Controversial Issues in Gestational Diabetes

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Overview

- Definition
- Metabolic changes in pregnancy
- Complications of GDM
- Screening & Diagnosis
  - HAPO study
  - IADPSG Consensus Panel
  - Guidelines (ADA, ACOG, NICE)
- Medical Management:
  - Lifestyle – diet & exercise
  - Insulin
  - Oral hypoglycaemic agents
WHO Definition

- Gestational diabetes mellitus (GDM)
  - Any degree of glucose intolerance with onset or first recognition during pregnancy
    - Whether insulin or only diet modification is used for treatment
    - Whether or not the condition persists after pregnancy

**PROBLEM:**
- Does not exclude the possibility that unrecognized glucose intolerance may have preceded or begun with the pregnancy
Prevalence of GDM

- Most common medical problem during pregnancy

- In US:
  - 6-7% of pregnancies complicated by DM
  - 85% of these cases represent GDM
GDM in Trinidad

- No prevalence data prior to 2008

- **Clapperton *et al***
  - Retrospective study at MHWH
  - January 2005 to December 2007
  - 720/12,655 deliveries reviewed

*Overall proportion of women with GDM was 4.31%*
GDM Prevalence in T&T

GDM in Trinidad

- Advancing maternal age (compared with <30 years)
  - 30-34 years - ↑4-fold
  - ≥35 years - ↑8-fold
- Ethnicity
  - South-East Indians – Risk ↑ 2.7 x Africans, 5.5 x Mixed
- Obesity
  - 9 x more likely to have GDM (compared with normal BMI)
Risk factors for GDM

- Overweight or obese (BMI ≥ 25 kg/m²)
- First degree relative with diabetes
- Predisposing ethnicity (Hispanic, African, Native American, Asian, Pacific Indian Ancestry)
- h/o baby weighing >9 lbs or Previous adverse pregnancy outcome
- Previous h/o of GDM or overt diabetes
- Glucosuria
Metabolic changes in Pregnancy

- Gestational hormones induce insulin resistance
- Inadequate insulin reserve and hyperglycemia ensues
Metabolic changes in Pregnancy

Figure 1. Reduced insulin sensitivity contributes to the problem of glucose homeostasis in pregnancy.

Figure 2. Hormonal changes that can influence glucose homeostasis in pregnancy.
GDM: Maternal Effects

- Women with GDM are at higher risk of:
  - Gestational hypertension
  - Preeclampsia
  - Caesarean delivery and its associated potential morbidities
  - Developing diabetes later in life
Progression to T2DM

~50% women with GDM develop diabetes 22–28 years after pregnancy

Progression to T2DM influenced by ethnicity and ↑ incidence of obesity:
- 60% of Latin-American women with GDM -> T2DM \textbf{5 years} after the index pregnancy

"Diabetes has increased dramatically over the past 10 years. That proves that diabetes is caused by global warming!"
GDM: Foetal Effects

- 1952: Jorgen Pedersen proposed mechanism

- Short-term:
  - Macrosomia
  - Neonatal hypoglycemia
  - Hyperbilirubinemia
  - Operative delivery
  - Shoulder dystocia
  - Birth trauma
GDM: Foetal Effects

- Those with fetal macrosomia:
  - Childhood overweight
  - Increase risk for cardiovascular disease

- Risk factor for diabetes/impaired glucose tolerance during female offspring’s pregnancies (Pima Indians)
Controversies in Diagnosis of GDM

- Who should be screened?

- Diagnostic criteria:
  - Screening methods: 1-step vs. 2-step approach
  - Cutoffs for glucose levels
Risk factors for GDM

- Overweight or obese (BMI $\geq 25$ kg/m²)
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- h/o baby weighing $>9$ lbs or Previous adverse pregnancy outcome
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### In 2013: Who Should Be Screened?

<table>
<thead>
<tr>
<th>ADA</th>
<th>ACOG</th>
<th>NICE</th>
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<tbody>
<tr>
<td><strong>High risk for GDM</strong> – screen at first visit using standard diagnostic criteria</td>
<td>All pregnant women (Universal screening) at 24-28 weeks</td>
<td>“At risk” pregnant women at 24-28 weeks: BMI ( \geq 30 \text{ kg/m}^2 ), previous baby ( \geq 4.5 \text{ kg} ), previous GDM, 1st degree relative with diabetes, certain ethnicities (South Asian, black Caribbean, Middle Eastern)</td>
</tr>
<tr>
<td>In pregnant women not previously known to have diabetes, screen for GDM at 24–28 weeks gestation</td>
<td>Earlier screening in at risk patients, if normal – repeat at 24-28 weeks</td>
<td>If h/o GDM, screen at 16-18 weeks; if normal, repeat at 28 weeks</td>
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<td><strong>Rationale</strong> (only 10% of population would be exempt from screening if selective method used)</td>
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<td>(~20–50% of women will have a positive screening result using these risk factors)</td>
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Diagnostic Criteria
Diagnostic Criteria Through The Years

1964 – O’Sullivan and Mahan 100g 3-h OGTT were:
- Fasting, 110 mg/dl
- 1-hour, 170 mg/dl
- 2-hours, 120 mg/dl
- 3-hours, 110 mg/dl
- 2+ values were enough to diagnose an abnormal test

1980-2010 – 50 g oral glucose challenge test (OGCT) for screening, followed by 100g OGTT if abnormal oral GCT (NDDG vs. Carpenter & Coustan criteria)
- Regardless of last meal or time of the day
- Venous plasma glucose cutoff of ≥ 140 mg/ one hour after the glucose load was considered abnormal
Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study

- Multicentre international study (15 centres, 9 countries)
- Blinded 75g 2-hour OGTT, 24-32 weeks gestation
- 25,862 non-diabetic pregnant women
- 25,505 screened -> 2.9% unblinded (prespecified criteria)
- 23,316 final analysis

<table>
<thead>
<tr>
<th>PRIMARY OUTCOMES</th>
<th>SECONDARY OUTCOMES</th>
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<tr>
<td>- Birth weight &gt;90&lt;sup&gt;th&lt;/sup&gt; percentile</td>
<td>- Preterm delivery</td>
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<tr>
<td>- Primary Cesarean Section</td>
<td>- Shoulder dystocia or birth trauma</td>
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<tr>
<td>- Clinical Neonatal Hypoglycemia</td>
<td>- Neonatal ICU care</td>
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<tr>
<td>- Cord Blood Serum C-Peptide &gt;90&lt;sup&gt;th&lt;/sup&gt; Percentile (fetal hyperinsulinemia)</td>
<td>- Hyperbilirubinemia</td>
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<tr>
<td></td>
<td>- Pre-eclampsia</td>
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- 2 maternal deaths (pulmonary embolism, respiratory failure secondary to pneumonia)
- 14 cases of eclampsia
- 321 cases of major malformation of the newborn
- 130 perinatal deaths (89 fetal and 41 neonatal or infant) (incidence 5.6 per 1000)
HAPO Study: Primary Endpoint Outcomes

Glucose categories
1 = <75 mg/dl
2 = 75-79 mg/dl
3 = 80-84 mg/dl
4 = 85-89 mg/dl
5 = 90-94 mg/dl
6 = 95-99 mg/dl
7 >=100 mg/dl

IADPSG Recommendations

- Used mean values for FPG (4.5 mmol/L), 1-h (7.4 mmol/L) and 2-h OGTT (6.2 mmol/L) plasma glucose concentrations for entire study cohort as reference
- Decided on OR of 1.75 (considered 1.5 and 2.0)

<table>
<thead>
<tr>
<th>Glucose measure</th>
<th>Glucose concentration threshold*</th>
<th>Above threshold (%)</th>
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<tbody>
<tr>
<td></td>
<td>mmol/l</td>
<td>mg/dl</td>
</tr>
<tr>
<td>FPG</td>
<td>5.1</td>
<td>92</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>10.0</td>
<td>180</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>8.5</td>
<td>153</td>
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*Cumulative percentages refer to the proportion of the study cohort above the threshold.
1-step vs. 2-step approach

<table>
<thead>
<tr>
<th>1-step</th>
<th>2-step</th>
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<tbody>
<tr>
<td>2-hour 75g OGTT</td>
<td>Oral glucose challenge (O’Sullivan and Mahan)</td>
</tr>
<tr>
<td>Measure fasting and 2-hour venous glucose</td>
<td>○ Threshold ≥140 mg/dl</td>
</tr>
<tr>
<td>If positive, 3-hour 100g OGTT</td>
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<thead>
<tr>
<th></th>
<th>75g</th>
<th>100g</th>
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<tbody>
<tr>
<td>Fasting</td>
<td>95 mg/dl</td>
<td>95 mg/dl</td>
</tr>
<tr>
<td>1 hour</td>
<td>180 mg/dl</td>
<td>180 mg/dl</td>
</tr>
<tr>
<td>2 hour</td>
<td>155 mg/dl</td>
<td>155 mg/dl</td>
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<tr>
<td>3 hour</td>
<td></td>
<td>140 mg/dl</td>
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## Criteria for GDM

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<tr>
<td>75g 2-hour OGTT</td>
<td>50g oral glucose challenge Proceed to 100g 3-hour OGTT if abnormal screening</td>
<td>75g 2-hour OGTT</td>
</tr>
<tr>
<td>Fasting ≥ 92 mg/dl</td>
<td>Fasting ≥ 95 mg/dl</td>
<td>Fasting ≥ 126 mg/dl</td>
</tr>
<tr>
<td>1 hour ≥ 180 mg/dl</td>
<td>1 hour ≥ 180 mg/dl</td>
<td>2 hour ≥ 140 mg/dl</td>
</tr>
<tr>
<td>2 hour ≥ 153 mg/dl</td>
<td>2 hour ≥ 155 mg/dl</td>
<td></td>
</tr>
<tr>
<td>• Performed following overnight fast for at least 8 hours</td>
<td>• 2 or more elevated values to establish diagnosis</td>
<td>• At least one abnormal value to establish diagnosis</td>
</tr>
<tr>
<td>• One abnormal value established diagnosis</td>
<td></td>
<td></td>
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</table>
~18% of the U.S. population have GDM using these criteria

- Some subpopulations, the proportion of women with GDM would be even higher

ADA endorsed the IADPSG criteria while acknowledging that adopting these cutoffs will significantly increase the prevalence of GDM
Concerns with New Recommendations

- The IADPSG criteria will likely diagnose GDM in 16%–18% of U.S. Pregnancies
  - How Can Any “Disease” Afflict Such a High Proportion of Pregnant Women?
- Cost to society?
  - Using 1-step approach
  - Treatment and education
- Identification and treatment trials all found individuals via a 2-Step screening process, whereas the new recommendations are for a 1-Step process
Medical Management of GDM
2005: Australian Carbohydrate Intolerance Study (ACHOIS) in Pregnant Women trial

- First large-scale (1,000 women) randomized treatment trial for GDM

Treatment was associated with a significant reduction in:

- Rate 1º outcome (composite of serious complications - perinatal death, shoulder dystocia, and birth trauma): 4% to 1% (P=0.01)
- Frequency of LGA infants from 22% to 13%
- Birth weight >4,000 g from 21% to 10%
- Among maternal outcomes, preeclampsia 18% vs. 12%
it’s gotta be triplets!
The ADA recommends:
- Nutritional counseling by a registered dietician
- Personalized nutrition plan based on the individual’s body mass index
- If no dietitian, clinician should be able to provide recommendations to the patient by remembering three major nutritional components
Dietary Recommendations

1) Caloric allotment
   Normal BMI: ~35 kcal/kg/day of present pregnancy weight
   Obese (BMI > 30 kb/m2): ~25 kcal/kg/day actual weight
   • Reduce hyperglycemia and plasma triglycerides, no increase in ketonuria

2) Carbohydrate intake
   • Restricting carbohydrates to 33–40% of calories -> decrease maternal glucose levels & improves maternal and fetal outcomes
   • Remaining calories: protein (20%) and fat (40%)
   • Complex carbohydrates preferred

3) Caloric distribution
   • 10% at breakfast, 20 –30% lunch & dinner, and 30% for snacks
Apparently, my nesting instinct was replaced by my much stronger "sit around and eat ice cream till I feel like puking" instinct.
Insulin

- Standard of treatment for GDM not controlled by diet and exercise

- Human vs. Analog insulins

- ?Long-acting analog insulin – safety?
### Short-acting Analog Insulins

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<thead>
<tr>
<th>Lispro</th>
<th>Aspart</th>
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<tr>
<td><strong>1999: First report of safety in GDM</strong>&lt;br&gt;Peak insulin action ( \leq 1 ) h after injection&lt;br&gt;One study: 213 patients who had GDM - Regular insulin 138; lispro 75&lt;br&gt;  - No significant differences in maternal or fetal outcomes&lt;br&gt;  - No increase in adverse events using lispro&lt;br&gt;  - Predelivery A1C values were lower and patient satisfaction higher than with Regular</td>
<td><strong>Peak blood level at 40 min</strong>&lt;br&gt;<strong>Lowers postprandial glucose levels significantly better than human insulin</strong>&lt;br&gt;<strong>69% the IGF-I activity of human insulin</strong>&lt;br&gt;<strong>Quicker onset of action and lower postprandial glucose than regular human insulin</strong>&lt;br&gt;<strong>Studies performed in rats and rabbits indicated that, like regular human insulin, insulin aspart at doses 3 to 200 times the typical human subcutaneous doses caused fetal abnormalities</strong></td>
</tr>
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Sulphonyureas

- 1st generation – cross placenta

- Glyburide – does not cross the placenta
  - high protein binding (99.8%)
  - short elimination half-life (10 h)
  - placenta actively pumping glyburide back into the maternal circulation

- Studies
Glyburide vs. Insulin

- 404 women: 201 glyburide (2.5-20 mg/d); 203 insulin
- 18 to 40 years
- 11 to 33 weeks gestation (after organogenesis)
- Similar degree of glycaemic control
- No significant differences in perinatal outcome, incidence of preeclampsia (6%) and cesarean section (23% vs 24%)
- Conversion from glyburide to insulin in 4% cases

Other studies confirm these findings

Metformin

- Improves insulin sensitivity, probably by activating AMP kinase
- No associated weight gain or hypoglycemia
- Metformin crosses the placenta and could affect fetal physiology directly
- Favourable reported outcomes generally
- Its use in pregnancy remains controversial?efficacy & safety
MiG Study

- 751 women -> 18 data not available
- 363 metformin, 370 insulin
- 1º outcome: composite of neonatal complications
- No statistically significant difference between groups (32.0% Metformin and 32.2% Insulin, P = 0.95)
- Supplemental insulin was required in 168 women (46.3%) in the metformin group – had higher BMI
- Metformin treatment was stopped in 27 women (7.4%) before delivery

MiG Study

- Metformin preferred (76.6% vs. 27.2% in a subsequent pregnancy)

- Post hoc analysis, non-inferiority design, proposed margin of 1.33 (33% change in complications): Metformin is not inferior to insulin (relative risk, 0.99; 97.5% CI, 0.78 to 1.26)
Hypothesis: Metformin exposure in utero would be associated with less central fat -> less insulin resistance in the offspring

No differences between groups in central fat measures, total fat mass, percentage body fat or central-to-peripheral fat

Metformin exposed: larger upper-arm circumferences, bigger biceps and subscapular skinfolds
- ? exposure to metformin in utero has led to more fat being stored in subcutaneous sites -> less ectopic or visceral fat in these children
These findings are important for two reasons:

1) Maternal metformin treatment during pregnancy may lead to a more favorable pattern of fat distribution for exposed children

2) Simple measures of central fat may not be adequate for determining the potential effects of in utero exposure to metformin
Metformin

- Safety in first trimester

- Studies (Glueck) using Metformin to treat women with PCOS -> ovulation
  - Decreased risk for spontaneous abortion
  - No increase in congenital malformations
Metformin vs. Glyburide

- RCT 149 women: 74 glyburide, 75 metformin
- Screened 50g OGCT (130 mg/dl), +ve 100g 3-hour OGTT used Carpenter & Coustan
- 1º outcome: achievement of glycemic control
  - FBG ≤105 mg/dL
  - 2-hour postprandial blood ≤120 mg/dL
- Counseled diet & exercise
- Inclusion: Fasting ≥105 mg/dl, 2h pp ≥120 mg/dl
- Exclusion criteria:
  - Renal or hepatic disease
  - Chronic hypertension necessitating medication
  - Substance misuse

Metformin vs. Glyburide: Outcomes

- 26 patients (34.7%) in Metformin group vs. 12 patients (16.2%) in Glyburide group (P=0.01)
  - 2.1 x higher failure rate with Metformin therapy

- No difference in mean fasting or 2-hour postprandial blood glucose values between the two treatment arms

- 11 cesarean deliveries Metformin group, two cesarean deliveries Glyburide group (P=0.02)

- Mean birth weight of babies in Metformin group smaller than in Glyburide group (P=0.02)
  - 3,329 g vs 3,103 g

Monitoring & Glycaemic targets

- Insufficient evidence for optimal frequency of blood glucose testing
- General recommendation is four times daily glucose monitoring
  - Fasting and either 1 hour or 2 hours after each meal
  - Once glucose levels are controlled by diet, frequency of glucose monitoring can be modified
- ADA and ACOG:
  - Fasting ≤95 mg/dL
  - 1-hour pp ≤140 mg/dL
  - 2-hour pp ≤120 mg/dL
Postpartum

- Screen between 6-12 weeks post-partum
- If test is positive -> diagnosis of T2DM established
Where Do We Stand?

- After 50 years, controversies still surround the diagnosis and management of GDM

- Need for standardized international guidelines for diagnostic testing and glucose criteria

- Long-term studies for safety & efficacy of oral hypoglycaemic agents

- Studies in Trinidad?
Questions?