

## Diabetes Mellitus in Pregnancy.

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**Abstract: Introduction:** Diabetes Mellitus is a common medical complication during pregnancy with maternal and fetal complications including complications specific to pregestational diabetes like nephropathy and ketoacidosis. Gestational diabetes is defined as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. Strategies of screening are controversial. A single glucose challenge test with 75 g of oral glucose load and diagnosing GDM if 2 hour PPG is > 140 mg/dL is recommended by WHO. The tenets of management are: diet; exercise; insulin therapy; ? Oral hypoglycemic. While there is no controversy about the need for strict fetal surveillance in diabetes, the most appropriate modality remains controversial with a combination approach being advocated by most experts. Induction is planned around 38 weeks. If EFW > 4.5kg-elective LSCS. If the EFW is 4-4.5kg, additional risk factors for shoulder dystocia should be considered. **Current status of ohas:** Use in pregnancy after first trimester is safe. In first trimester, main problem is degree of hyperglycemia not the drug. Glyburide is the only drug which does not cross placenta (RCT studied)

### INTRODUCTION

To say that Diabetes Mellitus is a common medical complication during pregnancy would be an understatement ;it is a major medical problem for both over and under – fed pregnant populations.It is a major cause of perinatal morbidity & mortality and a significant contributor to bad obstetric history ( BOH ).50% of GDM patients-develop type 2 Diabetes in next 20 years , so the long term complications too cannot be ignored<sup>1</sup>

**Incidence** is 1% - 14%<sup>2</sup> and varies according to ethnicity, selection criteria and diagnostic test Asians data suggests a local incidence of 5-8%<sup>3</sup> . 90% of them are of Gestational onset and Type 1 diabetes occurs in 7.5%<sup>3,4</sup>

### ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS <sup>5</sup>

**Type 1 diabetes( insulin dependent DM)** (a.) Immune mediated; (b.) Idiopathic

**Type 2 diabetes ( Non insulin dependent DM)**

**Other specific types**

- i. Genetic defects of  $\beta$ -cell function
- ii. Genetic defects in insulin action
- iii. Diseases of the exocrine pancreas
- iv. Endocrinopathies
- v. Drug- or chemical-induced
- vi. Infections
- vii. Uncommon forms of immune-mediated diabetes
- viii. Other genetic syndromes sometimes associated with diabetes

#### IV. Gestational diabetes mellitus (GDM)

##### **Gestational diabetes mellitus (GDM)**

GDM is the nightmare of epidemiologists. There is controversy about its definition, the best diagnostic criteria, and the population to be screened. The condition is define as carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy.<sup>6</sup> This is regardless of whether insulin is used for treatment or the condition persists after pregnancy; its prevalence in India is 16.55%.

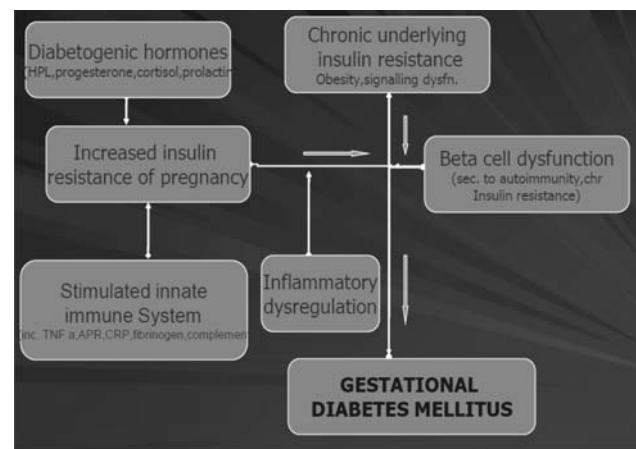


Fig 1: Etiopathogenesis of diabetes in pregnancy

### ETIOPATHOLOGY

The physiological details are beyond the scope of this review; Fig 1 attempts to summarise the same

### SCREENING

Ø **Whom to screen: according to ACOG and WHO; the individuals to be screened include:**

- (1.) Universal screening at 24-28 weeks. (2.) High risk women-screening at fist antenatal visit; where as according to ADA and the Society for Maternal Fetal Medicine as Risk factor analysis at the first prenatal visit and later at 24 to 28 weeks if indicated by use of an oral glucose tolerance test (OGTT). (Table 1)
- Indian women have an eleven fold increased risk of developing glucose intolerance during pregnancy compared to Caucasian women .Diagnosis is overlooked in about 1/3rd of the women where selective rather than universal screening is performed <sup>8</sup> . Hence in the Indian context, screening is essential in all pregnant women.

**Table 1: screening for and diagnosis of GDM (ADA 2008)**

Risk Determination	Risk Factors
<b>Very High Risk for GDM</b> <b>Screening:</b> Screening should be conducted using standard diagnostic testing (fasting plasma glucose, symptoms of hyperglycemia, a casual plasma glucose $\geq 200$ mg/dl, or a 2-hour plasma glucose $\geq 200$ mg/dl during an OGTT) as soon as possible after confirmation of pregnancy at first prenatal visit	<ul style="list-style-type: none"> <li>❖ Severe obesity</li> <li>❖ Prior history of GDM or delivery of large-for-gestational age infant</li> <li>❖ Presence of glycosuria</li> <li>❖ Diagnosis of PCOS</li> <li>❖ Strong family history of type 2 diabetes</li> </ul>
<b>Higher Than Low Risk:</b> Includes all women of higher than low risk of GDM, including those above not found to have diabetes early in pregnancy  <b>Screening:</b> Should undergo GDM testing at 24 to 28 weeks of gestation	<ul style="list-style-type: none"> <li>❖ &gt; 25 years old</li> <li>❖ Abnormal weight before pregnancy</li> <li>❖ High risk ethnic/racial heritage (Hispanic American, Native American, Asian American, African American, or Pacific Islander)</li> <li>❖ Family history of either type 1 or type 2 diabetes in first-degree relatives</li> <li>❖ History of abnormal glucose tolerance</li> <li>❖ History of poor obstetric outcome</li> <li>❖ History of fetal macrosomia (infant weight &gt; 4000 grams)</li> </ul>
<b>Low Risk Status:</b> Is limited to any woman who meets all of the following criteria listed  <b>Screening:</b> Does not require GDM screening	<ul style="list-style-type: none"> <li>❖ Age &lt; 25 years old</li> <li>❖ Weight normal before pregnancy (body mass index of 25 or less)</li> <li>❖ Member of an ethnic group with a low prevalence of GDM</li> <li>❖ No known diabetes in first-degree relatives</li> <li>❖ No history of abnormal glucose tolerance</li> <li>❖ No history of poor obstetric outcome</li> </ul>

## Ø SCREENING METHODS

**Blood tests:** (a) Random blood glucose (RBG); (b) Fasting blood glucose (FBG) <sup>9</sup>: Fasting glucose is not favored by the WHO for diagnosing GDM.<sup>10</sup>; (c) 1-hr 50 gm glucose challenge test (GCT); (d) 75 gm glucose tolerance test; (e) Fructosamine; (f) Glycated hemoglobin; (g) Glycated albumin

**Urinary tests:** Glycosuria

### GLUCOSE CHALLENGE TEST (GCT)

**This uses a 50g glucose load regardless of meals**

Diagnosis of GDM by oral GTT based on initial GCT screening leaves 21.5% undiagnosed. (Table 2&3)

**Table 2: Sensitivity and specificity of GCT**

	140mg/dl	130mg/dl
<b>Sensitivity</b>	79%	90%
<b>specificity</b>	87%	
<b>Need for GTT</b>	14-18%	20-25%

**With 140mg/dl as cut-off - good reproducibility**

If 1hr -140mg/dl: OGTT is warranted

If 200mg/dl - GDM :no further testing

**Table 3 : Cutoffs for 100g OGTT**

	O SULLIVAN & MAHAN	NDDG (1979)	CARPENTER & COUSTEN, 1982
<b>Medium</b>	Whole blood	Venus plasma	Venus plasma
<b>Method</b>	Somogy-Nelson	Enzymatic (Glucose oxidase)	Enzymatic (glucose oxidase)
<b>Fasting</b>	90mg/dl (5.0mmol/L)	105 mg/dl (5.8 mmol/L)	95 mg/ dL (5.3 mmo L)
<b>1 hr</b>	165mg/dl (9.17mmol/L)	190 mg/ dL (10.5 mmol/ L)	180 mg/dL (10.0 mmol/ L)
<b>2 hr</b>	145mg/dl (8.06mmol/L)	165 mg/ dL (9.2 mmol/ L)	155 mg per dL (8.6 mmol / L)
<b>3hr</b>	125mg/dl (6.94mmol/L)	145 mg per dL (8.0 mmol per L)	140 mg/ dL (7.8 mmol per L)
≥2 values elevated- GDM , 1 abnormal value- Impaired GTT			

## ONE STEP PROCEDURE FOR SCREENING

A single glucose challenge test with 75 g of oral glucose load and diagnosing GDM if 2 hour PPG is > 140 mg/dL is recommended by WHO. This method serves both as a one step screening and a

diagnostic procedure, and is easy to perform besides being economical. ADA criteria originally validated against the future risk of maternal diabetes and it is NOT based on the likelihood of adverse perinatal outcome. The pick up rate was four times more with WHO criteria. WHO test for glucose tolerance during pregnancy was abnormal in the greater percentage of women with adverse outcome than the more cumbersome two step NDDG (ADA) test.

## COMPLICATIONS OF GDM

**A. Obstetric:** Pre-eclampsia & non proteinuric HTN-10-20% <sup>11</sup>; Premature labour; Polyhydroamnios Still birth; Caesarean section & operative delivery; UTI & moniliasis; Recurrence (next pregnancy)- 33-50%

### Fetal effects

Macrosomia(20-30%) <sup>12</sup>; Shoulder dystocia(0.2-3%); Birth trauma

### Neonatal complications

Hypoglycemia (9%); Polycythemia (1%); Hypocalcemia (10-20%); Hyperbilirubinemia (29%); Respiratory distress syndrome (<3%); Renal vein thrombosis; Ventricular hypertrophy (upto 30%); Cardiac failure; Necrotising enterocolitis; Cerebral edema ; Small left colon syndrome; Electrolyte disturbances;

## PREGESTATIONAL DIABETES

### Disease Burden :

Pre existing diabetes mellitus now affects 1% of pregnancies. Successful outcome has somewhat related to the degree of glycemic control; but more to underlying cardiovascular/renal disease

### Complications

#### Obstetric

Congenital anomalies (6-10%); Spontaneous abortion; Polyhydroamnios; Preterm delivery(25%); Macrosomia; Unexplained fetal death (2/0.4%); Pre-eclampsia(21/5%); IUGR(1/3%); Traumatic delivery; Perinatal mortality : 20 -50%;

### Malformations<sup>13</sup>:

#### Cardiovascular

· TGA, VSD, ASD, Coarctation of aorta, situs inversus

#### CNS

· Acrania, anencephaly, NTDs, microcephaly

#### Skeletal system

· Hemivertebra, CAUDAL REGRESSION SYNDROME (252 times more common), femoral hypoplasia-unusual facies

#### Renal

· Renal agenesis, ureter duplication, hydronephrosis

#### Gastrointestinal

· Duodenal atresia, imperforate anus, small left colon

#### Single Umbilical Artery

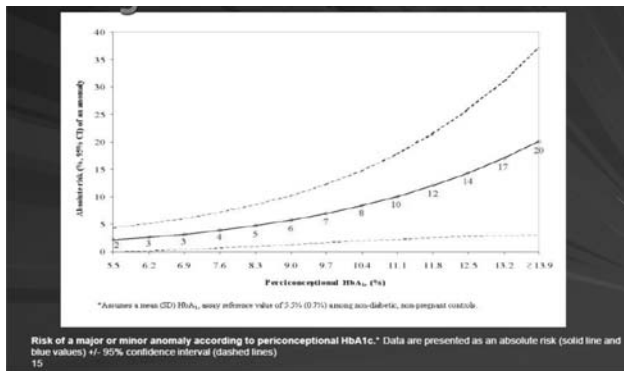
### Medical

Retinopathy; Nephropathy; Diabetic keto-acidosis; Hypertension(40%); Hypoglycemia(25%); Neuropathy; Infections  
 Most important risk factor for congenital anomalies is poor glycemic control preconceptionally. Hence preconceptional counseling and care is the most important intervention towards prevention  
**Spontaneous abortion rate** is related to degree of glycemic control with increased risk in type 1 DM and in patients with HbA1c >12% or persistent pre-prandial glucose >120mg/dl

## MACROSOMIA

**Macrosomia** is defined as birth wt more than **4.0 kg in diabetics**

fig 2: risk of congenital malformations against HbA1C levels



and more than 4.5 kg in non-diabetic<sup>14</sup>. LGA (Large for gestational age) is birth wt >90th percentile for gestational age and/or > 2 SD of normal population. Incidence is 1-10% of all deliveries<sup>15</sup>. Type 1 DM has incidence 40%<sup>16</sup>

**Complications of macrosomia**

**Maternal** : Injuries to the birth canal; Increased risk of LSCS - 30%<sup>17</sup> ; Complications of surgery & anesthesia

**Fetal** : Intrapartum asphyxia; Birth trauma (e.g. Clavicular fractures); Shoulder dystocia; Brachial plexus injury; Fetal death (0.4%) and perinatal mortality (5%).

**Shoulder Dystocia**: Incidence is 0.2-3.0%<sup>18</sup>. In infants with birth weight >4.0kg it is 5-7% . Brachial plexus injury occurs in 21% of all shoulder dystocia situations.there may be other injuries including fractures and severe birth asphyxia even stillbirth.

**Perinatal death/stillbirth in diabetes:**

Poor glycemic control leads to decreased uteroplacental blood flow (placental dysfunction) leading to fetal hypoxia & acidosis.apparently hypercarbia is the terminal trigger.Fetal hyperinsulinemia leads to increased oxygen requirement in fetus.Placental vasculopathy and villous edema leads to fetal hypoperfusion. Maternal ketacidosis has a perinatal mortality of 20-50%<sup>19</sup>.Electrolyte disturbances and fetal hypertrophic cardiomyopathy also contribute to stillbirth. Still births within 72 hrs of seemingly normal FHR have been reported,which raises the question of suitable tests for fetal monitoring in these patients.<sup>20</sup>

**Diabetic Retinopathy:**

It occurs in the following forms.

- 1) Background Retinopathy (NPDR):** Capillary closure & dilation; Micro-aneurysms; A-V shunts; Dilated veins; Hemorrhages (dots & blots)
- 2) Proliferate retinopathy (PDR):** New vessels; Vitreous hemorrhage; Retinal detachment; Diabetic retinopathy;

**Effect of pregnancy on retinopathy**

There is a 10.3% risk of developing NPDR.In 21.1%, there is some progression of disease. 54.8% demonstrated progression of their disease.

**DIABETIC NEPHROPATHY**

It is the leading cause of end-stage renal disease in affluent societies. Pregnancy does not worsen this condition. About 6% of pregnant type I diabetics present with clinically significant renal impairment<sup>21</sup>.

**Definition**

An albumin excretion rate >300mg/day or total protein excretion rate >500mg/day in the absence of bacteriuria in first 20 wks POG.

Best predictors of perinatal outcome are persistant proteinuria and decreased creatinine clearance

**Consequences of overt diabetic nephropathy include** Nephrotic syndrome; Hypertension (12-40%) mostly chronic hypertension ;may occurs due to superimposed preclampsia

**DIABETIC KETOACIDOSIS**

Most common in **type 1 DM and seen in around 5 to 10 % cases.** Infection , missed insulin treatment , hyperemesis gravidarum, beta-sympathomimetic tocolytics,

corticosteroids for fetal lung maturation and insulin pump failure are some common contributors to this grave condition. Perinatal mortality has dropped from 35 to 10% over the last three decades as a result of better understanding of the pathophysiology leading to more aggressive and suitable management<sup>22</sup>

Hypoglycemia mostly occur in first 20 weeks due to missing a meal, insulin overdose or vigorous exercise. Although teratogenicity not documented in human embryos,still patient and family education is necessary.

**Management: of Gestatimal Diabetes**

The tenets of management are:

- Ø Diet
- Ø Exercise
- Ø Insulin therapy
- Ø ? Oral hypoglycemics

Treatment of GDM using the WHO criteria could significantly improve the perinatal morbidity

**Dietary management:** Treatment is generally started with diet and blood sugar monitoring 1-2 weekly till 36 weeks and weekly after 36 weeks. Resistance exercises are encouraged and five-point blood sugar profile ( FBS,post meal) done. **Postprandial** monitoring and control blood sugar results in more improved glycemic control in GDM

**Composition Of Diabetic Diet**

Euglycemic Diet Or Hypoglycemic Diet is essential to avoid postprandial hyperglycemia; calculation is shown in table 4

Table 4: Calculation of diabetic diet

BMI (based on wt before pregnancy)	Calorie intake kcal/kg (ideal body weight)
<19 kg/m <sup>2</sup>	35
19-27 kg/m <sup>2</sup>	30
>27 kg/m <sup>2</sup>	25

**Glycemic goals: The target planned glucose levels to be achieved include:**

Fasting=< 95mg/dl; 1<sup>st</sup> hour postprandial=< 140mg/dl; 2<sup>nd</sup> hour postprandial =<120mg/dl

Glycemic goals for management of diabetes in pregnancy<sup>23</sup>

**Indicators for starting insulin**

Maternal: If MNT fails to achieve glycemic goals within 2 weeks

Fetal : Fetal abdominal circumference at 29-33 wks >75 percentile

**Table 5:** Target glucose levels during pregnancy

Time	Venous plasma glucose levels (mg/dl)
Fasting (BBF)	60-90
Before lunch, dinner , bedtime snack	60-105
After meals(2h)	<120
2:00 to 6:00am	>60

**Table 6:** the various commercial insulin preparations:

TYPE	ONSET	PEAK	DURATION
ULTRA-SHORT ACTING Lispro, Aspart, Glulisine	0-15min	30-90min	4-5hrs
SHORT-ACTING REGULAR	30-45min	2-4hrs	6-8hrs
INTERMEDIATE ACTING NPH Lente (semilente+ultralente)	1-2hrs 1-2.5hrs	4-10hrs 6-12hrs	18-24hr 20-24hr
LONG-ACTING Ultra-lente Glargine	4- 8hrs 1hr	8-12hrs <u>none</u>	36hrs 24hrs

**Monitoring Glycemia :** Daily self-monitoring of blood glucose (SMBG) is superior to intermittent office monitoring of plasma glucose. For women treated with insulin, postprandial monitoring superior to preprandial monitoring Urine glucose monitoring is not useful.

**Ketonemia :** Urine ketone monitoring useful in detecting inadequate caloric or carbohydrate intake in women treated with calorie restriction.

## TYPES OF INSULIN

One unit of insulin neutralizes 30 mg/dl of glucose, thus the dosage can be titrated. Absorption is maximum and fastest at abdomen (15-30min) as compared with arm (30-45min) and thigh (45-60min). (for regular insulin)

### ♦ **Insulin Lispro/Aspart (FDA Category B)**

It is safe in pregnancy<sup>24</sup> with the following advantages over regular insulin: (1) Can be injected at start of meals (regular insulin must be injected 30 min before meals); (2) Peak occurs during highest glucose excursion; (3) No delayed hypoglycemia; (4) Better compliance

### ♦ **Insulin Glargin (Peakless Insulin)**

This is Prepared from recombinant DNA; its absorption is delayed and it creates a steady insulin state with no peak. It has a 24 hr duration of action. It is FDA Category C drug and should not be mixed with other insulins. It is given as single dose at bedtime or in morning.

**Assessment of glycemic control** should be done by HbA1c levels in each trimester (5-6% - average glucose 90-120mg/dl)

## FETAL SURVEILLANCE

While there is no controversy about the need for strict fetal surveillance in diabetes, the most appropriate modality remains controversial with a combination approach being advocated by most experts

**GDM On diet:** (i) Clinical estimation & USG for detection of macrosomia; (ii) >40 weeks - biweekly NST. If history of still birth, Hypertension, Uncontrolled blood sugars, then biweekly NST at 32

weeks onwards

**GDM On insulin:** The patient is followed up with antepartum fetal surveillance as pregestational DM; elective induction is recommended at 38-39 wks.

### **Role of preconception care**

- 1) **Counseling** has to be done on the following issues: (1) Effect of pregnancy on diabetes; (2) Effect of diabetes on pregnancy; (3) Need of contraception until glycemia is well / maximally controlled;
- 2) **Evaluation** of maternal health status: History and physical examination; Medical and gynecological evaluation; Laboratory evaluation: HbA1c levels (goal: lowest possible HbA1c levels without undue hypoglycemia); 24h urine for creatinine and protein; Thyroid studies (type 1 DM)

**Special studies:** ECG; Fundus evaluation

General advice should include folic acid supplementation, cessation of smoking and alcohol intake.

## INSULIN THERAPY IN PREGESTATIONAL DM

Human insulin is the drug of choice<sup>25</sup>. The ADA currently recommends that people with type 1 diabetes SMBG at least 3 times daily. Those with type 2 diabetes at least daily blood glucose monitoring

**First trimester:** Baseline evaluation of retinopathy & nephropathy and biochemical screening at 10 weeks (PAPP-A,  $\alpha$  HCG) are disease specific care. USG at 12 weeks is indicated to measure Nuchal Translucency.

**Second trimester:** There is need for increased insulin dosage so intensive monitoring and management of obstetric and medical complications is imperative.

Fetal monitoring is achieved by: 1) Triple screen; 2) Level II USG: 18-24 weeks; 3) Fetal echo: 20-24 weeks; 4) 26 weeks: growth & liquor volume.

### **Antepartum Fetal Surveillance**

**Table 7 :** Antepartum fetal surveillance scheme in pregestational diabetes.

1) DFMC	daily	All patients
2) NST	twice weekly	controlled IDDM- start at 32 -34 wks
	Start at 28-32 weeks if	IUGR, PIH, Nephropathy, insulin req >100U/day, prev still birth
3) Biophysical profile	weekly	
4) Doppler umbilical artery	in early detection of IUGR in patients with vasculopathy, IUGR, preeclampsia	

## DIABETIC RETINOPATHY

**Preconceptional Management:** Ideally PDR should be diagnosed & treated before conception

**During pregnancy:** Minimal retinopathy at conception needs fundus examination every trimester. Moderate background retinopathy needs fundus examination each visit (4-6 weekly); Proliferative DR needs laser photocoagulation; Development of high risk mandates laser photocoagulation. A patient with untreated proliferative retinopathy at term should be delivered by caesarean section because of the risk of retinal and vitreous haemorrhage as a

result of straining and Valsalva manoeuvre in the second stage of labour .

### TIMING OF DELIVERY IN DIABETES IN PREGNANCY

Induction is planned around 38 weeks. If EFW > 4.5kg-elective LSCS<sup>26</sup>. If the EFW is 4-4.5kg, additional risk factors for shoulder dystocia should be considered .

**Elective LSCS** is planned for early morning and the patient should take her usual bedtime dose

Morning dose is withheld and patient kept fasting overnight. Blood sugar monitoring is done 2 hrly to avoid hypoglycemia and kept on normal saline drip and 5% dextrose if blood sugar is less than 70mg/dl. Insulin infusion is started if blood sugar >100mg/dl

Table 9 shows the intrapartum glycemic management. Blood sugars are done two hourly in latent phase and hourly in active phase of labour in diabetic patients.

**Table 9** shows the intrapartum glycemic management. Blood sugars are done two hourly in latent phase and hourly in active phase of labour in diabetic patients.

Blood glucose (mg/dl)	Insulin dosage (U/hr)	Intravenous fluids (125 ml/hr)
<100	0	5%D
100-140	1.0	5%D
141-180	1.5	Normal saline
181-220	2.0	Normal saline
>220	2.5	Normal saline

#### Post-partum management

Insulin requirement decreases rapidly (first 24-72 hrs). After **Vaginal delivery** in GDM on diet - no monitoring required while if on insulin - fasting & PP values should be done before discharge  
In Pregestational DM , one half of the pre-pregnancy dose is advocated or 1/2-1/3 of pre-delivery dose ( if pre pregnancy not known).

**After cesarean delivery**, Blood sugar monitoring is done 4-6 hrly and insulin given accordingly .Insulin requirement decreases in lactating women

**Post partum glucose testing is done at 6 weeks post partum usually with a 75 g OGTT.**

#### Oral Hypoglycemic Agents in Pregnancy

##### Metformin

##### Biguanide –Category B drug

##### Metformin in PCOS

MiG study (Metformin in gestational diabetes) this was an RCT including 751 women with GDM(20-33 wksPOG) *The highlights of the trial is shown in table*

**Table :** MiG study (Metformin in gestational diabetes)

	Metformin gp	Insulin gp
No. of patients	363 -92.6% recvd metformin -46.3% req insulin	
Primary outcome-neonatal hypoglycemia, prematurity, RDS, phototherapy need, low apgar score	32%	32.2%
Secondary outcome-maternal glycemic control, hypertensive complications, postpartum glucose tolerance, Rx acceptability	No significant difference between 2 groups  76.6% women preferred to take metformin in next pregnancy	

### CURRENT STATUS OF OHAS

Use in pregnancy after first trimester is safe. In first trimester, main problem is degree of hyperglycemia not the drug. Glyburide is the only drug which does not cross placenta (RCT studied) The widespread use of metformin should await the demonstration of safety for the fetus, since fetal levels are approximately half of maternal levels. Acarbose may be a worthwhile approach if the published preliminary data from a randomized trial are confirmed in the final report and if the issue of gastrointestinal disturbance can be overcome. Given the available evidence regarding placental transfer, and the lack of data from pregnancy, thiazolidinediones should not be used until more information is available. Incretin mimetics do not yet show promise for use in gestational diabetes.

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