Gestational Diabetes Mellitus
Practice guidelines

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Definition and classification:
Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varying severity, detected for the first time in pregnancy.

A practical classification of diabetes in pregnancy is:
1. **Pre-gestational diabetes** – The diagnosis of diabetes precedes conception (It could be Type 1 and Type 2 and other types- MODY (Maturity onset diabetes of young), Pancreatic diabetes etc.). It constitutes about 2% of diabetes in pregnancy.
2. **Gestational Diabetes Mellitus** - constitutes 98% of diabetes in pregnancy.

There is usually an overlap between GDM and Type 2 diabetes. These are usually women who do not know that they are diabetic and are diagnosed to have diabetes while being tested during pregnancy.

Epidemiology
Prevalence of GDM varies worldwide and among different racial and ethnic groups and depending on the diagnostic criteria used for screening.
In the USA, the prevalence among Caucasian (white) women is about 3.8% and among Asian women is about 7.4% by CC criteria. In India, prevalence ranges between 14 – 22%. It is more prevalent in urban than in rural areas.

Risk factors for developing GDM
- Prior GDM (in preceding pregnancy)
- Obesity
- Acanthosis nigricans
- Family history of diabetes

Maternal and fetal complications of GDM
The detection and treatment of GDM is important as it has consequences for both the mother and child.

Maternal complications
Women with pre existing diabetes have a risk of worsening of pre-existing long term complications like retinopathy, proteinuria and decline in GFR. There is also a higher risk of hypertension and cardiovascular disease and infection in this population.
Important materno-fetal risks include macrosomia & Cesarean delivery, spontaneous abortion, polyhydramnios, preeclampsia, preterm delivery, respiratory distress syndrome, perinatal mortality

Neonatal complications
- Macrosomia with or without birth injury (shoulder dystocia, brachial plexus injury).
- Hypoglycemia, hypocalcemia & hypomagnesemia. Both hypoglycemia and hypocalcemia can increase the risk of seizures in neonates.
- Hyperbilirubinemia, Respiratory problems

Congenital anomalies
Congenital anomalies are more common in mothers with GDM in the first trimester of pregnancy and when the diabetes is poorly controlled (A1C <10.4% risk of 4 to 5%, A1C ≥10.4% risk of 11%) 2/3rd of anomalies involve the cardiovascular or central nervous system. Cardiac anomalies are most common (including great vessel anomalies). Other anomalies - Central nervous system (spina bifida/ anencephaly) : 7.2%
Skeletal: cleft lip/palate,
Caudal regression syndrome is specific to diabetes.
Genitourinary tract and gastrointestinal (anorectal atresia)

Complications of overtreatment of hyperglycemia

Over-aggressive treatment of GDM results in small for gestational age babies and unnecessary intervention including increased antenatal visits, increased induction rates and caesarean section rates.

SCREENING & DIAGNOSIS

Who should be screened?
It is recommended that all Indian women be screened in view of ethnicity (Indian women are at moderate to high risk).

SCREENING TESTS

Diagnosis of overt Diabetes (Non-challenge test)

<table>
<thead>
<tr>
<th>Measure of glycemia</th>
<th>Consensus threshold*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>≥126 mg/dl</td>
</tr>
<tr>
<td>HbA1C</td>
<td>≥6.5%</td>
</tr>
<tr>
<td>RBS/ prandial Post</td>
<td>≥200 mg/dl, confirmed with fasting glucose/HbA1C</td>
</tr>
</tbody>
</table>

*IAny one abnormal level is diagnostic of overt diabetes.

Diagnosis of GDM (based on 75 gm glucose OGTT)

International Association of Diabetes and Pregnancy Study Group (IADPSG) came up with these recommendations for screening of GDM

IADPSG consensus panel criteria to diagnose GDM

<table>
<thead>
<tr>
<th>Glucose measure</th>
<th>Glucose concentration threshold*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>5.1</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>10.0</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>8.5</td>
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</tbody>
</table>

*One or more high value is diagnostic of GDM.

Risk classification

High risk for GDM
- Marked obesity
- Prior GDM (30-60% risk for recurrence)
- Strong family history

Intermediate risk for GDM
- No high risk factors
- All Indian women are at intermediate risk even in the absence of other risk factors. (age< 25 yrs, normal BMI, no glucose intolerance, no family h/o diabetes, no bad obstetric history)

When should these tests be done?

1) At first prenatal visit - measure FPG or random plasma glucose on all or only high-risk women.
If results indicate overt diabetes, treatment and follow-up are done as per preexisting diabetes. Fasting ≥ 92 mg/dl but <126 mg/dl, diagnose as GDM. Fasting <92 mg/dl, test for GDM at 24 to 28 weeks’ gestation with a 75-g OGTT.

2) 24 to 28 weeks’ gestation – do a 75-g OGTT (2 hours) on those with intermediate risk and those who have not been diagnosed of diabetes in the first visit.

Diagnose as overt diabetes, if fasting blood glucose ≥126 mg/dl, GDM - if one or more values equals or exceeds thresholds and Normal - if all values on OGTT less than thresholds.

**MANAGEMENT OF GDM**

**Glycaemic control in pregnancy**

The objective of care in ‘diabetes in pregnancy’ is to achieve pregnancy outcomes similar to those without diabetes. The management is straightforward – good glycemic control.

Type I diabetes is always controlled with medical nutritional therapy (MNT) and insulin. Most women with Type II diabetes would need similar treatment but with Metformin now being safely used in first trimester this seems to be the acceptable mode of treatment in milder forms of Type II pre-gestational diabetes.

Peri-conceptional glycaemic control is the hallmark of the management of pre-gestational diabetes. Glycosylated haemoglobin level more than or equal to 10.4% is associated with 11% risk of congenital anomalies, as compared to 4-5% risk below HbA1c of 10.4%.

**It should be emphasized that 80% of the women with gestational diabetes can be treated with medical nutritional therapy (MNT) and only 20% need additional therapy.** Of the women requiring additional therapy, only 25% need insulin therapy. The majority 75% have moderate hyperglycaemia (i.e. fasting plasma glucose ≤99 mg/dl and ≤130mg/dl and/or 2 hour post prandial levels ≥ 120mg/dl and<250mg/dl) and they can be treated only with oral hypoglycaemics and may not need additional insulin.

**Medical nutrition therapy**

**Goals**
- Achieve normoglycemia
- Prevent ketosis
- Provide adequate weight gain
- Contribute to fetal well-being

**Calorie allotment**

The number of calories depends on the BMI.

<table>
<thead>
<tr>
<th>Pre pregnancy BMI (Kg/m2)</th>
<th>K Cal/Kg current body weight</th>
</tr>
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<tbody>
<tr>
<td>&lt;22</td>
<td>40</td>
</tr>
<tr>
<td>22-25</td>
<td>30</td>
</tr>
<tr>
<td>26-29</td>
<td>24</td>
</tr>
<tr>
<td>&gt;30</td>
<td>12-15</td>
</tr>
</tbody>
</table>

Carbohydrates should contribute only 33-40% of calories, Proteins -20% and Fats -40%
A minimum of 1600 – 1800 Kcal is required to prevent ketosis during pregnancy.

**Calorie distribution**

Breakfast should contain the least proportion of calories - 10% of total calories, and should predominantly contain protein. Carbohydrate intake at breakfast should be limited because insulin resistance is greatest in the morning.

- Lunch — 30% of total calories
- Dinner — 30% of total calories
- Snacks — 30% (distributed in 3 snacks)
BED TIME SNACK SHOULD BE EMPHASIZED to prevent early morning hypoglycemia.

Recommended breakfast in South India- sundal (boiled lentils) with milk or Ragi kanji with roasted chana/ moong dal.

Recommendations for diet control and medication
If the FPG at diagnosis ≥ 120 mg/dl, consider immediate pharmacological therapy.
If FPG at diagnosis < 120 mg/dl, medical nutrition therapy for 1-2 weeks, with glucose monitoring (fasting and 1 hour post meal)
If majority of FPG > 95 or 1 hr PPG > 140 mg/dl then start on OAD/ insulin.

DRUGS

Oral anti-diabetic agents
Metformin
- Safe throughout pregnancy
- A significant proportion (35-50%) eventually require addition of insulin

Glibenclamide
- No safety data available for first trimester
- Transplacental transport minimal
- No excess anomalies
- Some increased risk of neonatal hypoglycemia and jaundice

Insulin
Insulin is safe throughout pregnancy.
Dose- 0.7 to 2 units per kg present pregnant wt.
Requirements are lower in the first trimester and become higher as the pregnancy advances.

Insulin regimens in pregnancy
The best regimen is the basal-bolus regimen as it is more physiological.

Basal-bolus regimen: 3-4 injections/day [0.7-2 units/kg body wt]
Thrice daily regular insulin (or short acting analogues) prior to meals PLUS NPH once/twice daily (As a basal insulin)

It is easy to achieve targets with this regimen as it is more physiological.

Premixed Insulin is used occasionally for the following reasons
- Convenient twice daily injections
- Easy to learn dose adjustment
Insulin pump may be required in persons in whom blood glucose levels are difficult to control.

GLYCAEMIC GOALS

Glycaemic goals as suggested by American Diabetes Association

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Blood glucose (mg/dl)</th>
</tr>
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<tbody>
<tr>
<td>Fasting</td>
<td>60-90</td>
</tr>
<tr>
<td>Pre-meal</td>
<td>60-105</td>
</tr>
<tr>
<td>Post prandial</td>
<td>100-120</td>
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In day to day practice in CMC, the glycemic goals followed are
Fasting blood glucose level - < 100 mg/dl
1 hour post prandial - < 140 mg/dl
2 hours post-prandial - < 120 mg/dl

During the intrapartum period, the plasma glucose levels are maintained between 70-140 mg/dl.

Patient education is very important and is the key to achieve these targets. Group education often helps because the feeling of loneliness is overcome.

Case Illustration
33 years old Mrs. S is G2P1L1 with 9 weeks gestation. She had diabetes from the 7th month of her last pregnancy and was on insulin. Pre-pregnancy
BMI - 28 Kg/m². In this pregnancy her Plasma glucose values
- Fasting -130 mg/dl
- 2h Post meal - 230 mg/dl

What is the diagnosis?
Overt diabetes mellitus

How do you manage this patient?
1. Advise MNT - 24 K cal/Kg body weight with 3 meals and 3 snacks, and protein predominant breakfast. Bed-time snack is important.
2. Exercise (walking 15 minutes after each meal)
3. Metformin started at 500mg BD if no vomiting
4. If she has significant vomiting - start Insulin

Masked Hypoglycemia in pregnancy
Asymptomatic (masked) hypoglycemia is seen in both normal pregnant women as well as pregnant women with GDM on Insulin. Somogyi phenomenon (counter-regulatory hormone response that increases glucose levels) is also impaired in pregnancy. So it is important to emphasize a bed-time snack to avoid unrecognized nocturnal hypoglycemia.

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OBSTETRIC MANAGEMENT

Fetal monitoring: Baseline ultrasound: fetal size
At 18-22 weeks: major malformations
fetal echocardiogram

Recommendations for timing of delivery (weeks of gestation):
Women on medical nutritional therapy (diet control) alone – 40-41 weeks
Women on OHA’s alone (easily controlled blood sugars) – 39-40 weeks
Women on OHA’s alone (difficult to control blood sugars) – 37-39 weeks
Women on high doses of insulin – 37-38 weeks
Vaginal delivery is preferred. Caesarian section only for obstetric indication or fetal weight > 4000 gm.

Management of labour and delivery
Maternal hyperglycemia in labour worsens neonatal hypoglycemia. It should be noted that Insulin requirements come down during labour.

During the intrapartum period, the plasma glucose levels are maintained between 70-140 mg/dl. If the level goes beyond 140 mg/dl, insulin infusion needs to be given according to a sliding scale protocol.
Monitor glucose at 1-4 hourly intervals during labour
In later stages of labour: start dextrose (nutritional requirement) and continue hourly blood glucose monitoring.

Immediate management of neonate
Hypoglycemia is a common problem. It is seen in 50% of macrosomic infants and in 5–15% of neonates with optimally controlled GDM in the mother. Hypoglycemia in a neonate is defined as a blood glucose <45 mg/dl.
Management: Give a bolus of 2-4 ml/kg IV of 10% dextrose, check after 15 minutes and start feeds. If blood glucose is persistently low, start IV dextrose infusion.
• Encourage early breast feeding
• Examine infant for congenital anomalies

Post partum follow up
In women with pre-gestational diabetes, the tight control is relaxed. For those on insulin, one third to half of end pregnancy insulin dosage is usually recommended. We have to be very careful to avoid hypoglycemia because that may be fatal. Hypoglycemia kills, hyperglycemia does not kill. Lactating mothers need less insulin.

In gestational diabetes, treatment in the postpartum period will need to be individualized. Those on diet
control or on oral hypoglycemic agents during pregnancy usually do not need any treatment in the postpartum period.

**Women with gestational diabetes should be asked to have their blood glucose levels checked 6 weeks after delivery** as they may be reclassified as Type II diabetes and will need continued treatment.

**Points to note**
- Check blood glucose before discharge for women who were on oral anti-diabetic drugs or insulin.
- Breast feeding helps in weight loss
- Insulin is compatible with breast feeding
- Glibenclamide is not secreted in breast milk.
- Metformin secreted - no adverse effects
- Lifestyle modification should continue irrespective of glucose levels in-order to prevent permanent diabetes.

**Future risks - Mother**
Do a 75 g OGTT for all GDM 6-12 weeks after delivery.
75-80% are normoglycemic, 20% have impaired glucose tolerance.
Risk of developing Type 2 diabetes - 3.7% at 6months, 4.9% at 15months and 35-60% develop diabetes over the next 10 yrs
Risk of recurrence of GDM – 30-69%.

**Risk of developing DM in offspring**
If the father has type 1 diabetes – the risk is 6-8%, it is 2 to 5% if the mother has type 1 diabetes, and is 10-25% if both are affected.

**Type 2 Diabetes mellitus**
If a single parent is diabetic, the risk is-
- 14% if the parent was diagnosed at <50 years of age
- 8% if the parent was diagnosed at >50 years of age
The risk is 50-60% if both are affected.

**Preconception counseling**
Advice contraception for spacing and until glycemic control is achieved. Inj. Depot Provera 150 mg every 3 months is a good temporary method of contraception for diabetics.

**Pre-existing diabetes**: glycemic control should be achieved to target HbA1c < 6.5%
Folic acid supplementation: 5 mg/day [begin 3 months before planning pregnancy.
- Try and achieve normal body weight with diet modification and exercise.
- Stop unsafe oral hypoglycemic drugs, ACE inhibitors/ARBs, β blockers, statins, fibrates and niacin.

**References:**
4. Surapaneni et al. Obstet Med September 2013 vol. 6 no. 3 125-128
6. BE Metzger at al. DIABETES CARE, Volume 30, Supplement 2, July 2007

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**Where it is a duty to worship the sun, it is pretty sure to be a crime to examine the laws of heat.**     John Morley

**He who injured you, if he is weaker, spare him and if he is stronger, spare yourself.**       Seneca

**Many a man fails as an original thinker simply because his memory is too good.**       Friedrich Nietzsche

**Excessive scruple is only hidden pride.**       Goethe

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ORAL HYPOGLYCAEMIC AGENTS (OHA’S) IN PREGNANCY

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The main concerns with the use of OHAs in pregnancy are that there is limited experience, limited literature, doubts about teratogenicity, concerns about prolonged neonatal hypoglycaemia and controversy about placental transfer. However over the years evidence for the use of OHA’s has shown that they are comparable with insulin in treating women with moderate gestational diabetes and can be safely used. Our experience in CMC has been similar.

The advantages of OHAs over insulin are several.
1. Risk of hypoglycaemia is less,
2. Less chance of insulin resistance
3. It is less expensive and
4. Compliance is obviously better.

Glibenclamide and Metformin are the two most studied drugs in pregnancy.

Glibenclamide:
Glibenclamide acts by releasing of insulin from Beta cells. There is a reduction of serum glucagon levels and it potentiates the action of insulin on the target organ. Recent studies have shown that cord plasma levels of Glibenclamide are almost 70% of maternal concentration.

Dosing: Glibenclamide is started with 2.5mg once a day and can be increased to a maximum of 7.5 mg twice daily. This is given before food.

Metformin:
Metformin is a much better drug than Glibenclamide. It is well known to improve insulin sensitivity, it causes suppression of hepatic glucose output causes increased insulin mediated glucose disposal and increased intestinal glucose use. It crosses the placenta but has no effect on placental transport or placental glucose uptake. In pregnancy it is a class B drug with no adverse fetal effects. It is the only drug shown to be safe in the first trimester.

Dosing: Metformin can be increased gradually from a dose of 500mg/day to a maximum of 3 gms/day. It is given after food. Dose is increased every week. Duration of action is 10-12 hours, so dosage has to be twice a day. It is contraindicated in liver impairment and renal insufficiency. Lactic acidosis and gastritis are the main side effects but these are not common.

Comparison between Glibenclamide and Metformin
Both Glibenclamide and insulin can cause weight gain and hypoglycaemia, but this is rare with metformin therapy. Metformin has the added advantage of being able to decrease appetite. Glibenclamide increases fasting insulin levels while metformin decreases levels. Metformin increases insulin sensitivity.

Concerns about OHA’s in pregnancy:
Glibenclamide, a sulphonylurea (SU) is known to stimulate pancreas to release insulin, and foetal hyperinsulinism is implicated in perinatal mortality.

Evidence for the use of oral hypoglycaemic agents in pregnancy
Initial evidence of the safety of use of oral hypoglycaemic agents in pregnancy was from South Africa where OHAs were being used for over 30 years. A cohort study published by Coetzee and Jackson showed that there was no difference in perinatal mortality rate. Interestingly, the authors had started using OHA’s because women refused to take insulin.

In 2000, a landmark randomized control study published by Oded Langer et.al. in the NEJM confirmed that pregnancy outcomes with the use of glyburide (Glibenclamide) was similar to insulin. This study was done on 404 women – 201 got glyburide and 203 got insulin. Diagnosis of gestational diabetes was based on a 100 gm OGGT. They found that hypoglycemia, hypocalcemia, hyperbilirubinemia, Polycythemia were similar between the two groups. Perinatal mortality, still births and neonatal death rates were similar. 4 % of women in glyburide had to switch to insulin. 4 women in glyburide and 41 in insulin group had hypoglycemic episodes with blood glucose levels < 39.6 mg/dl (p = 0.03).
There were no episodes of severe hypoglycaemia in either group. Incidence of pre eclampsia and caesarean section were similar in both groups.

In 2008 the MiG study also published in the NEJM. 751 women were randomized to two groups – 373 were given Metformin and 378 were given insulin. Composite neonatal complications were similar in both groups. Neonatal hypoglycaemia rates in neonates of women treated with Metformin was (highly) significantly lesser than in those given insulin.

The CMC experience:
We started using oral hypoglycemic agents in pregnancy in 2001. Neonatologists were initially concerned about complications in the baby and rigorously monitored babies whose mothers had been on OHA’s. After about a year, they realized these babies were doing much better than those whose mothers were on insulin. This was not because metformin was in any way superior to insulin but because mothers on insulin usually had higher levels of hyperglycemia and OHA’s were given only to those women with moderate hyperglycemia.

We published our retrospective cohort study in the Indian Journal of Medical Sciences in October 2011. We did not find any disadvantage with the use of oral hypoglycaemic agents in pregnancy. Women treated with insulin had babies with higher incidence of hyperbilirubinemia, again because these women had more severe hyperglycemia. In March 2013, a cohort study published in Indian Pediatrics by the Neonatology department of CMC confirmed this. There was no difference in perinatal outcomes. A randomized trial conducted in our institution comparing Metformin with Glibenclamide has shown a statistically significant decrease in neonatal hypoglycaemia in the group treated with Metformin.