

Gestational Diabetes: Detection and Management

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Gestational Diabetes: Detection and Management

Learning Objectives (cont'd):

3. Discuss the need to detect gestational diabetes in pregnancy, and methods presently in use for screening and diagnosis.
4. Explain the use of dietary therapy, the indications for insulin and oral agents (glyburide, metformin), and strategies for monitoring maternal glucose control.

Gestational Diabetes: Detection and Management

Learning Objectives:

At the conclusion of this presentation, the participant will be able to:

1. Describe the metabolic changes in pregnancy which produce a "diabetogenic stress."
2. Describe the short-term and long-term morbidities for the woman with gestational diabetes mellitus and her infant.

Diabetes Trends Among Delivery Hospitalizations in the U.S., 1994-2004

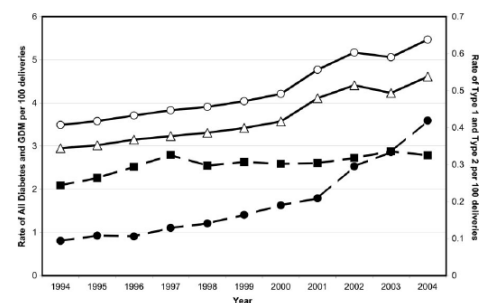


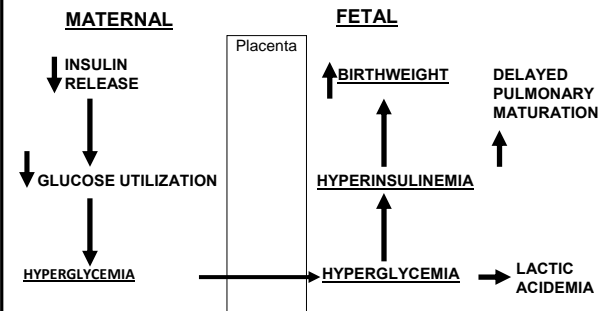
Figure 1—Trends for all diabetes (○), GDM (△), type 1 diabetes (■), and type 2 diabetes (●) among delivery hospitalizations in the U.S., 1994–2004.

Albrecht SS, et al. Diabetes Care. Apr 2010. 33:4. 768-73.

“Coming events cast their shadows before. The woman destined to develop diabetes divulges her future fate by producing infants which are dead or large”

W.P.U. Jackson, Studies in Pre-diabetes; BMJ (1952)

Effect of GDM on the Fetus



Pathophysiology of GDM

- Insulin resistance
- Impaired insulin secretion
- Increased hepatic glucose production

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. The definition applies whether insulin or diet modification is used for treatment . . . It does exclude the possibility that unrecognized glucose intolerance may leave antedated or begun concomitantly with the pregnancy.

American Diabetes Association
Fifth Int'l Workshop
Conference on GDM 2005

Consequences of Gestational Diabetes: Why Bother to Screen?

Maternal

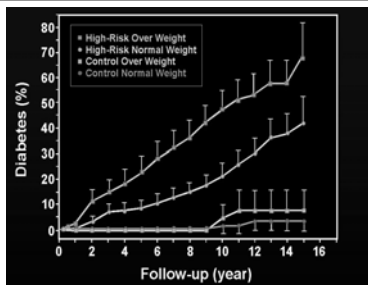
Subsequent diabetes mellitus, 35-60% with type 2 diabetes mellitus especially in first decade postpartum; shortened life expectancy

Type 2 Diabetes Mellitus After Gestational Diabetes: a Systematic Review and Meta-Analysis

“Women who have had gestational diabetes have at least a seven-fold increased risk of developing type 2 diabetes mellitus in the future compared with those who have had a normoglycaemic pregnancy.”

Bellamy L, et al. *Lancet*. May 23, 2009;373(9677):1738-40.

Incidence of Type 2 Diabetes Mellitus After Pregnancy Complicated by GDM



Cumulative incidence of diabetes in high-risk and control participants. Yellow squares indicate overweight control subjects; orange triangles, normal-weight control subjects; green squares, overweight high-risk subjects; blue triangles, normal-weight high-risk subjects.

J.B. O'Sullivan, Body Weight and Subsequent Diabetes Mellitus, *JAMA* 1982;248(8):949-52



Consequences of Gestational Diabetes: Why Bother to Screen?

Fetal and Neonatal

- Maternal hyperglycemia leads to fetal hyperglycemia and hyperinsulinemia.
- Macrosomia and trauma including shoulder dystocia; Hypoglycemia, Hypocalcemia, Hyperbilirubinemia
- Increased perinatal mortality associated with fasting hyperglycemia
- Long term morbidity: obesity, carbohydrate intolerance

Gestational Diabetes Mellitus Approaches to Screening and Diagnosis

High Risk: Clinical characteristics consistent with a high risk of GDM (severe obesity, PCOS, history of GDM or delivery of LGA infant, glycosuria, strong family history of type 2 diabetes), test as soon as possible. If negative, retest at 24-28 weeks gestation.

Note: fasting >120 mg/dL or $HbA_{1c} \geq 7\%$ indicates need for ultrasound screening for anomalies

Gestational Diabetes Mellitus Approaches to Screening and Diagnosis

Detection: All pregnant women should be screened for glucose intolerance since selective screening based on clinical attributes or past obstetric history has been shown to be inadequate.

Gestational Diabetes Mellitus Approaches to Screening and Diagnosis

Average Risk: Testing at 24- 28 weeks gestation

GDM: Approaches to Screening and Diagnosis

Low Risk:	Includes women with <u>all</u> of the following characteristics: <ul style="list-style-type: none"> • <25 years of age • Normal weight before pregnancy • No first degree relative with diabetes mellitus • Not a member of an ethnic group an increased risk for type 2 diabetes • No history of abnormal glucose metabolism • No history of poor obstetric outcome • No glucose testing required
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Gestational Diabetes Mellitus Diagnostic Criteria

Two or more of the following venous plasma concentrations must be met or exceeded:

	<u>O-Sullivan</u>	<u>NDDG</u>	<u>Carpenter/Coustan</u>
Fasting	90 mg/dL	105 mg/dL	95 mg/dL
1-hour	165 mg/dL	190 mg/dL	180 mg/dL
2-hour	145 mg/dL	165 mg/dL	155 mg/dL
3-hour	125 mg/dL	145 mg/dL	140 mg/dL

Detection

- Screening with a 50g glucose load or in high risk women, a diagnostic OGTT
- 50g oral glucose load, administered between the 24th and 28th week, without regard to time of day or time of last meal, to all pregnant women who have not been identified as having glucose intolerance before the 24th week
- Venous plasma glucose measured one hour later. Value of 130-140 mg/dL or above in venous plasma indicates the need for a full diagnostic glucose tolerance test

Hyperglycemia and Adverse Pregnancy Outcomes The HAPO Study Cooperative Research Group

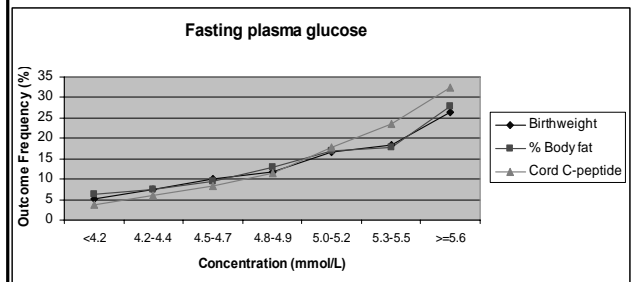
Conclusions

Our results indicate strong, continuous associations of maternal glucose levels Below those diagnostic of diabetes with Increased birth weight and increased cord-blood serum C-peptide levels.

Participants Completing an OGTT and Included in Analyses

- 75 gram, 2-hour OGTT at 24-32 weeks (avg 28 weeks)
- Venous samples at F, 1 hr, 2 hrs
- Total OGTTs: 25,505
- Unblinded: 746 (2.9%)
- Did not complete: 1,443 (5.7%)
- Analytic cohort: 23,316

What is the Nature of the Relationship between Maternal Glucose values and These Three Outcomes?



Major Outcomes

Associations of maternal glycemia with frequency of:

1. Infants with birth weight > 90th percentile for gestational age
2. Delivery by primary cesarean section
3. Clinical neonatal hypoglycemia
4. Cord C-peptide >90th percentile

Proposed Definition of GDM

Any one of the following:			<u>% GDM</u>
Fasting	92 mg/dl	alone	8.3%
1-hour	180 mg/dl	plus	5.7% = 14%
2-hour	153 mg/dl	plus	2.1% = 16.1%
		plus	1.7% = 17.8%*

*1.7% were unblinded because of FPG ≥105 mg/dl &/or 2h ≥200 mg/dl

IADPSG
Diab Care. 2010;33:676-682

Gestational Diabetes Mellitus Treatment

Mark Landon, MD
The Ohio State University Medical Center

Exercise and GDM

- A program of moderate physical exercise is recommended
- 30 minutes daily or 10 minutes after each meal

Gestational Diabetes Mellitus Treatment

- Visits every 1-2 weeks until 36 weeks; then weekly
- Dietary management:
 - ✓ 2000-2200 calorie, no-concentrated-sweets diet
 - ✓ Capillary blood glucose monitoring

Surveillance of Maternal Diabetes

- Check fasting and 1-hour or 2-hour postprandial glucose levels daily to assess efficacy of diet with self monitoring of capillary blood glucose.
- Check fasting urine ketones in patients on caloric restriction.
- If fasting capillary value > 95mg/dL and/or 1-hour value > 140 mg/dL or 2-hour value > 120mg/dL, insulin or glyburide therapy is required.

Neonatal Outcomes in Women with Weekly Office-Based Glucose Monitoring Compared with Women Using Daily Monitoring

Characteristic	Weekly (n=675)	Daily (n=315)	P
Birth weight (g)	3,690±612	3,536±603	<.001
More than 4,000 g	199 (29.5)	69 (21.9)	.013
Large for gestational age*	232 (34.4)	73 (23.1)	<.001

Hawkins JS, et. Al
Obstetrics and Gynecology, June 2009. Vol.113. No.6. 1307-1312.

Oral Agents for GDM

“In our experience, glyburide has become the first choice of our patients with GDM who require therapy beyond diet.”

Gabbe and Graves
Obstet Gynecol 2003; 102: 857

Oral Agents for GDM

“Further study is recommended before the use of newer oral hypoglycemic agents can be supported for use in pregnancy.”

ACOG Practice Bull. #30 Sept. 2001

“Glyburide... further studies are needed in a larger patient population to establish its safety.”

ADA, Position Statement
Diabetes Care 26: S103-105, 2003

Glyburide vs. Insulin

- 404 women with GDM randomized to insulin or glyburide (Micronase, DiaBeta)
- Both therapies showed comparable improvement in glucose control
 - ✓ 8% of glyburide patients required insulin
- Hypoglycemia (<40 mg/dL) more frequent with insulin (20% vs. 2%, p=0.03)
- No differences in maternal complications, cesarean delivery rate, neonatal outcomes
- Conclusion: In women with GDM, glyburide is a clinically effective alternative to insulin therapy

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

Risk Factors for Glyburide Failure

- Diagnosis of GDM before 25 weeks
- Higher baseline fasting glucose (112 mg/dL vs. 102 mg/dL)
- Maternal age (34 years vs. 29 years)
- Higher gravidity (4.3 vs. 2.7)
- Higher parity (2 vs. 1)
- Obesity

Kahn et al., *Obstet Gynecol* 2006;107:1303-9

Are We Optimizing Gestational Diabetes Treatment With Glyburide? The Pharmacologic Basis for Better Clinical Practice

- Mean umbilical cord / maternal glyburide concentration ratio was 0.7 ± 0.4

Hebert et al
Clin Pharm Therapeutics; 85:609,2009

Glyburide vs. Insulin: Summary

- Maternal fasting and postpartum glycemia is improved with glyburide Rx.
- Glyburide failure rate 15-20%.
- Glyburide failures associated with earlier dx of GDM, fasting > 110-115 mg %.
- Comparable neonatal outcomes
- Significant cost savings.

Metformin (Glucophage)

- Class B drug, decreases hepatic glucose production, crosses placenta
- In PCOS, use of metformin is associated with a 10-fold reduction in GDM (31% to 3%). (Glueck, et al. *Fertil Steril* 2002;77:250-5)
- Use in pregnancy controversial. May be continued through 12 weeks to decrease risk of miscarriage in patients with PCOS.

Metformin in Gestational Diabetes Trial (MIG)

- Prospective randomized multicenter trial
- Insulin vs. Metformin (n=750)
- Enrollment 20-33 wks gestation
- Primary outcome – composite neonatal morbidity
- Planned 2 and 5 yr. follow-up of offspring

J. Rowan et al
NEJM 2008; 358:2003

Metformin vs. Insulin for the Treatment of GDM

	Metformin (n=363)	Insulin (n=370)	p
Primary Composite	116 (32.0)	119 (32.2)	0.95
NN Hypoglycemia	55 (15.2)	69 (18.6)	0.21
RDS	12 (3.3)	16 (4.3)	0.47
Phototherapy	29 (8.0)	31 (8.4)	0.85
Trauma	16 (4.4)	17 (4.6)	0.90
Preterm Birth	44 (12.1)	28 (7.6)	0.04
Spontaneous PTB	26 (7.2)	15 (4.1)	0.07

(Rowan et al, NEJM 2008;2003-15)

Metformin vs. Insulin for the Treatment of GDM (Rowan et al, NEJM 2008;358:2003-15)

Glycemic Control (mg/dl)

	Metformin	Insulin	p
Fasting	90 ± 10.8	88.2 ± 12.6	0.16
2 hr pp	109.8 ± 12.6	111.6 ± 18.0	0.19

Metformin Versus Insulin for the Treatment of Gestational Diabetes

Conclusions

In women with gestational diabetes mellitus, metformin (alone or with supplemental insulin) is not associated with increased perinatal complications as compared with insulin. The women preferred metformin to insulin treatment.

Rowan JA, et al.
N Engl J Med 358(19):2003-15

Benefits and Risks of Oral Diabetic Agents Compared with Insulin in Women with GDM

- Overall strength of evidence from RCTs and observational studies – very low for reported maternal and neonatal outcomes
- No consistent evidence for increase in adverse maternal or neonatal outcomes with oral agents vs. insulin

(Nicholson et al, *Obstet Gynecol* 2009;113:193)

Delivery

- Allow to go to term
- If undelivered at 40 weeks, begin fetal assessment with twice weekly nonstress tests (NST): Patients who have had a previous stillbirth or have hypertension should be followed with twice weekly NSTs at 32 weeks.
- Clinical estimation of fetal size and ultrasonographic indices should be used to detect fetal macrosomia: Evaluate for cesarean delivery if estimated fetal weight $\geq 4500\text{g}$

Benefits and Risks of Oral Diabetic Agents Compared with Insulin in Women with GDM

- Obstetricians now have evidence to support use of glyburide as well as insulin in management of GDM. Metformin also appears to be effective.
- Further studies with sufficient power to detect meaningful differences in maternal and neonatal outcomes are needed.

(Nicholson et al, *Obstet Gynecol* 2009;113:193)

Delivery

- Patients with GDM who require insulin as well as diet to maintain normal glucose levels should be followed with a program of antepartum fetal surveillance identical to that used for women with pre-gestational diabetes, twice weekly NSTs.
- Infant to be observed closely for hypoglycemia, hypocalcemia, hyperbilirubinemia.

GDM: Treatment Benefit?

For the population to benefit from the diagnosis of GDM, there should be an effective treatment for the condition... there is little information regarding the effectiveness of treatment versus no treatment.

*ACOG Practice Bulletin No. 30
September 2001*

Study Design

Women with mild GDM

2 of these abnormal {
Fasting <95 mg/dl
1 hour \geq 190 mg/dl
2 hour \geq 155 mg/dl
3 hour >140 mg/dl

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes

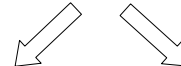
Mark B. Landon, M.D., Catherine Y. Spong, M.D., Elizabeth Thom, Ph.D.,
Marshall W. Carpenter, M.D., Susan M. Ramin, M.D., Brian Casey, M.D.,
Ronald J. Wapner, M.D., Michael W. Varner, M.D., Dwight J. Rouse, M.D.,
John M. Thorp, Jr., M.D., Anthony Sciscione, D.O., Patrick Catalano, M.D.,
Margaret Harper, M.D., George Saade, M.D., Kristine Y. Lain, M.D.,
Yoram Sorokin, M.D., Alan M. Peaceman, M.D., Jorge E. Tolosa, M.D., M.S.C.E.,
and Garland B. Anderson, M.D., for the Eunice Kennedy Shriver National
Institute of Child Health and Human Development Maternal-Fetal
Medicine Units Network*

Study Design

Women with mild GDM

2 of these abnormal {
Fasting <95 mg/dl
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Randomized to:



Study Design

Women with mild GDM

2 of these abnormal {

- Fasting <95 mg/dl
- 1 hour \geq 190 mg/dl
- 2 hour \geq 155 mg/dl
- 3 hour >140 mg/dl

Randomized to:

Treatment

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

A Prospective Multicenter Randomized Treatment Trial of Mild Gestational Diabetes

Conclusions:

- Whereas treatment of mild GDM does not reduce the frequency of several commonly observed neonatal morbidities associated with diabetic pregnancy, it does lower the risk for fetal overgrowth, shoulder dystocia, and cesarean delivery.

Landon M., et al. N Eng J Med. 2009;361:1339-48

Study Design

Women with mild GDM

2 of these abnormal {

- Fasting <95 mg/dl
- 1 hour \geq 190 mg/dl
- 2 hour \geq 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

RCTs of Treatment of GDM: Results

	MFMU ¹	ACHOIS ²
Preeclampsia	↓	↓
Weight gain	↓	↓
LGA	↓	↓
Fetal fat	↓	-
Shoulder dystocia	↓	NS

1-Landon. NEJM 2009;361:1339

2-Crowther. NEJM 2005;352:2477

Evaluation for Carbohydrate Intolerance Postpartum Care

- Check fasting or random plasma glucose, 1-3 days after delivery
- At 6-12 weeks postpartum, all patients who had carbohydrate intolerance during pregnancy (GDM) should be evaluated and reclassified as follows:

Evaluation for Postpartum Carbohydrate Intolerance

- 1 year postpartum
 - 75g 2 hour oral GTT, then every 3 years
- Annual Fasting Glucose

Evaluation for Postpartum Carbohydrate Intolerance

<u>Normal</u>	<u>Impaired</u>	<u>Diabetes Mellitus</u>
Fasting <100mg/dL	100-125 mg/dL	≥ 126 mg/dL
and	and	and
2hr <140mg/dL	2 hr ≥ 140-199mg/dL	2hr ≥ 200mg/dL

Gestational Diabetes Mellitus Key Points

1. Pregnancy has been characterized as a diabetogenic state because of increased postprandial glucose levels in late gestation.
2. GDM is an important health care problem affecting approximately 200,000 women annually. Proposed diagnostic criteria would increase this number significantly.
3. Perinatal mortality is not increased in most cases of GDM, although increased morbidity, primarily macrosomia, is found in the offspring of women with GDM.

Gestational Diabetes Mellitus Key Points

4. At the present time, universal screening for GDM using measurements of blood glucose should be performed at 24-28 weeks gestation except for women identified as low risk based on clinical attributes.
5. Recent data have helped us define the level of glycemic control which poses a risk for fetal and neonatal complications such as macrosomia.
6. The key element in treating gestational diabetes mellitus is dietary therapy. Moderate exercise is also valuable.

Gestational Diabetes Mellitus Key Points

7. Insulin or glyburide are utilized when significant fasting or postprandial hyperglycemia occurs despite dietary treatment. Metformin may also prove to be an acceptable oral agent.
8. A program of fetal surveillance is appropriate for patients with GDM requiring insulin or glyburide, or those with hypertension or a previous stillbirth.
9. Women with GDM are at high risk for developing type 2 diabetes. Regular medical evaluations are therefore recommended.