in kgs

<80% ideal body weight: 40 kcal/kg/day

80-120% ideal body weight: 30 kcal/kg/day

120-150% ideal body weight: 24 kcal/kg/day

>150% ideal body weight: 12-20 kcal/kg/day

The British Diabetic Association also advised that maximal fiber intake is beneficial in pregnancy in order to reduce the degree of postprandial hyperglycemia.

Restrictive dietary advice leads to an increase in ketonaemia. Although there is wide individual variation, it is generally accepted that ketonaemia in pregnancy tends to increase with gestation.

### **FIRST TRIMESTER:**

Careful monitoring of glucose control is essential to management. For this reason, many clinicians hospitalize these patients during early pregnancy to institute individualized glucose control programme and to provide education concerning the ensuing months of pregnancy. It also provides an opportunity to assess the extent of vascular complications of diabetes and to precisely establish gestational age.

The goals of self-monitored capillary blood glucose control recommended during pregnancy are shown in below table.

| <b>Specimen</b>     | <b>Blood Glucose (mg/dl)</b> |
|---------------------|------------------------------|
| Fasting             | 60-90 (3.3-5.0 mmol )        |
| Premeal             | 60-105 (3.3-5.8 mmol )       |
| Postprandial 1 hour | 100-120 (5.5-6.7 mmol )      |
| 0200-0600           | 60-120 (3.3-6.7 mmol )       |

Self-monitoring of capillary glucose levels using the glucometers is strongly recommended as this involves the woman in her own care.

New technology is under development that offers the future possibility of noninvasive glucose monitoring such as automatic and painless means to obtain blood glucose information would greatly facilitate patient compliance with glucose control during pregnancy. The device extracts glucose through the skin using electrical potentials- a process known as iontophoresis.

### **INSULIN TREATMENT:**

Maternal glycemic control can usually be achieved with **multiple daily insulin injections** and adjustment of dietary intake. Oral hypoglycemic agents are not used because they may cause fetal hyperinsulinemia. Also increased rates of congenital malformations in infants of women treated during early pregnancy with oral hypoglycemic drugs.

Subcutaneous insulin infusion by a calibrated pump may be used during pregnancy. The pump has both advantages and disadvantages. The risk of neonatal hypoglycemia is increased during pregnancy and, therefore, great care should be taken in selecting patients for this therapy.

The committee on maternal nutrition of the National Research Council has recommended a total caloric intake of 30 to 35 kcal/kg of ideal body weight, given as three meals and three snacks daily.

Criteria recommended for the initiation of insulin therapy in women with gestational diabetes.

| <b>Fasting Glucose concentration (mg/dl)</b> | <b>Postprandial Glucose concentration (mg/dl)</b> |
|--|---|
| >80  | 1 hour >140                                       |
| 105  | none  |
| >95  | 2 hour >120                                       |
| >100   | 1 hour >130                                       |
| >90  | 1 hour > 120                                      |

In a normal (non-diabetic) pregnancy, the fasting plasma glucose concentration ranges between 55 and 70 mg/dl, the 1 hour postprandial glucose level is <120 mg/dl.

If the fasting plasma glucose concentration on the OGTT is  $\geq 120$  mg/dl, the patient is started on insulin immediately. Others are seen within 3 days and are also taught SMBG to be performed before breakfast and 2 hours after each meal.

Insulin is started within 1 to 2 weeks if majority (ie., at least 4 of 7 per week) of fasting blood glucose values exceed 95 mg/dl.

Similarly, if the majority of postprandial values after a particular meal exceed 120 mg/dl, insulin could be low as 4 units and adjusting the dose of insulin on follow-up.

A few GDM patients may require combination of short acting insulin and intermediate acting insulin in the morning and evening. If a

patient has elevated pre-lunch blood glucose, regular insulin is usually necessary in the morning to handle the post-breakfast hyperglycemia because of the lag period before the intermediate-acting insulin begins to work.



If the post-dinner blood sugar is high, a small dose of regular insulin is necessary before dinner in addition to the regular and intermediate acting insulin given in the morning. Combination of regular and intermediate acting insulin before dinner may be necessary if fasting blood sugar is high.

This combination of short and intermediate acting insulin in the morning as well as in the evening is known as mixed and split dose of insulin regimen. In this regimen two-third of total daily dose of insulin is given in the morning and one-third in the evening. For each combination one-third dose should be regular insulin and two-third intermediate acting insulin.

With this regimen if the patient continues to have fasting hyperglycemia, the intermediate acting has to be given at bedtime instead of before dinner.

It is ideal to use highly purified porcine or human insulin, which are least immunogenic. Though insulin does not cross the placenta, the anti-insulin antibodies due to bovine insulin can cross the placenta, and the stress the fetal beta cells, increase insulin production and induce macrosomia.

The goals of therapy are to keep the glucose concentration below the levels used to initiate therapy. (Fasting plasma glucose <95 mg/dl and 2 hours postprandial blood glucose <120 mg/dl)

### **SECOND TRIMESTER:**

Placental serum alpha-fetoprotein concentration at 16 to 20 weeks is used in association with targeted ultrasound at 18 to 20 weeks in an attempt to detect neural tube defects and other anomalies.

Maternal serum alpha-fetoprotein values may be lower in diabetic pregnancies.

### **THIRD TRIMESTER:**

Weekly visits to monitor glucose control and to evaluate for pre-eclampsia are a typical recommendation.

Serial ultrasonography at 3 to 4 week intervals is performed to evaluate both excessive and insufficient fetal growth as well as amniotic fluid volume.

Hospitalization is recommended for women whose diabetes is poorly controlled and for those with hypertension.

## **DELIVERY:**

### (1) TIME OF DELIVERY:

- Controlled DM between 38-40 weeks
- Uncontrolled DM 37-38 weeks
- Poorly controlled DM, severe pre-eclampsia 36 weeks
- Earlier if fetal distress

### (2) MODE OF DELIVERY:

#### (a) Vaginal delivery is expected in the following:

- Average estimated weight of fetus <4000 gm
- Satisfactory fetal well-being
- Cephalic presentation
- Satisfactory progress and descend during the first and second stage
- Absence of obstetric complication

#### (b) Caesarean section is given in the following:

- Macrosomic fetus (risk of shoulder dystocia) >4000 gm
- Certain cases of IUGR or fetal distress
- Malpresentations
- Slow progress and descent during labour
- Complication such as hypertension, polyhydroamnios
- Placenta praevia
- Severe vaginal infections especially with primigravida

It is important to considerably reduce or delete the dose of long acting insulin given on the day of delivery.

Regular insulin should be used to meet most or all of the insulin needs of the mother at this time, because insulin requirements typically drop markedly after delivery. Low-dose insulin infusion for the diabetic woman during the intrapartum period.

| <b>Blood Glucose (mg/dl)</b> | <b>Insulin Dosage U/hr</b> | <b>Fluids (125ml/hr)</b> |
|------------------------------|----------------------------|--------------------------|
| <100                         | 0                          | D5 Lactated Ringer       |
| 100-140                      | 1                          | D5 Lactated Ringer       |
| 141-180                      | 1.5                        | Normal Saline            |
| 181-220                      | 2                          | Normal Saline            |
| >220                         | 2.5                        | Normal Saline            |

### **(C) POSTNATAL MANAGEMENT:**

Immediately after delivery, insulin and glucose infusions should be discontinued. If this is not done hypoglycemia is likely to occur as a consequence of the increase in insulin sensitivity following the delivery of the placenta.

For the insulin dependant woman, it is simplest to revert to the insulin regimen she was taking before pregnancy and to wait until breast-feeding is established before attempting more precise diabetic control.

Women with GDM or IGT who have been treated with insulin during pregnancy usually do not require any form of treatment, but should

have blood glucose measurements made before leaving hospital to check that hyperglycemia has not persisted.

Breast-feeding should be encouraged, but because of increased nutritional demands, an extra 50 gm carbohydrate a day in the dietary intake is recommended.

Women who have had GDM or IGT should have a 50 gm glucose tolerance test done about 6-12 weeks after delivery. If it is normal they should be warned that the condition is likely to recur in a subsequent pregnancy.

All women who have had IGT or GDM particularly those who are overweight (>120% of ideal body weight) should be encouraged to either reduce their weight or maintain it if they are within the range of their ideal body weight.

The largest follow-up was by O'sullivan who has shown that in women whose glucose tolerance reverts to normal after pregnancy there was 50% risk of developing diabetes at 22-28 years of follow-up.