Controversial Issues in Gestational Diabetes

DR. NICOLE TILLUCKDHARRY
CONSULTANT ENDOCRINOLOGIST
ERIC WILLIAMS MEDICAL SCIENCES COMPLEX

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

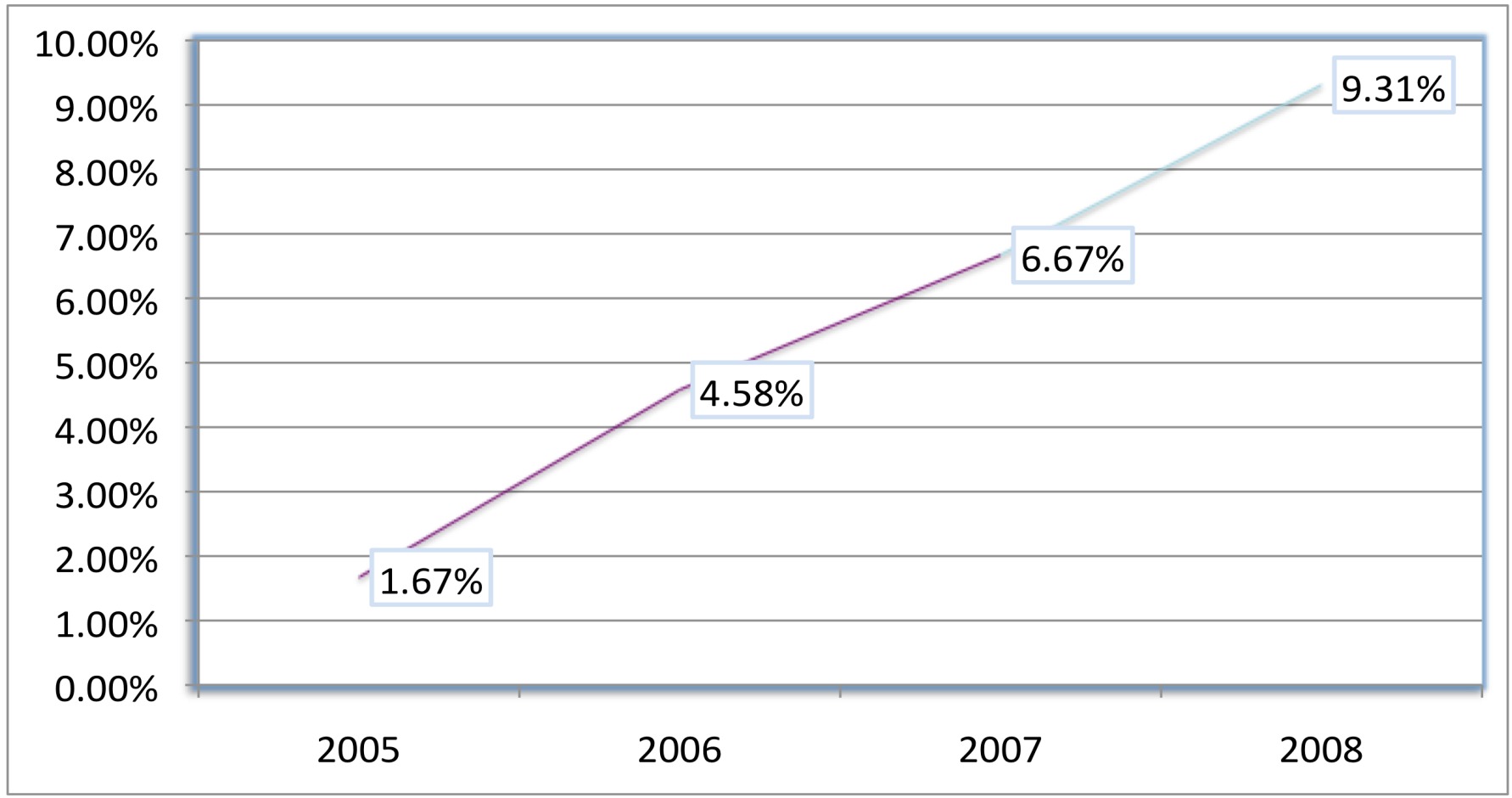
GDM in Trinidad

- 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



Clapperton *et al.* Obstet Gynecol Int 2009.

GDM in Trinidad

	Pearson chi-square	Odds ratio	95% Confidence interval Lower	Upper
Age				
30–34/<30	0.0001	4.07	1.96	8.45
>35/<30	0.0001	8	2.17	29.5
Ethnicity				
South-East Asian/Africans	0.016	2.73	1.17	6.35
South-East Asian/Mixed	0.011	5.52	1.27	24.07
BMI				
Obese/Healthy	0.013	8.97	1.14	70.58

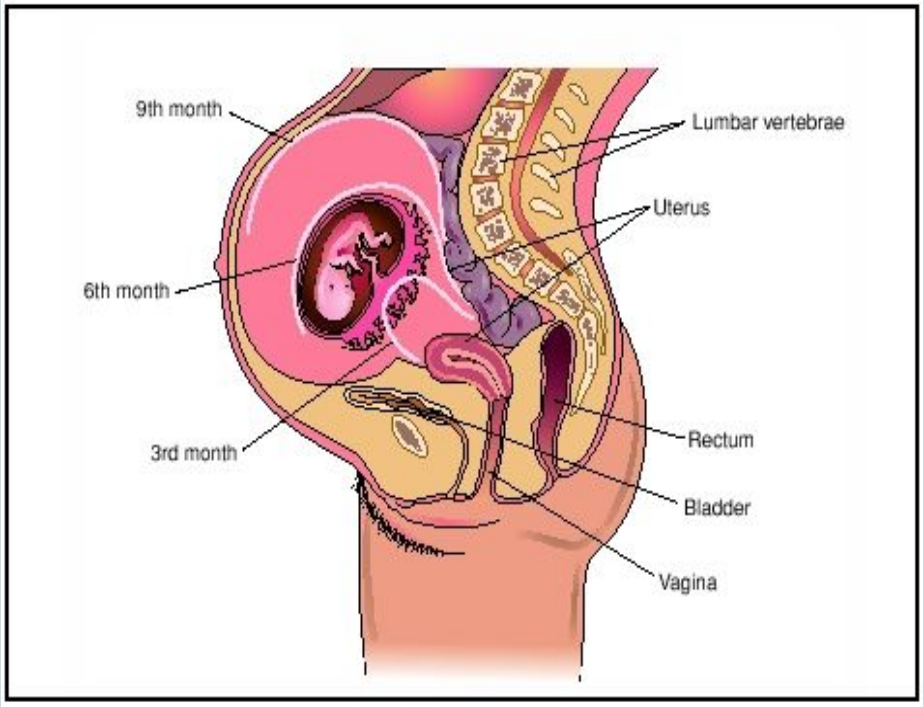
- Advancing maternal age (compared with <30 years)
  - 30-34 years - ⇧4-fold
  - ≥35 years -⇧8-fold
- Ethnicity
  - South-East Indians – Risk ⇧ 2.7 x Africans, 5.5 x Mixed
- Obesity
  - 9 x more likely to have GDM (compared with normal BMI)

Risk factors for GDM

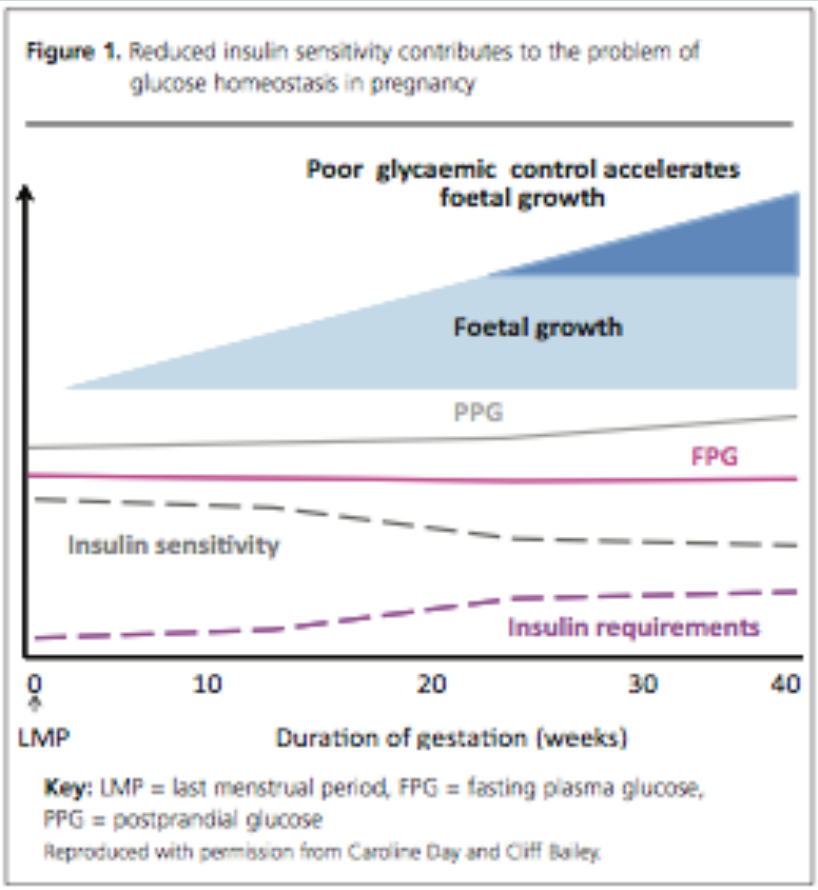
- Overweight or obese (BMI ≥ 25 kg/m²)
- First degree relative with diabetes
- Predisposing ethnicity (Hispanic, African, Native American, Asian, Pacific Indian Ancestry)
- h/o baby weighing >9 lbs or Previous adverse pregnancy outcome
- Previous h/o of GDM or overt diabetes
- Glucosuria

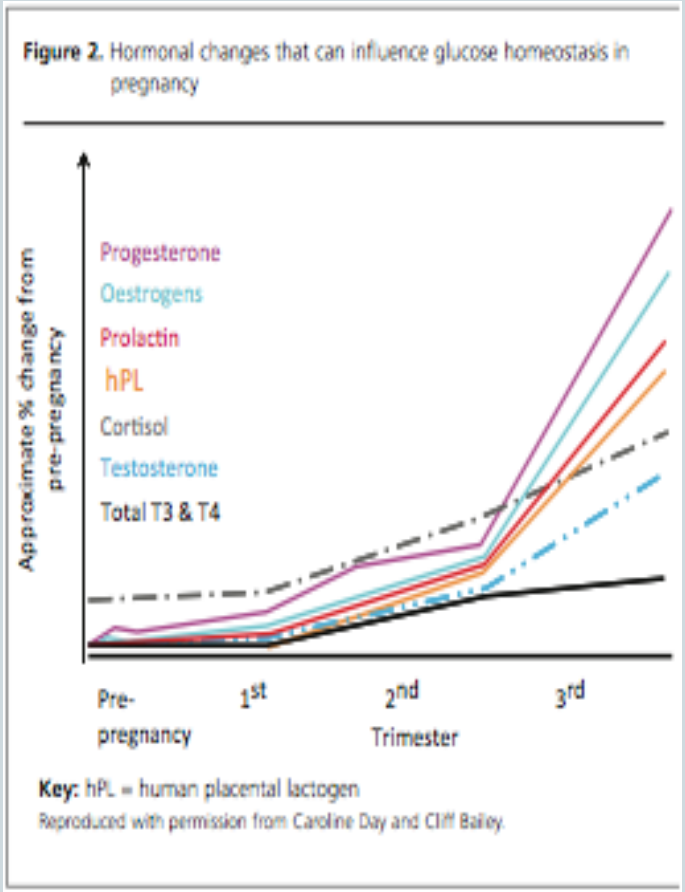
Metabolic changes in Pregnancy

- Gestational hormones induce insulin resistance
- Inadequate insulin reserve and hyperglycemia ensues



Metabolic changes in Pregnancy





Br J Diabetes Vasc Dis 2009; 9: 27–31

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

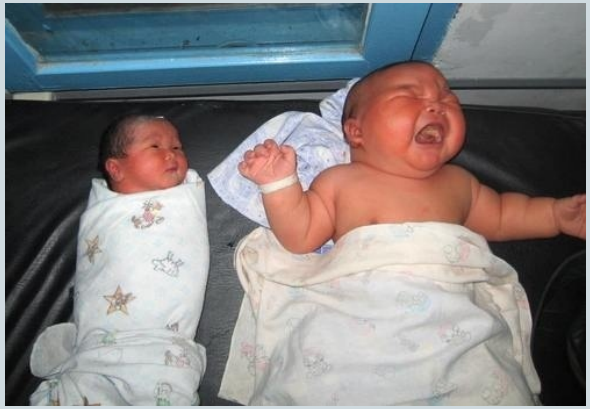
- ~50% women with GDM develop diabetes 22–28 years after pregnancy
- Progression to T2DM influenced by ethnicity and ⇧ incidence of obesity:
  - 60% of Latin-American women with GDM -> T2DM **5 years** after the index pregnancy

"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 ≥ 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

In 2013: Who Should Be Screened?

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

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

N Engl J Med 2008;358:1991-2002.

HAPO Study

PRIMARY OUTCOMES

- Birth weight >90th percentile
- Primary Cesarean Section
- Clinical Neonatal Hypoglycemia
- Cord Blood Serum C-Peptide >90th Percentile (fetal hyperinsulinemia)

SECONDARY OUTCOMES

- Preterm delivery
- Shoulder dystocia or birth trauma
- Neonatal ICU care
- Hyperbilirubinemia
- Pre-eclampsia

- 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

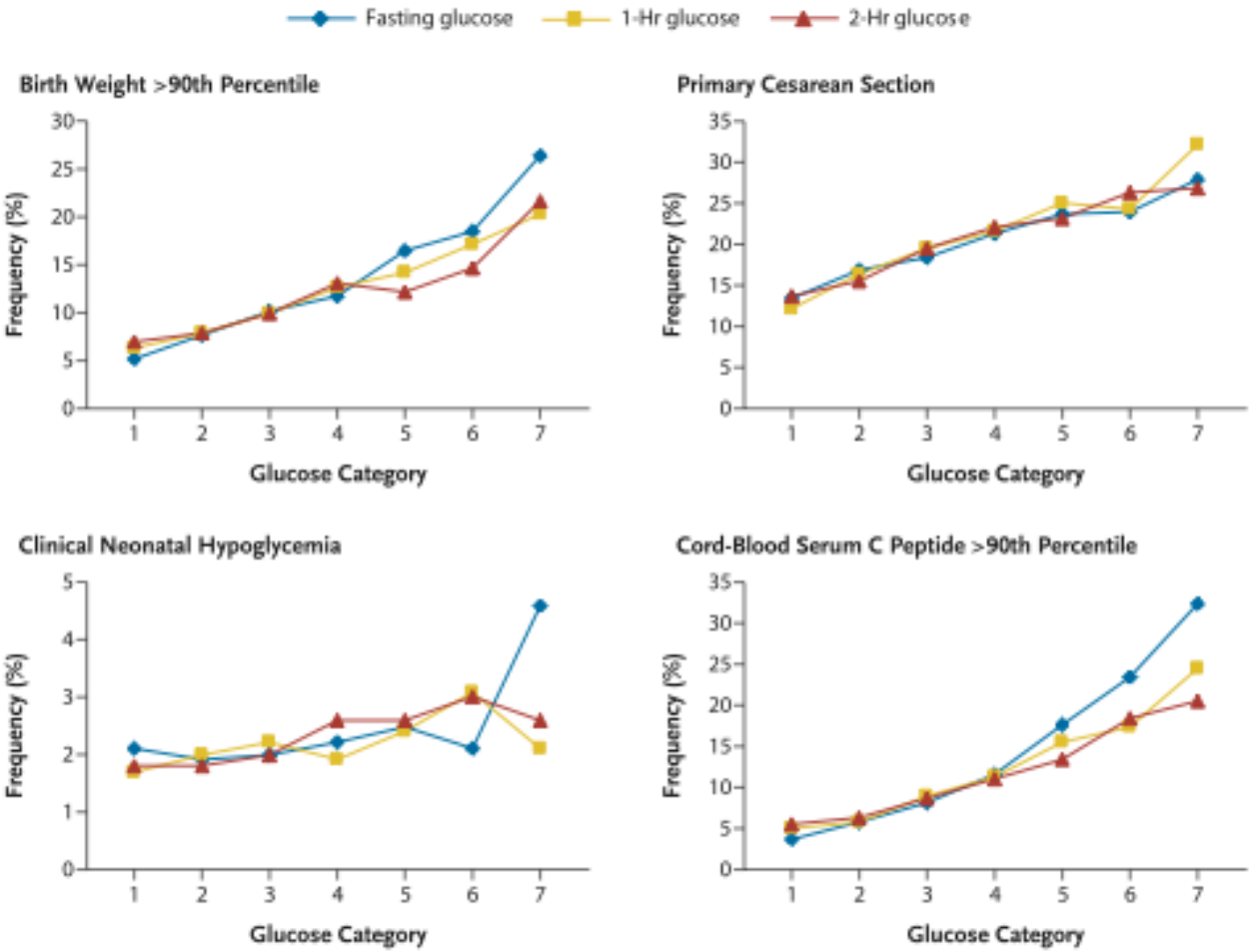


Fig. 1. Frequency of perinatal and maternal outcomes in relation to maternal glycemia. Reprinted from HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002. © 2008, Massachusetts Medical Society.

Landon. Gestational Diabetes Mellitus. Obstet Gynecol 2011.

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 concentrarions for entire study cohort as reference
- Decided on OR of 1.75 (considered 1.5 and 2.0)

	Glucose concentration threshold*		Above threshold (%)
Glucose measure	mmol/l	mg/dl	Cumulative
FPG	5.1	92	8.3
1-h plasma glucose	10.0	180	14.0
2-h plasma glucose	8.5	153	16.1†

Diabetes Care 2010; 33(3): 676-682

1-step vs. 2-step approach

1-step

- 2-hour 75g OGTT
- Measure fasting and 2-hour venous glucose

	75g	100g
Fasting	95 mg/dl	95 mg/dl
1 hour	180 mg/dl	180 mg/dl
2 hour	155 mg/dl	155 mg/dl
3 hour		140 mg/dl

2-step

- Oral glucose challenge (O'Sullivan and Mahan)
  - Threshold ≥140 mg/dl
- If positive, 3-hour 100g OGTT

Criteria for GDM

ADA	ACOG	NICE
75g 2-hour OGTT	50g oral glucose challenge Proceed to 100g 3-hour OGTT if abnormal screening	75g 2-hour OGTT
Fasting ≥ 92 mg/dl 1 hour ≥ 180 mg/dl 2 hour ≥ 153 mg/dl	Fasting ≥ 95 mg/dl 1 hour ≥ 180 mg/dl 2 hour ≥ 155 mg/dl 3 hour ≥ 140 mg/dl	Fasting ≥ 126 mg/dl 2 hour ≥ 140 mg/dl
• Performed following overnight fast for at least 8 hours • One abnormal value established diagnosis	•2 or more elevated values to establish diagnosis	•At least one abnormal value to establish diagnosis

Cutoffs: IADPSG Consensus Panel

- ~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

Lifestyle

- 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!
POTATO CHIPS

Diet

- 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
© 2007 baby-gaga.com

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

Lispro

- 1999: First report of safety in GDM
- Peak insulin action ≤1 h after injection
- One study: 213 patients who had GDM - Regular insulin 138; lispro 75
  - No significant differences in maternal or fetal outcomes
  - No increase in adverse events using lispro
  - Predelivery A1C values were lower and patient satisfaction higher than with Regular

Aspart

- Peak blood level at 40 min
- Lowers postprandial glucose levels significantly better than human insulin
- 69% the IGF-I ac-tivity of human insulin
- Quicker onset of action and lower postprandial glucose than regular human insulin
- 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

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

Langer *et* al. N *Engl J Med* 2000;343:1134-8

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

Rowan JA *et al. N Engl J Med* 2008;358:2003-15

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)

MiG TOFU

- 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

MiG TOFU

- 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

Diabetes Care 34:2279–2284, 2011

Metformin

- ?Safety in first trimester
- Studies (Glueck) using Metformin to treat women with PCOS -> ovulation
  - Decreased risk for spontaneous abortion
  - No increase in congential 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

Moore LE *et al.* Obstet Gynecol 2010;115:55–9

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

Moore LE *et al.* Obstet Gynecol 2010;115:55–9

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?