Gestational Diabetes Update

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Objectives

- Define diabetes and the associated morbidities
- Review treatment options for GDM (oral and insulin)
- Implications of trials of mild GDM
- Review HAPO, hyperglycemia and pregnancy outcome
- Recommendations for new screening methods

Diabetes in Pregnancy: *Historical Perspective - Survival*

- 1880's: 10/22 newborns; 6/15 mothers alive 1 year after delivery
- 1920's 30% miscarriage, 50% stillbirth, 14% neonatal death
- late 1920's insulin introduced
- 1930's fetal death rate reduced 1/2
- 1970's home blood sugar monitors reduce perinatal mortality from 35% to 10%

Prevalence

- 1 to 14% (estimated at 7%) of pregnancies are complicated by diabetes mellitus; 90% of these are gestational diabetes mellitus (GDM)

White Classification of Diabetes Mellitus in Pregnancy

White's Class	Age at Onset (years old)	Duration (years)	Complications
A	Any	Any	Diagnosed during pregnancy
B	≥ 20 or	<10	No vascular disease
C	10-19 or	10-19	No vascular disease
D	<10	≥ 20	Background retinopathy only or hypertension
F			Nephropathy (>500 mg/day proteinuria)
H			Arteriosclerotic heart disease
R			Proliferative retinopathy or vitreous hemorrhage
T			After renal transplantation

Gestational Diabetes Screening

(1) Screening tests were designed to identify women at risk of developing diabetes after pregnancy or were based on non-pregnant women. They were not to identify women with increased risk of adverse pregnancy outcome.

(2) Universal screening versus targeted screening is debated. In US most recommend screening all pregnant women.

(3) When and how to screen for gestational diabetes: *First-trimester screening vs third-trimester screening*

GDM Screening: First trimester

Test high risk patients for occult Type II DM

Risk factors include:

- advanced maternal age
- obesity
- family history
- body habitus
- ethnicity

GDM Screening: third trimester

Outside US: *2 hr* 75 gram oral glucose load

US: *1 hr* 50 gram oral glucose load

Positive screen is ≥ 135 mg/dl.

	Venous Plasma	Carpenter and Coustan
Fasting	105 mg/dl	95 mg/dl
1 Hour	190 mg/dl	180 mg/dl
2 Hour	165 mg/dl	155 mg/dl
3 Hour	145 mg/dl	140 mg/dl

GDM complications

- Maternal
- Perinatal
- Neonatal

Maternal Complications:

- Retinopathy
- Nephropathy
- Cardiovascular: cHTN, PE, MI
- DKA

Perinatal Complications

- **Miscarriage:** 2-fold increase
- **Congenital anomalies**
  - – ↑ with ↑ blood sugar.
  - – Hgb $A_1C \geq 10$ associated with 25% chance of major congenital anomaly
- **Growth abnormalities**
  - – Fetal growth restriction
  - – Macrosomia >28 wks; ↑ PP maternal glc levels
- **Stillbirth**
  - – ↑ with ↑ blood sugar, vascular complications

Neonatal Morbidity and Mortality

Polycythemia and Hyperviscosity
Neonatal Hypoglycemia
Neonatal Hypocalcemia
Hyperbilirubinemia
Hypertrophic & Congestive Cardiomyopathy
Respiratory Distress Syndrome
Childhood Impaired Glucose Tolerance

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Principles of Diabetic Therapy

a) Diet: Low-glycemic foods; carb counting
b) Exercise
c) Avoiding Nocturnal Hypoglycemia and ketosis
d) Hypoglycemic agents when indicated
- Oral hypoglycemics
- Insulin

Principles of Glucose Monitoring

Glycohemoglobin: long term measure of glucose control, not useful for individual insulin adjustments

Home Glucose Monitoring: elevated postprandial values correlate most closely with fetal macrosomia
- fasting >65 mg/dl but <95mg/dl,
- 2 hour postprandial <120 mg/dl

Management of GDM

Dietary Therapy - mainstay of treatment, controlled carbohydrates distributed throughout meals, exercise

Medical Therapy ~10% with gestational diabetes will require medication

- Glyburide
- Insulin

Dietary management

- Most pregnant women: extra 300 cal/d
- 1 serving carbohydrate = 12-15 gm carbs
- Example 2200 cal / day diet
  - Breakfast: 3 carbs
  - Snack: 1 carb
  - Lunch: 4 carbs
  - Snack: 1 carb
  - Dinner 5 carbs
  - Snack: 1 carb

Use of Medical Therapy

Insulin

Oral Agents

- Glyburide used more commonly
- Metformin: PCOS

Glyburide vs Insulin in GDM

- 404 singleton GDM gestations
- FBS > 95 mg/dl or if they failed diet control
- Randomized between 11 – 33 weeks
- Glyburide vs intensive insulin protocol
- Primary objective: glycemic control
- Secondary objective: maternal/neonatal complications

Langer et al. NEJM 2000;343:1134-8

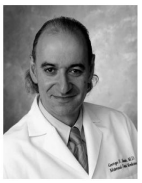
Glyburide vs Insulin: Results

- Pretreatment glucose levels similar
- Mean glucose similar
  - 105 ± 16 [gly] vs 105 ± 18 [ins] mg/dl)
- Only 4% (n=8) in glyburide group needed insulin
- No severe side effects from glyburide
- Similar levels of cord insulin
- No glyburide detected in cord serum

Langer et al. NEJM 2000;343:1134-8

EDITORIAL

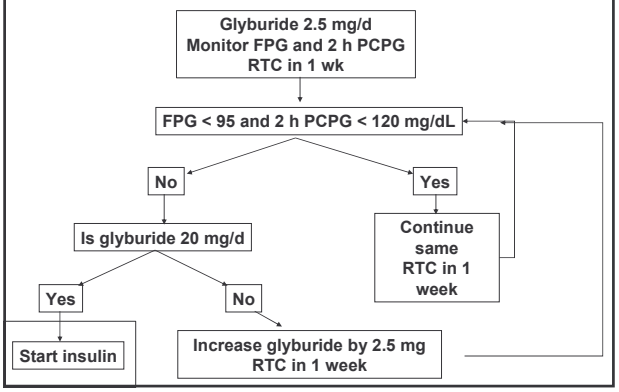
Gestational Diabetes Mellitus: A Pill or a Shot?



The current screening and management approaches in gestational diabetes mellitus (GDM) are being questioned, and some of the practice patterns are being evaluated. At present, pregnant women are expected to undergo screening for GDM, and those with abnormal glucose tolerance test results will receive nutritional intervention followed by pharmacologic therapy when the latter does not achieve the desired glycemic control. Until recently, pharmacologic therapy for GDM in the United States was limited to insulin, and the use of oral hypoglycemics was uncommon, despite the experience in other countries dating back to the 1960s.[1,2] In 2000, a new trial conducted in the United States revived the interest in oral hypoglycemics.[3] In this study, 404 women with GDM requiring pharmacologic treatment were randomly assigned at 11–33 weeks of gestation to receive either subcutaneous insulin or oral glyburide starting

Obstet Gynecol 2005;105:456-7

Suggested Management Algorithm



Management of GDM

Glyburide
- Start with 2.5 mg/d
- Maximum 20mg/d (may be split am/pm)

Insulin initiation
- Based on maternal weight in kg * 0.7 - 0.9
  - 2/3 dose in am; 1/3 in pm
  - AM dose, 2/3 NPH, 1/3 Regular
  - PM dose ½ NPH, ½ Regular

Management of GDM

Monitor blood sugar 4x/day
- FBS, 2h PP
  - goal: FBS <90 mg/dL
  - goal: 2h PP <120 mg/dL

Management of GDM

Antepartum testing if well controlled, APT not needed until 40 weeks, if medication required, APT at 36 weeks or earlier if indicated 2x/wk

Delivery – if well controlled, delivery ≥ 39 wks; assess fetal size for route of delivery

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Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)

- Multicenter RCT of mild GDM (1993-2003)
- 24-34 weeks randomized to intervention or routine care
- Reduced
  - Serious perinatal complications 4% to 1%
  - Macrosomia 21% to 10%

Followup of ACHOIS trial

- 199 mothers from RCT
- Trained nurses measured height and weight of children at preschool visits (age 4-5)
- Primary outcome: age and sex specific BMI Z score

Treatment of mild GDM on child BMI at 4-5 yrs

Table 2—*Effect of treatment of mild gestational diabetes on child BMI at age 4- to 5-years*

	Intervention	Routine care	Unadjusted treatment effect	Adjusted* treatment effect
Age at measurement (years)	4.7 (0.2)	4.7 (0.4)	Regression estimate (95% CI)	
Weight (kg)	19.1 (2.9)	19.4 (4.2)	−0.31 (−1.33 to 0.70)	−0.37 (−1.40 to 0.66)
Height (cm)	107.9 (4.6)	108.5 (5.8)	−0.61 (−2.08 to 0.86)	−0.66 (−2.16 to 0.85)
BMI Z score†	0.49 (1.20)	0.41 (1.40)	0.08 (−0.29 to 0.44)	0.08 (−0.29 to 0.45)
	N (%)		Relative risk (95% CI)	
BMI>85th%	33%	28%	1.19 (0.78–1.82)	1.17 (0.77–1.78)

*Adjusted for maternal race, parity, age, and socio-economic index; †calculated from standards of the International Obesity Task Force.[12]

Although treatment of GDM substantially reduced macrosomia at birth, it did not result in a change in BMI at age 4- to 5-years-old

Gillman et al, Diabetes Care 2010

Mild gestational diabetes trial

- **Aim:** To test whether identification and dietary treatment of mild GDM reduces composite outcome
- **Design:** RCT with additional observational cohorts
- **Eligibility criteria:** 24-29 wks gestation, normal FBS, abnormal 3h-GTT
- **Intervention:** treatment (counseling, dietary management) vs standard non-GDM care
- **Primary outcome:** Fetal composite
- **Status**: 1,889 patients enrolled

Landon et al, NEJM 2009

STUDY DESIGN

- Randomized multicenter clinical trial
- 50 gram (GLT) value 135-200 mg% between 24 0/7 - 29 6/7 wks
- Blinded 3 hr 100gm OGTT analyzed centrally

Landon et al, NEJM 2009

STUDY DESIGN

Women with mild GDM

2 of these abnormal
- Fasting <95 mg/dl
- 1 hour ≥180 mg/dl
- 2 hour ≥155 mg/dl
- 3 hour >140 mg/dl

Randomized to:

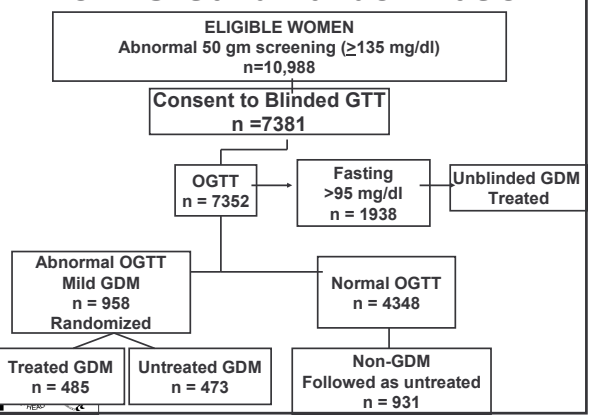
Treatment
- **Nutrition counseling**
- **SBGM/memory meter**
- **Insulin if necessary**

No Treatment
- **Standard OB care**

Providers and patients Unaware of GTT results

Landon et al, NEJM 2009

Enrollment and Randomization



PRIMARY OUTCOME: COMPOSITE

- Stillbirth/Neonatal Mortality
- Neonatal Hypoglycemia
- Hyperbilirubinemia
- Neonatal Hyperinsulinemia
- Birth Trauma

Landon et al, NEJM 2009

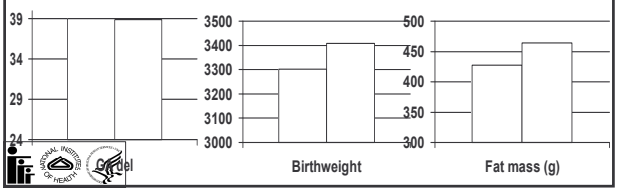
PRIMARY OUTCOME

	Treated GDM	Untreated GDM	RR (95% CI)	P value
Composite	**149/460 (32.4)**	**163/440 (37.0)**	**0.87 (0.73, 1.05)**	**0.143**
Hypoglycemia	62/381 (16.3)	55/357 (15.4)	1.06 (0.75, 1.47)	0.747
Hyper-bilirubinemia	43/450 (9.6)	54/418 (12.9)	0.74 (0.51, 1.08)	0.116
Elevated Cord c-peptide	75/423 (17.7)	92/403 (22.8)	0.78 (0.59, 1.02)	0.068
Stillbirth/NND	0	0	--	--
Birth Trauma	3/476 (0.63)	6/455 (1.32)	0.48 (0.12, 1.90)	0.332

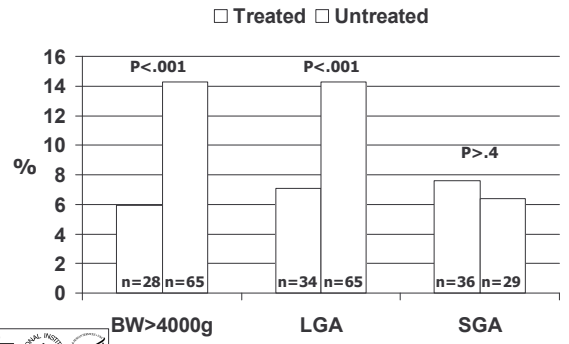
Landon et al, NEJM 2009

SECONDARY OUTCOMES

	Treated GDM	Untreated GDM	RR	p
GA del (wk)	39.0±1.8	38.9±1.8	--	0.904
BW (g)	3302±502	3408±589.4	--	0.0005
Fat mass (g)	427.0 ±197	464.3±222.3		0.0030

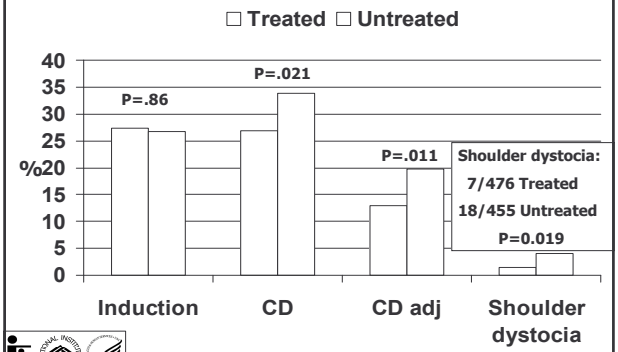


GDM trial: BW, LGA, SGA



Landon et al, NEJM 2009

Mild GDM Delivery



Landon et al, NEJM 2009

Mild GDM: conclusions

- Treatment of mild GDM did not reduce the frequency of several commonly observed morbidities associated with diabetic pregnancy
- However, treatment did decrease
  - Birthweight
    - Macrosomia by 50%
  - Neonatal fat mass
  - Shoulder dystocia
  - Cesarean delivery
  - Preeclampsia and gestational hypertension

Landon et al, NEJM 2009

Identification & treatment of mild GDM is associated with significant benefits:

	NNT	95% CI
Macrosomia	12	(8, 22)
Shoulder Dystocia	40	(21, 262)
Cesarean Delivery	14	(8, 95)
Gest HTN/ Preeclampsia	20	(11, 103)

Landon et al, NEJM 2009

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HAPO

- 25,505 women 15 centers/9 countries
- 75g OGTT at 24-43 weeks
- Data blinded unless fasting ≥105mg/dL or 2 hr >200 mg/dL
- Primary outcome
  - BW>90th centile
  - Primary CD
  - Clinically diagnosed neonatal hypoglycemia
  - Cord c-peptide >90th centile

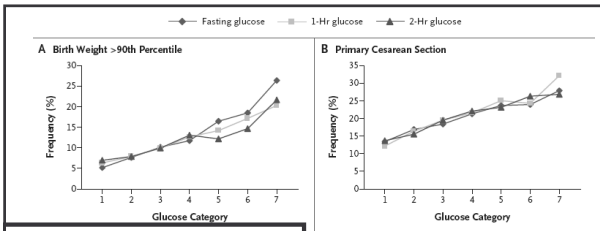
HAPO, *NEJM* 2008; 358:1991-2002

HAPO

Increasing levels of fasting, 1 and 2-h plasma glucose
- Birth weight > 90th %
- Cord blood serum C-peptide level > 90th %

Increasing plasma glucose levels
- premature delivery
- shoulder dystocia or birth injury,
- intensive neonatal care
- hyperbilirubinemia

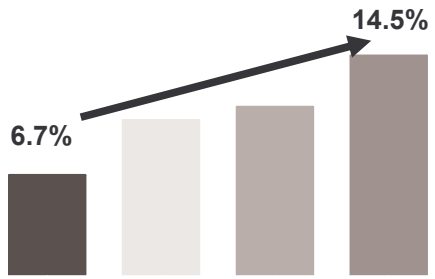
HAPO, *NEJM* 2008; 358:1991-2002



Group	FPG(mg/dL)
1	< 75
2	75-79
3	80-84
4	85-89
5	90-94
6	95-99

HAPO, *NEJM* 2008; 358:1991-2002

Mild GDM trial: LGA Infant



HAPO & Mild GDM trial

- A significant relationship exists between increasing maternal glycemia and perinatal morbidity
- Similar frequencies of morbidity among offspring of women with one abnormal OGTT value compared to untreated mild GDM
- Risk for LGA and other morbidity present at fasting and 1-hour glucose levels below current criteria for diagnosis of GDM
- Risks not significant until 2 and 3-hour values exceed Carpenter-Coustan thresholds

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International Association of Diabetes in Pregnancy Study Group (IADPG)

- New screening recommendations and diagnostic criteria based on HAPO study
- Based on pregnancy outcomes
- Cut offs based on OR for adverse outcomes

REVIEW ARTICLE

International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy

Diabetes Care Vol 33 #3, March 2010, 676-682

IADPG Diagnosis of hyperglycemia in pregnancy

Table 1—*Threshold values for diagnosis of GDM or overt diabetes in pregnancy*

To diagnose GDM and cumulative proportion of HAPO cohort equaling or exceeding those thresholds

	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†

To diagnose overt diabetes in pregnancy

Measure of glycemia	Consensus threshold
FPG‡	≥7.0 mmol/l (126 mg/dl)
A1C‡	≥6.5% (DCCT/UKPDS standardized)
Random plasma glucose	≥11.1 mmol/l (200 mg/dl) + confirmation§

*One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM. †In addition, 1.7% of participants in the initial cohort were unblinded because of FPG >5.8 mmol/l (105 mg/dl) or 2-h OGTT values >11.1 mmol/l (200 mg/dl), bringing the total to 17.8%. ‡One of these must be met to identify the patient as having overt diabetes in pregnancy. §If a random plasma glucose is the initial measure, the tentative diagnosis of overt diabetes in pregnancy should be confirmed by FPG or A1C using a DCCT/UKPDS-standardized assay.

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Diagnosis of hyperglycemia in pregnancy

Table 2—*Strategy for the detection and diagnosis of hyperglycemic disorders in pregnancy**

First prenatal visit

Measure FPG, A1C, or random plasma glucose on all or only high-risk women†
- If results indicate overt diabetes as per Table 1
  - Treatment and follow-up as for preexisting diabetes
- If results not diagnostic of overt diabetes
  - and fasting plasma glucose ≥5.1 mmol/l (92 mg/dl) but <7.0 mmol/l (126 mg/dl), diagnose as GDM
  - and fasting plasma glucose <5.1 mmol/l (92 mg/dl), test for GDM from 24 to 28 weeks' gestation with a 75-g OGTT‡

24–28 weeks' gestation: diagnosis of GDM

2-h 75-g OGTT: perform after overnight fast on all women not previously found to have overt diabetes or GDM during testing earlier in this pregnancy
- Overt diabetes if fasting plasma glucose ≥7.0 mmol/l (126 mg/dl)
- GDM if one or more values equals or exceeds thresholds indicated in Table 1
- Normal if all values on OGTT less than thresholds indicated in Table 1

*To be applied to women without known diabetes antedating pregnancy. Postpartum glucose testing should be performed for all women diagnosed with overt diabetes during pregnancy or GDM. †Decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is to be made on the basis of the background frequency of abnormal glucose metabolism in the population and on local circumstances. ‡The panel concluded that there have been insufficient studies performed to know whether there is a benefit of generalized testing to diagnose and treat GDM before the usual window of 24–28 weeks' gestation.

IADPG recommendations

- If adopted, criteria will double GDM diagnosis, 1 in 5 (18%)
- Significant impact on health resource utilization and economics
  - Expenditures would be $2.5 billion annually
- No evidence that identification and treatment of this new cohort will improve outcome

GDM screening recommendations

- ACOG evaluating data
- Consideration of NIH Consensus Conference

Conclusions: Incorporating New Data

- Increasing hyperglycemia associated with adverse pregnancy outcome
- Oral hypoglycemics an option for GDM
- Changes in GDM screening in US likely
  - May be based on pregnancy outcome
  - 1h followed by 3h vs 2h
  - Thresholds for diagnosis may change
  - Ongoing evaluation by professional bodies, consideration of NIH Consensus Conference

Objectives: Accomplished!

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Eunice Kennedy Shriver
NICHD
National Institute of Child Health
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The goal: healthy children and mothers…