Screening for Gestational Diabetes Mellitus: Challenges and Controversies

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Disclosures

- David G. Grenache has no financial conflicts of interest to disclose

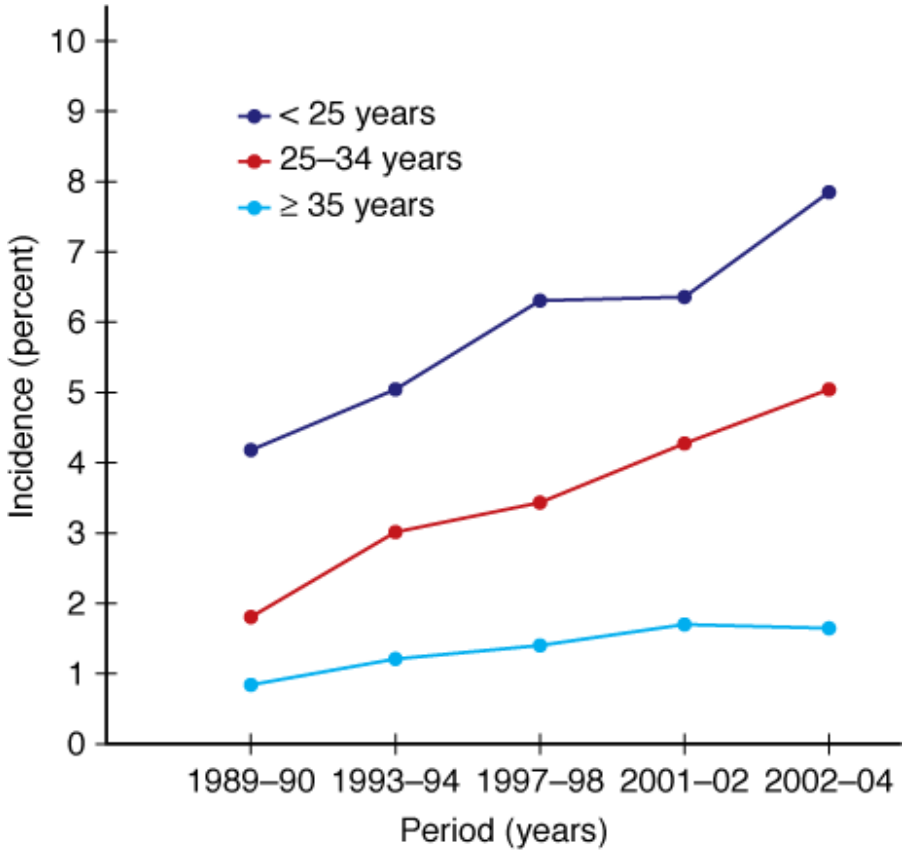
Objectives

- Describe the risk factors and adverse outcomes associated with GDM
- Explain the objective and the results of the HAPO study
- Compare and contrast recommendations for screening and diagnosing GDM

Gestational Diabetes Mellitus (GDM)

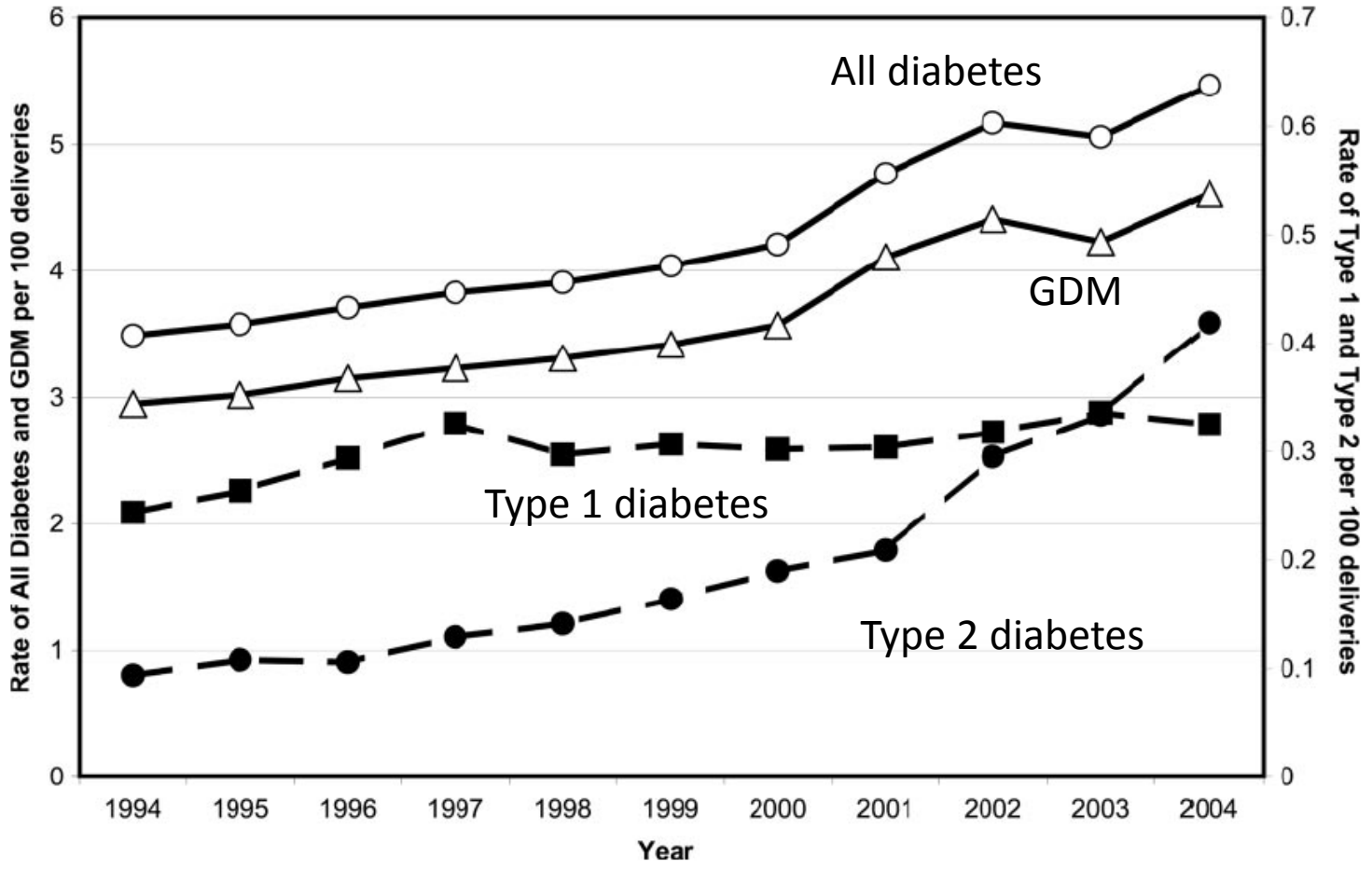
- Most frequent metabolic complication of pregnancy
- Any degree of glucose intolerance with onset or first recognition during pregnancy that is not overt diabetes
- Accounts for 90% of diabetes in pregnancy
- Affects ~7% of all pregnancies (range 1-14%)
  - Highest in ethnic groups with high frequencies of type 2 diabetes (Hispanic, African, Native America, Asian, and Pacific Island ancestry)

U.S. GDM Trends



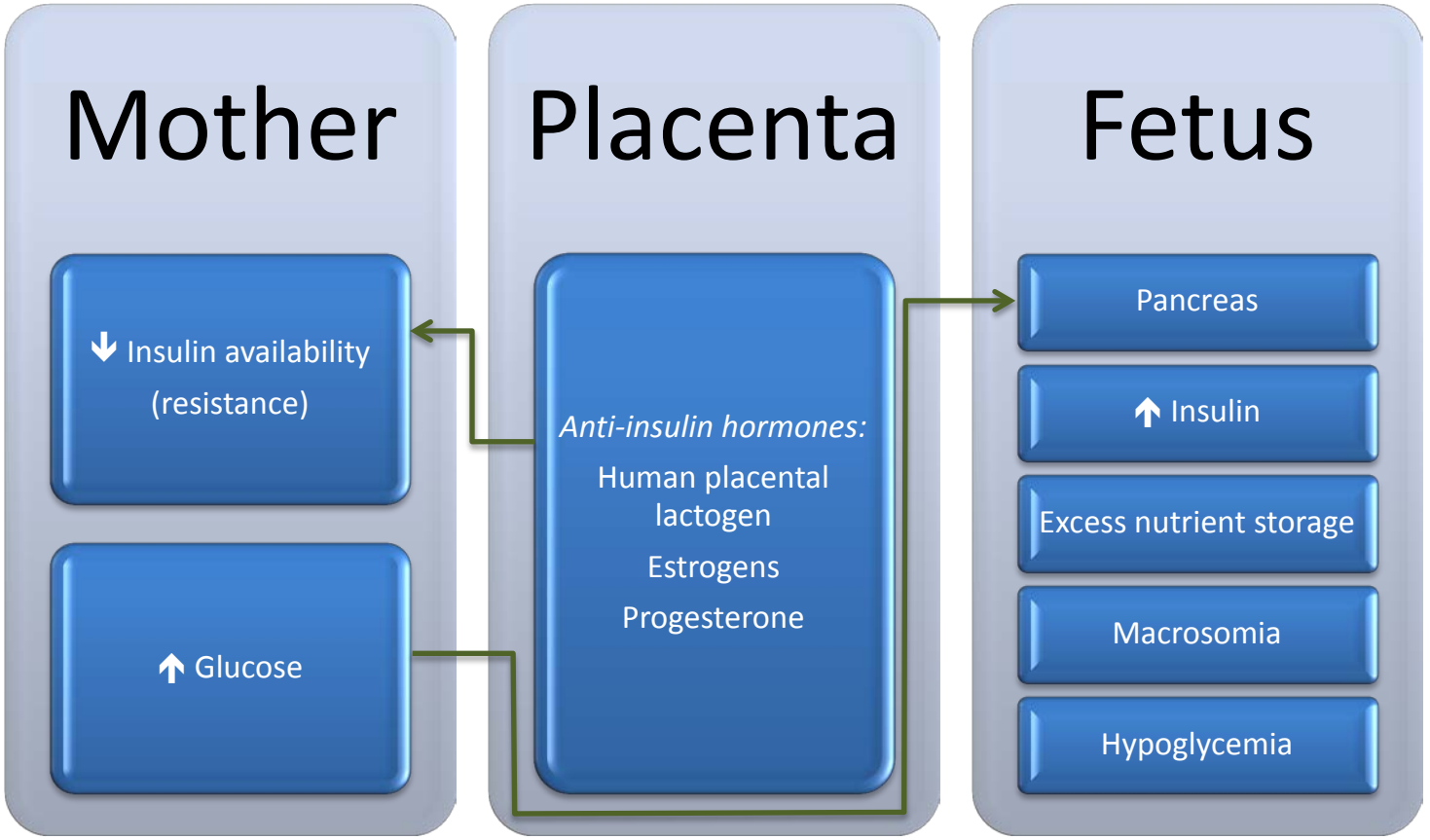
AJOG 2008;198:525.e1-5

U.S. Diabetes Trends in Pregnancy



Diabetes Care 2010;33:768–773

Pathophysiology of GDM



Consequences of GDM

Maternal Morbidity

- Hypertension
- Preeclampsia
- Increased likelihood of C-section
- Development of diabetes after pregnancy

Fetal Morbidity

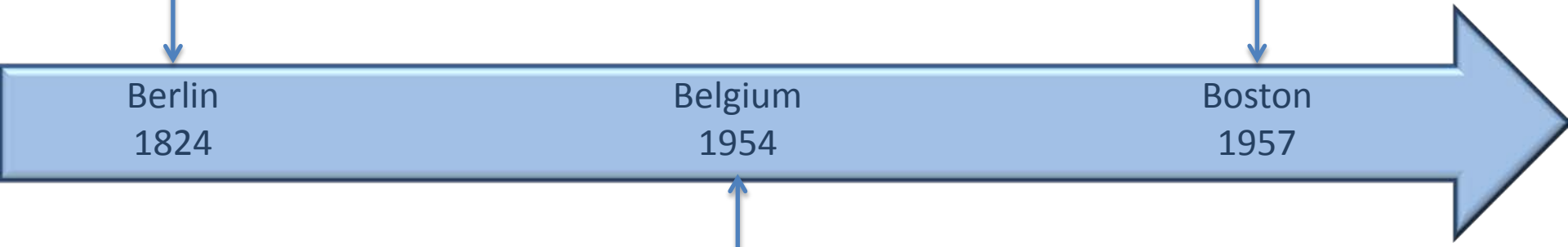
- Macrosomia (excessive birth weight)
- Neonatal hypoglycemia
- Polycythemia
- Increased perinatal mortality
- Congenital malformation
- Hyperbilirubinemia
- Respiratory distress syndrome
- Hypocalcemia

Heinrich Gottlieb Bennewitz

- First recorded case of diabetes in pregnancy
- “An unquenchable thirst, ” polyuria, glycosuria
- 12 pound infant died during delivery
- Glycosuria and large baby is “one aspect of a wider kind of disease not yet adequately researched”

Hugh Wilkerson

- Use of 50 gram 1 hour screening test (cutoff 130 mg/dL)

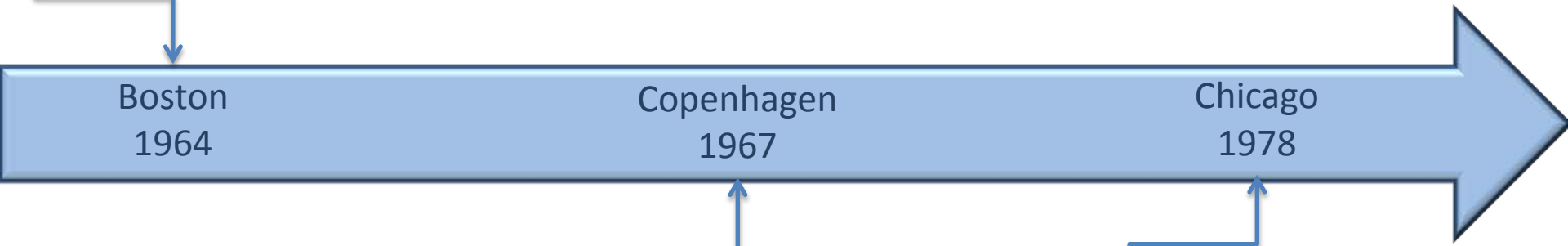


J.P. Hoet

- Published “Carbohydrate Metabolism During Pregnancy”
- Described as “metagestational diabetes”

O'Sullivan & Mahan

- 100 g 3 hour OGTT given to 752 pregnant women
- Whole blood glucose by Somogyi method
- Cutoffs established as 2 SD of the mean for each time point (predicted increased risk of diabetes after pregnancy)
  - Fasting: 90 mg/dL
  - 1 hour: 165 mg/dL
  - 2 hour: 145 mg/dL
  - 3 hour: 125 mg/dL
- Required 2 abnormal results to avoid "misclassification due to laboratory error"



Jorgen Pedersen

- "Gestational diabetes"

ACOG

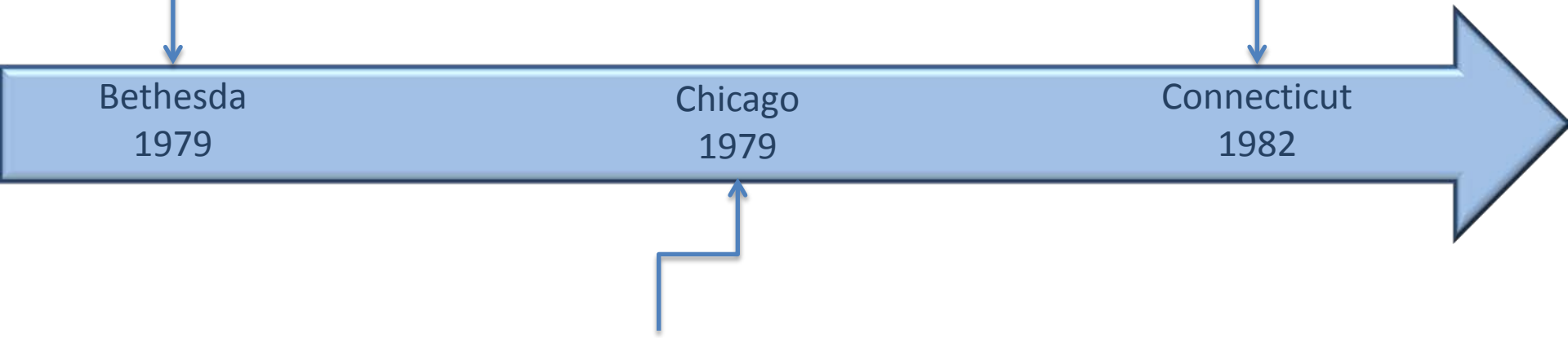
- Recommends use of O'Sullivan criteria to diagnose GDM

NDDG

- Increases O'Sullivan cutoffs by ~15% due to use of plasma/serum (not whole blood) glucose
  - Fasting: 105 mg/dL
  - 1 hour: 190 mg/dL
  - 2 hour: 165 mg/dL
  - 3 hour: 145 mg/dL

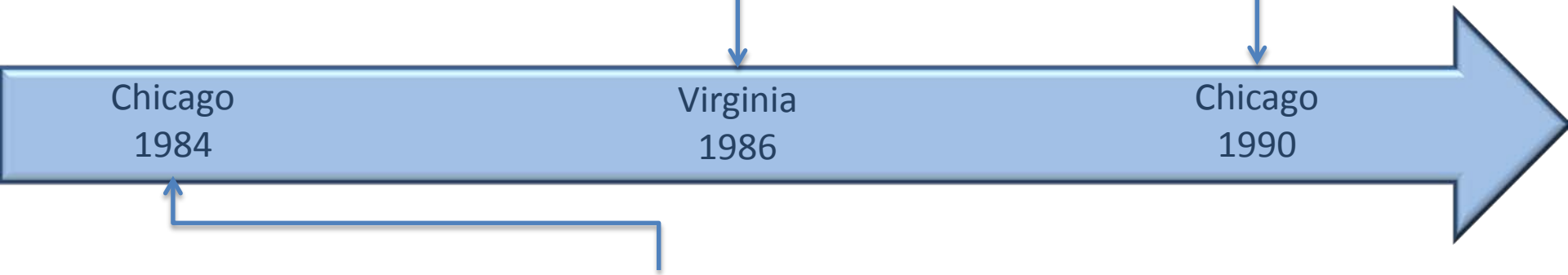
Carpenter & Coustan

- Modified O'Sullivan cutoffs to reflect use of enzymatic glucose methods (-5 mg/dL + 14%)
  - Fasting: 95 mg/dL
  - 1 hour: 180 mg/dL
  - 2 hour: 155 mg/dL
  - 3 hour: 140 mg/dL



1st International Workshop-Conference on GDM

- Universal testing at 24-28 weeks
- 100 g 3 hour OGTT with NDDG cutoffs



ADA

- Recommends 100 g 3 hour OGTT with NDDG cutoffs

3rd International Workshop-Conference on GDM

- No change in diagnostic criteria

2nd International Workshop-Conference on GDM

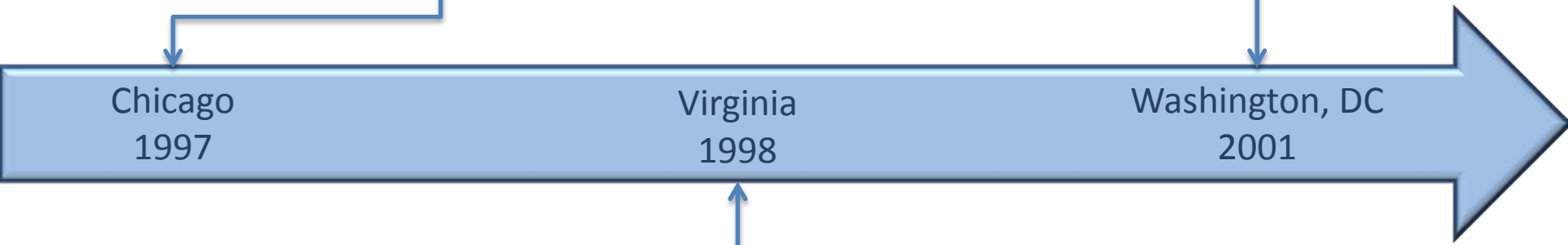
- Universal screening at 24-28 weeks
- Use 50 g 1 hour screening test (cutoff 140 mg/dL)
- 100 g 3 hour OGTT with NDDG cutoffs

4th International Workshop-Conference on GDM

- Risk-based screening strategy
- 1- or 2-step testing
  - Use 50 g 1 hour screening test (cutoff 130 or 140 mg/dL)
  - 100 g 3 hour OGTT with Carpenter/Coustan cutoffs

ACOG

- Recommends risk-based testing and 1- or 2-step testing
  - Use 50 g 1 hour screening test (cutoff 130 or 140 mg/dL)
  - 100 g 3 hour OGTT with NDDG or Carpenter/Coustan cutoffs



ADA

- Adopts recommendations of 4th IWC on GDM

5th International Workshop-Conference on GDM

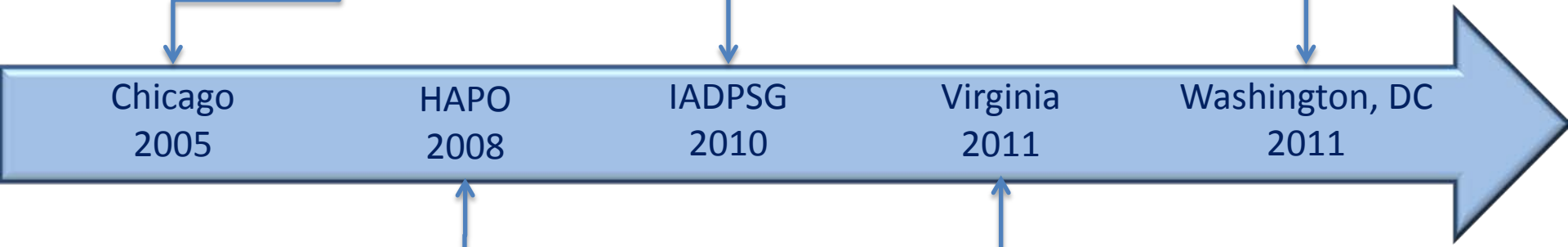
- No change in diagnostic criteria

International Association of Diabetes and Pregnancy Study Groups

- Publishes revised GDM testing protocol based on HAPO study

ACOG

- Reaffirms its 2001 guideline



Hyperglycemia and Adverse Pregnancy Outcome Study Cooperative Research Group

- Publishes results of its 6-year study

ADA

- Adopts IADPSG recommendations

GDM Testing Protocols

WHO	ACOG	ADA (pre-2011)	ADA (2011)
Test all pregnant women at 24-28 weeks	Test is risk-based	Test is risk-based	Test all pregnant women without overt diabetes at 24-28 weeks
1-step	2-step (2 versions)	1-step or 2-step	1-step
75 g glucose, exceeds 1 of the following: Fasting: ≥110 2 h: ≥140 and <200	50 g glucose, exceeds 130-140 *AND* 100 g glucose, exceeds 2 of the following: Fasting: ≥95 1 h: ≥180 2 h: ≥155 3 h: ≥140	100 g glucose, exceeds 2 of the following: Fasting: ≥95 1 h: ≥180 2 h: ≥155 3 h: ≥140	75 g glucose, exceeds 1 of the following: Fasting: ≥92 1 h: ≥180 2 h: ≥153
	50 g glucose, exceeds 130-140 *AND* 100 g glucose, exceeds 2 of the following: Fasting: ≥105 1 h: ≥190 2 h: ≥165 3 h: ≥145	50 g glucose, exceeds 130-140 *AND* 100 g glucose, exceeds 2 of the following: Fasting: ≥95 1 h: ≥180 2 h: ≥155 3 h: ≥140	

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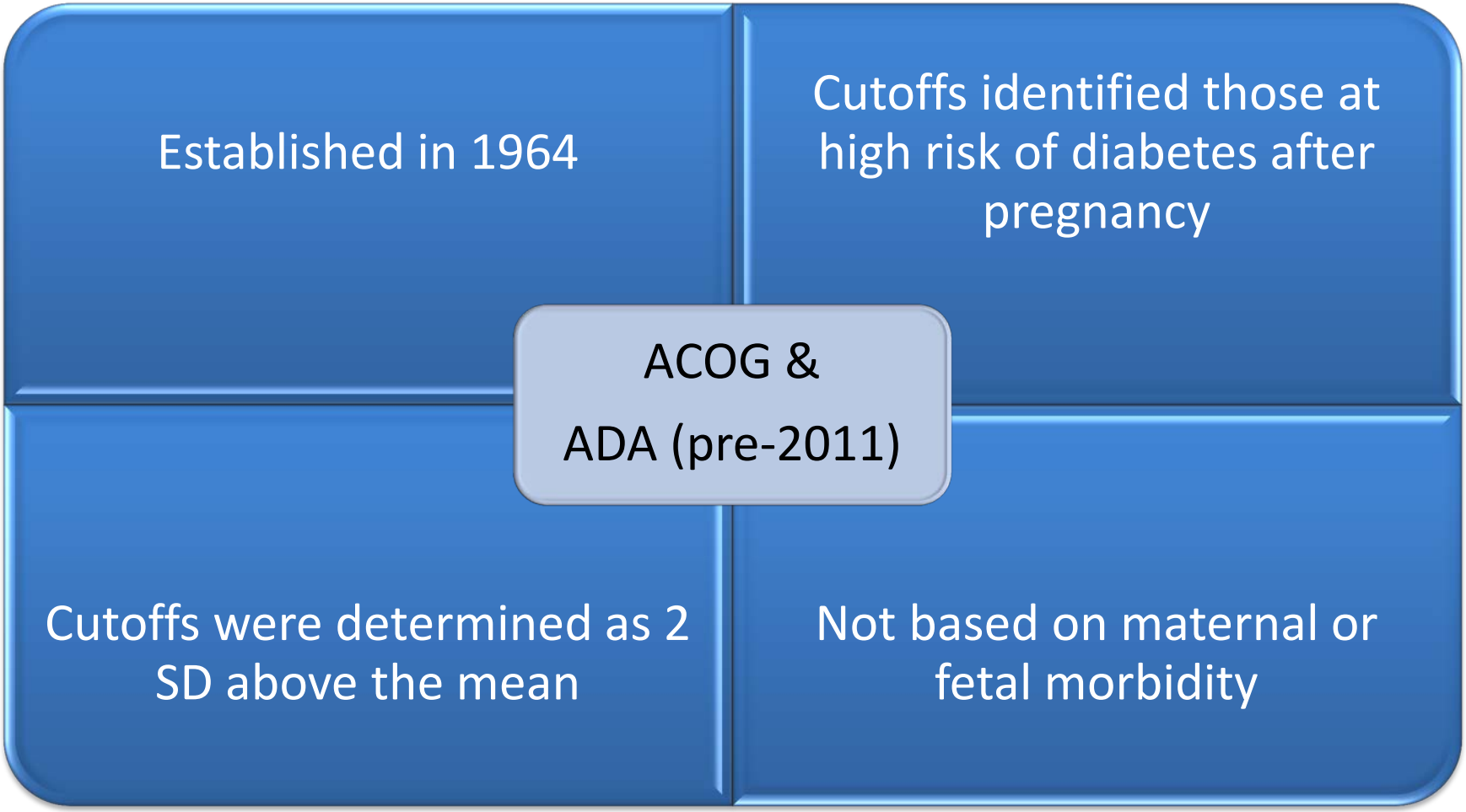
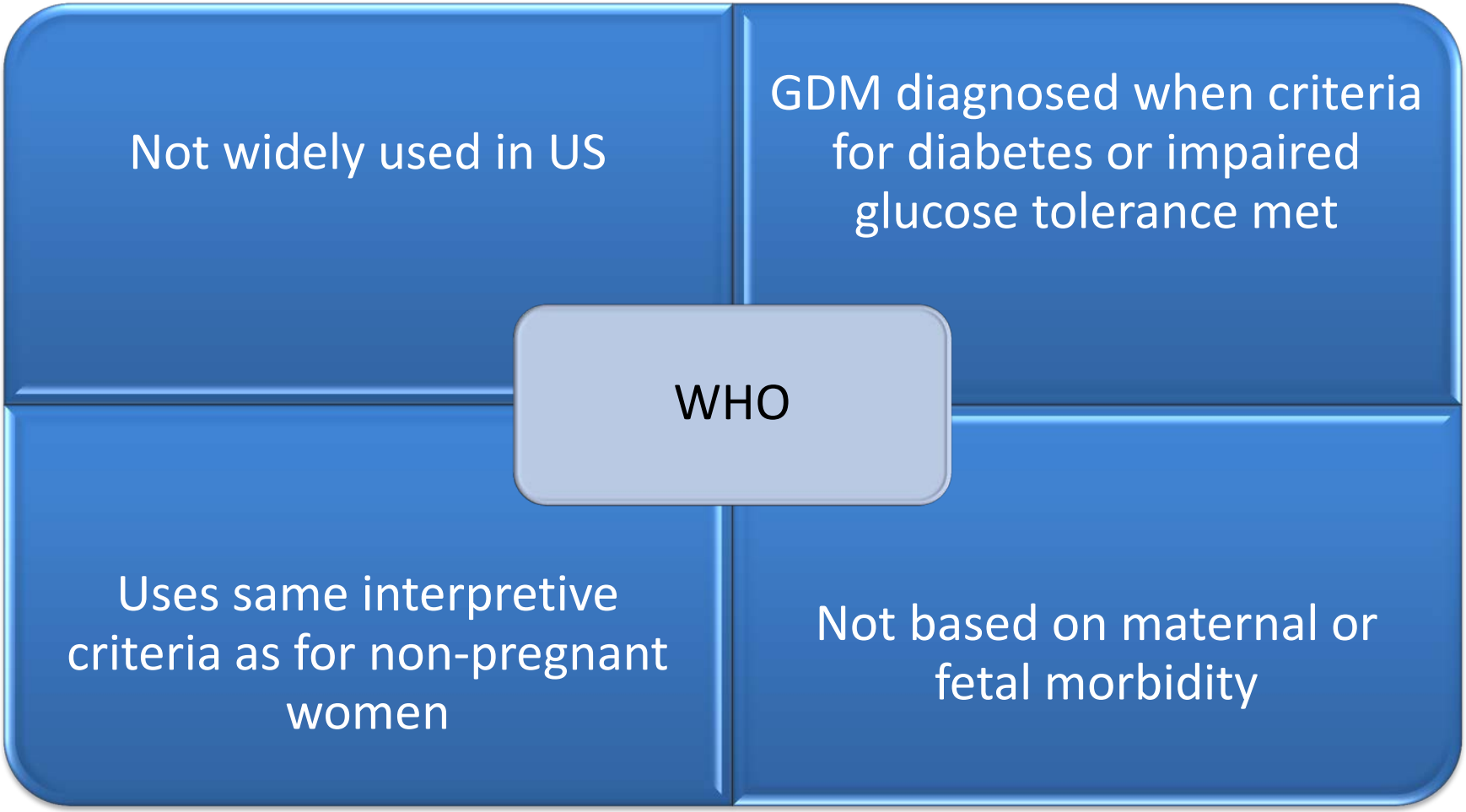
Risk-based Testing

Low Risk	Average Risk	High Risk
• Of ethnic group with low GDM prevalence • No diabetes in 1st degree relatives • Age <25 years • Weight normal before pregnancy • No history of abnormal glucose metabolism • No history of poor obstetric outcome	• Not low or high risk	• Severe obesity • Strong family history of type 2 diabetes • History of GDM, impaired glucose metabolism, or glucosuria
No need to test	Test at 24-28 weeks	Test immediately

Protocol Limitations



Protocol Limitations



Protocol Limitations

- No universal protocol
- Impossible to compare different studies of GDM
- What is the true prevalence of GDM?
- What are the risks associated with maternal hyperglycemia?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 8, 2008 VOL. 358 NO. 19

Hyperglycemia and Adverse Pregnancy Outcomes

The HAPO Study Cooperative Research Group*

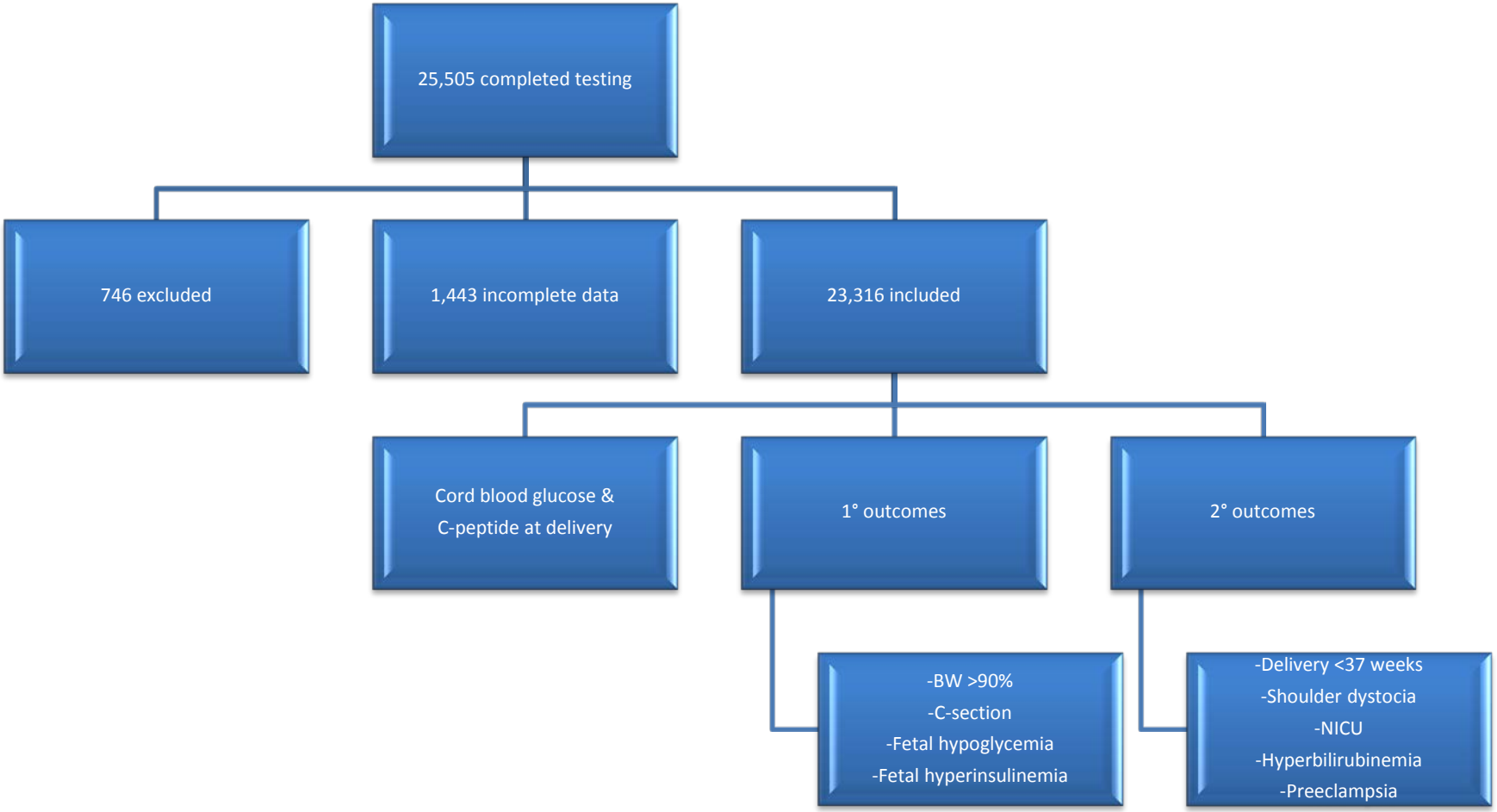
Objective: to clarify the risks of adverse outcomes associated with various degrees of maternal glucose intolerance less severe than that in overt diabetes mellitus

HAPO Study

- 23,316 pregnant women without overt diabetes
- 15 centers in 9 countries over 6 years (July 2000 – April 2006)
- 75 g OGTT at 24 – 32 weeks
- Random glucose at 34 – 37 weeks
- Excluded
  - Fasting OGTT >105 mg/dL
  - 2 h OGTT >200 mg/dL
  - Random glucose ≥160 or <45 mg/dL

NEJM 2008;358:1991-2002

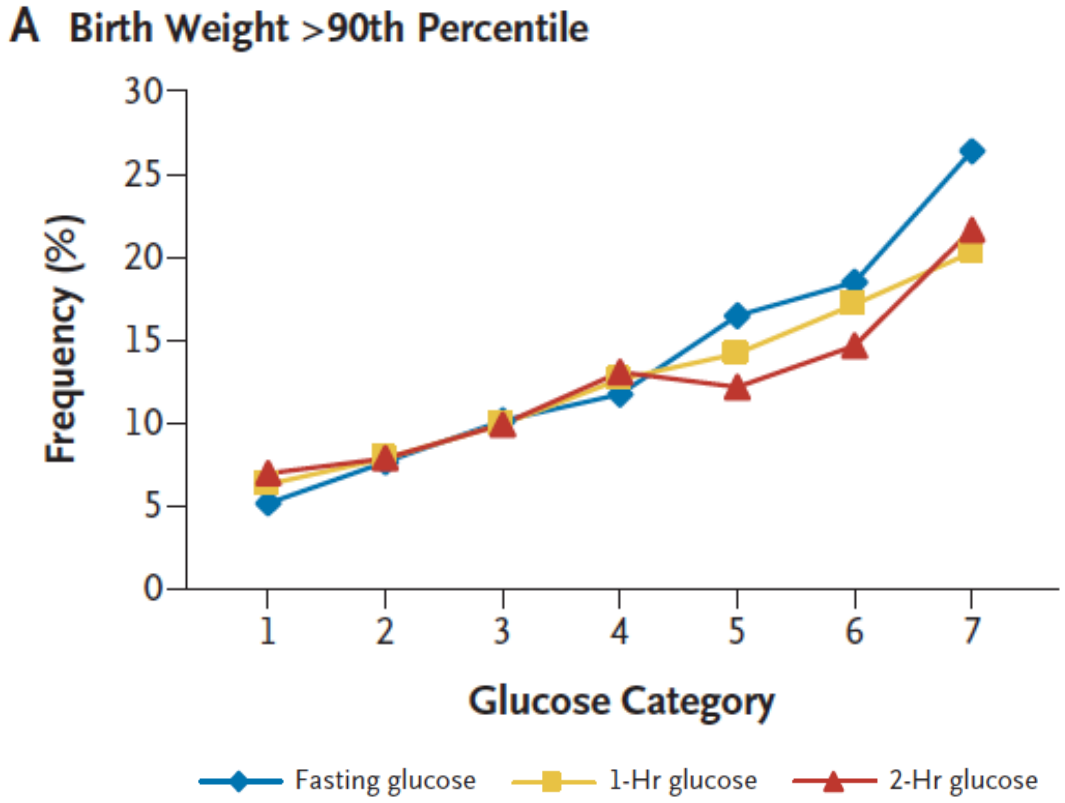
HAPO Study



NEJM 2008;358:1991-2002

1° Outcome:

Birth weight >90th Percentile

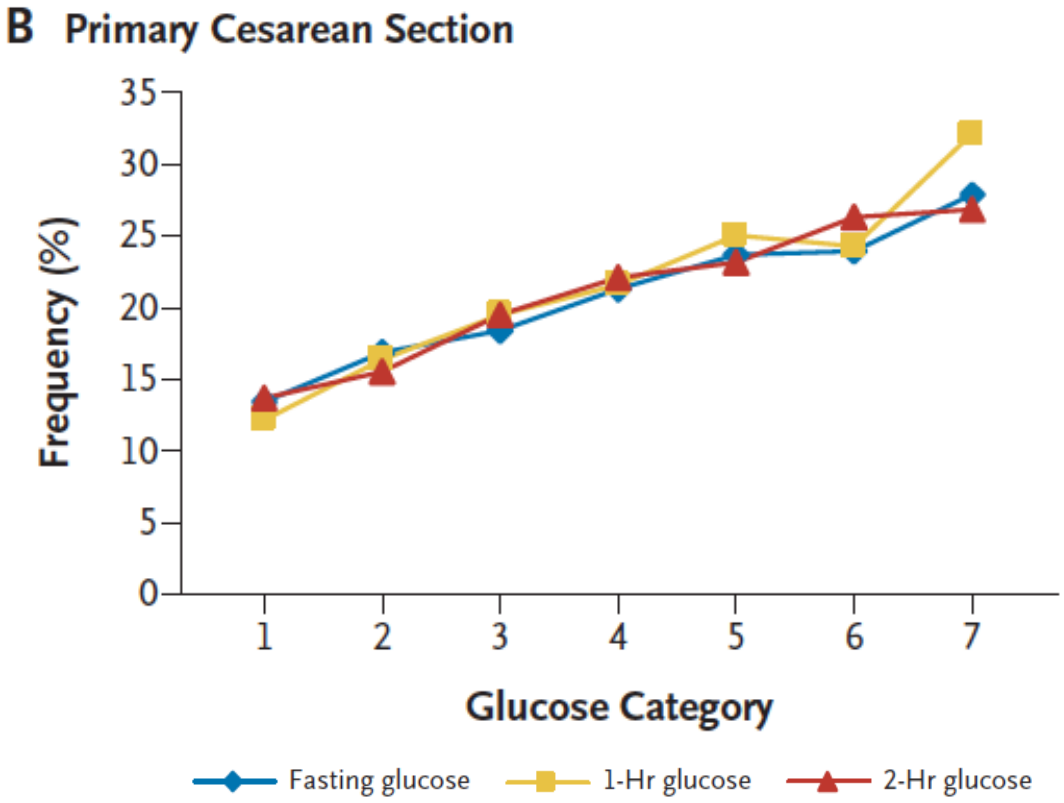


Category	Fasting (mg/dL)	1 hour (mg/dL)	2 hour (mg/dL)
1	<75	≤105	≤90
2	75-79	106-132	91-108
3	80-84	133-155	109-125
4	85-89	156-171	126-139
5	90-94	172-193	140-157
6	95-99	194-211	158-177
7	≥100	≥212	≥178

NEJM 2008;358:1991-2002

1° Outcome:

C-section



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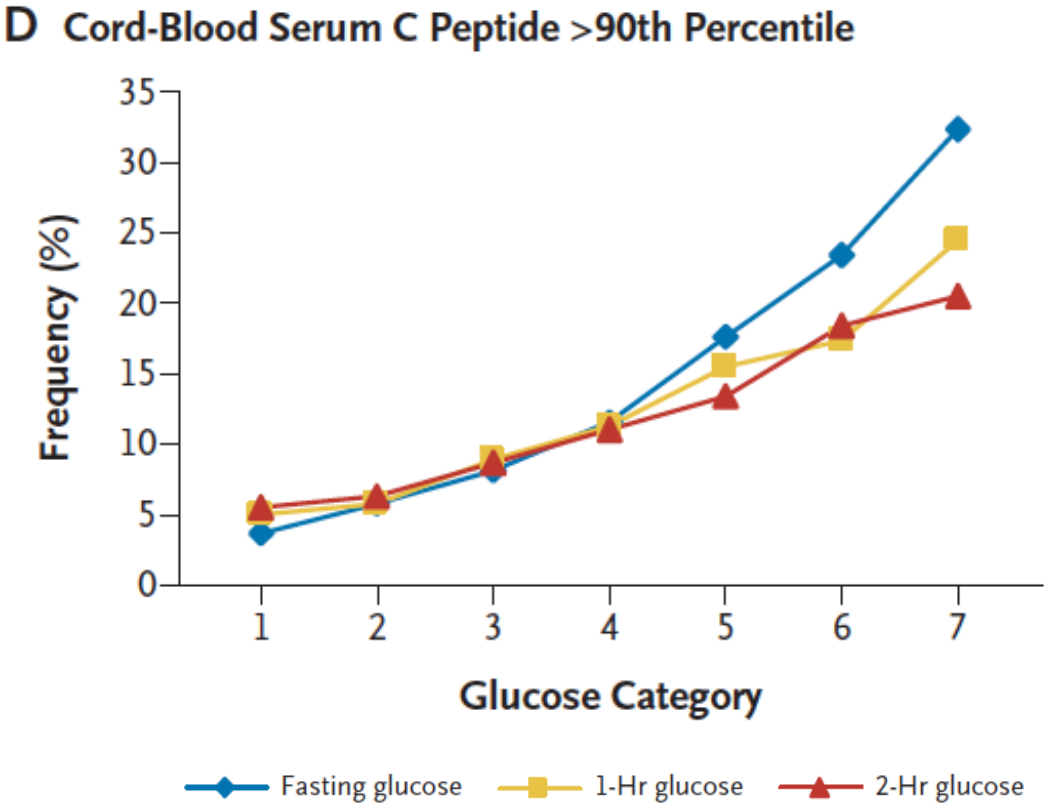
NEJM 2008;358:1991-2002

1° Outcome:

Fetal Hyperinsulinemia



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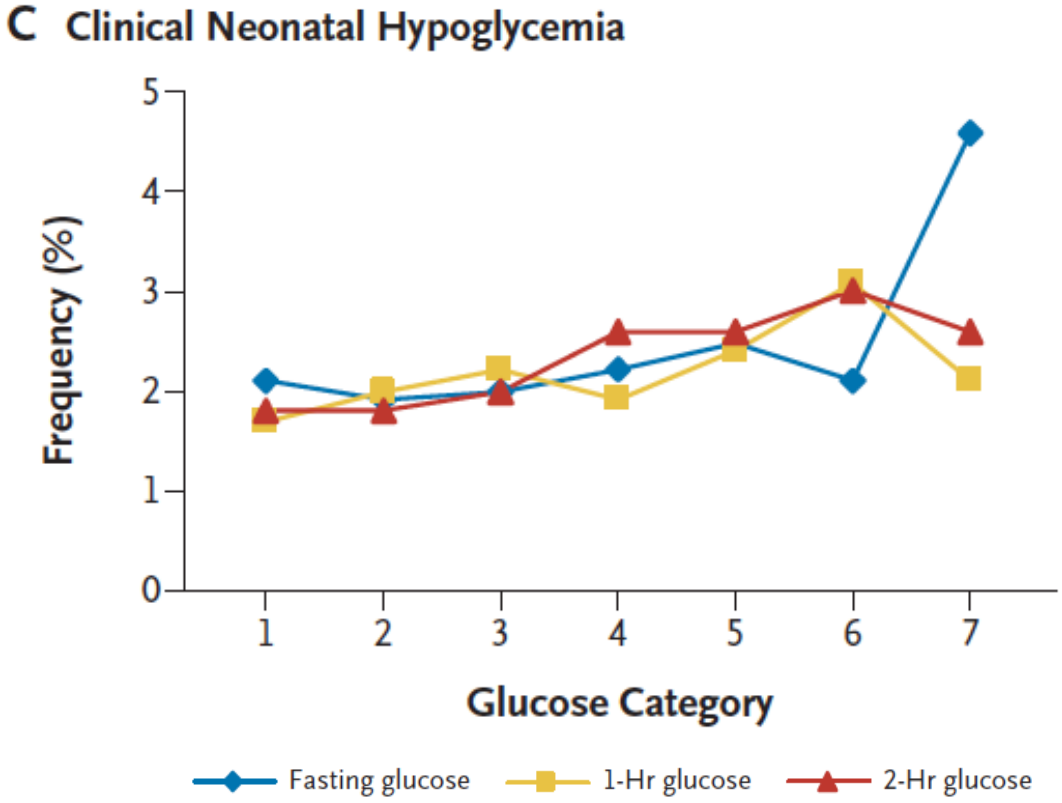
NEJM 2008;358:1991-2002

1° Outcome:
Neonatal Hypoglycemia



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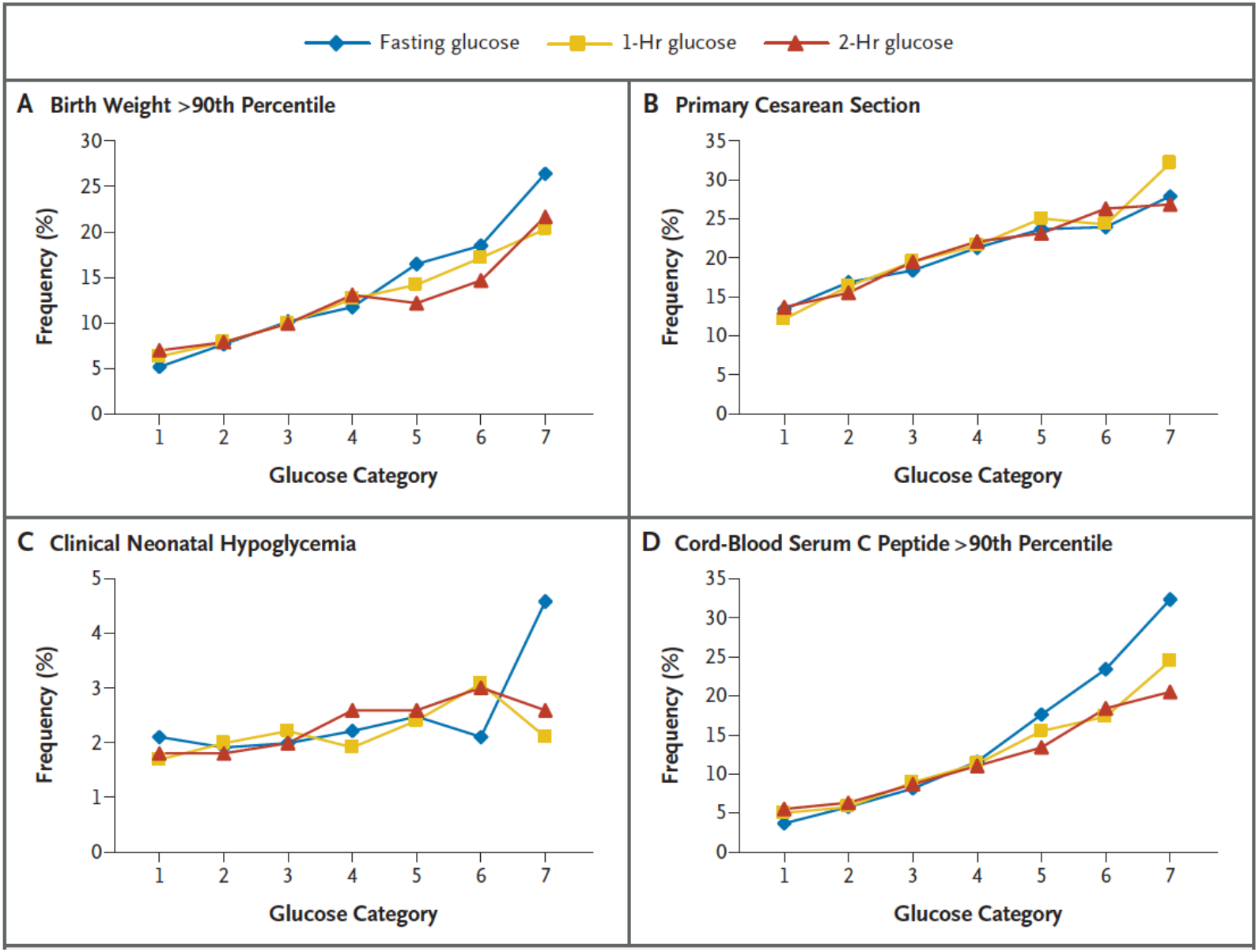


NEJM 2008;358:1991-2002

Maternal Glucose as Continuous Variable: Primary Outcomes

Primary outcome	Odds Ratios		
	Fasting	1 hour	2 hour
Birth weight >90th percentile	1.38	1.46	1.38
Primary C-section	1.11	1.10	1.08
Neonatal hypoglycemia	1.08*	1.13	1.10*
Cord C-peptide >90th percentile	1.55	1.46	1.37

*Not significant

NEJM 2008;358:1991-2002

Maternal Glucose as Continuous Variable: Secondary Outcomes

Secondary outcome	Odds Ratios		
	Fasting	1 hour	2 hour
Delivery <37 weeks	1.05*	1.18	1.16
Shoulder dystocia or birth injury	1.18	1.23	1.22
NICU	0.99*	1.07	1.09
Hyperbilirubinemia	1.00*	1.11	1.08
Preeclampsia	1.21	1.28	1.28

*Not significant

NEJM 2008;358:1991-2002

HAPO Conclusions

- Strong, continuous associations with maternal glucose and increased birth weight and neonatal hyperinsulinemia
- Broad inclusion criteria and geographic diversity supports the development of universal outcome-based criteria for classifying glucose metabolism in pregnancy
- No obvious risk cutoffs make translating results into clinical practice challenging
- Current criteria for diagnosing hyperglycemia during pregnancy need to be reconsidered

Consensus Needed for New Criteria

- International Association of Diabetes in Pregnancy Study Groups (IADPSG)
- 2008 conference to review HAPO and related studies data
- Establish new diagnostic criteria for GDM

Diabetes Care 2010;33:676-682

Establishing IADPSG Cutoffs

- Reference values needed to evaluate potential cutoffs
  - Mean glucose for entire HAPO cohort selected
    - Fasting: 80.9 mg/dL
    - 1 hour: 134.1 mg/dL
    - 2 hour: 111.0 mg/dL

- Determined mean glucose concentrations at which the odds for three specific outcomes reached 1.75 times the reference values
  - Birth weight >90th percentile
  - Cord C-peptide >90th percentile
  - Percent body fat >90th percentile

Diabetes Care 2010;33:676-682

IADPSG Cutoffs

Time relative to 75 g OGTT	Glucose (mg/dL)	Above cutoff (%)	Above cutoff (cumulative %)
Fasting	92	8.3	8.3
1 hour	180	5.7	14.0
2 hour	153	2.1	16.1

- One or more cutoffs must be equaled or exceeded to make a diagnosis of GDM
- 16.1% of HAPO cohort diagnosed with GDM using these cutoffs
  - Increases to 17.8% when those excluded by study design are considered

Diabetes Care 2010;33:676-682

Outcome Frequency by IADPSG Criteria

Outcome	All results <cutoffs (%)	One or more result ≥cutoff (%)
Primary C-section	16.8	24.4*
Cord C-peptide >90th percentile	6.7	17.5*
Percent body fat >90th percentile	8.5	16.6*
Birth weight >90th percentile	8.3	16.2*
Hyperbilirubinemia	8.0	10.0*
Delivery <37 weeks	6.4	9.4*
NICU	7.8	9.1**
Preeclampsia	4.5	9.1*
Neonatal hypoglycemia	1.9	2.7**
Shoulder dystocia/birth injury	1.3	1.8**

*p<0.001 **p<0.01

Diabetes Care 2010;33:676-682

IADPSG GDM Detection Strategy

Fasting glucose, random glucose, or Hb A1c at 1st prenatal visit

Fasting ≥126 mg/dL or Random ≥200 mg/dL or HbA1c ≥6.5%	Fasting ≥92 mg/dL and <126 mg/dL	Fasting <92 mg/dL
Overt diabetes	GDM	75 g 2 hour OGTT at 24-28 weeks

Diabetes Care 2010;33:676-682

POSITION STATEMENT

Diagnosis and Classification of Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

Table 4—Screening for and diagnosis of GDM

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 h, at 24-28 of weeks gestation in women not previously diagnosed with overt diabetes.
The OGTT should be performed in the morning after an overnight fast of at least 8 h.
The diagnosis of GDM is made when any of the following plasma glucose values are exceeded ● Fasting: ≥92 mg/dl (5.1 mmol/l) ● 1 h: ≥180 mg/dl (10.0 mmol/l) ● 2 h: ≥153 mg/dl (8.5 mmol/l)

Diabetes Care 2011;34(Suppl 1):562-569

The American College of Obstetricians and Gynecologists

Women's Health Care Physicians

COMMITTEE OPINION

Number 504 • September 2011

Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Screening and Diagnosis of Gestational Diabetes Mellitus

- Continues to recommend a 2-step approach to screening and diagnosis
  1. IADPSG criteria more than doubles the incidence of GDM
  2. No evidence its use would produce clinically significant improvements in maternal and neonatal outcomes
  3. Would significantly increase in health care costs

ACOG vs. IADPSG

ACOG (2-step)	IADPSG (1-step)
50 g 1 h >130-140 mg/dL	No screen
100 g 3 h OGTT Fasting: ≥95 1 h: ≥180 2 h: ≥155 3 h: ≥140 (2 or more above cutoff)	75 g 2 h OGTT Fasting: ≥92 1 h: ≥180 2 h: ≥153 (1 or more above cutoff)
~4-7% GDM	~18% GDM

GDM Treatment and Outcomes

- Is there evidence that use of the IADPSG protocol would produce clinically significant improvements in maternal and neonatal outcomes?

1. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group
   - To determine whether treatment of GDM reduced the risk of perinatal complications

2. National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network Study
   - To determine whether treatment of women with mild GDM reduces perinatal and obstetrical complications

ACHOIS Design

1,000 pregnant women at 24-34 weeks

(GDM risk factors or abnormal 50 g 1 hour test)

WHO OGTT (75 g 2 hour test)

Fasting: <140 mg/dL

2 hour: 140-198 mg/dL

Intervention group (N=490)	Control group (N=510)
Self-glucose monitoring Diet counseling Insulin to keep fasting/pre-meal glucose <99 mg/dL	Routine care (replicated clinical care in which screening for GDM is not available)

NEJM 2005;352:2477-2486

ACHOIS Results

(partial list)

Outcome	Intervention group	Control group	P
Birth weight (g)	3,351 ± 551	3,482 ± 660	<0.001
Birth weight >90th percentile (%)	13	22	<0.001
Macrosomia (%)	10	21	<0.001
Preeclampsia (%)	12	18	0.02
Hypoglycemia requiring therapy (%)	7	5	0.16

NEJM 2005;352:2477-2486

NICHD-MFMU Study

19,665 pregnant women at 24-30 weeks

(Abnormal 50 g 1 hour test)

7,298 completed 100 g 3 h OGTT

900 with "mild" GDM

Fasting: <95 mg/dL *and* ≥2 timed results abnormal

1 h: >180 mg/dL 2 h: >155 mg/dL 3 h: >140 mg/dL

Treatment group (N=460)

Nutrition counseling/diet therapy

Insulin (if required)

Control group (N=440)

Usual prenatal care

NEJM 2009;361:1339-1348

NICHG-MFMU Results

(partial list)

Outcome	Treatment group	Control group	P
Birth weight (g)	3,302 ± 502	3,408 ± 589	<0.001
Birth weight >90th percentile (%)	7.1	14.5	<0.001
Macrosomia (%)	5.9	14.3	<0.001
Preeclampsia (%)	2.5	5.5	0.02
C-section (%)	26.9	33.8	0.02
C-peptide >90th percentile (%)	17.7	22.8	0.07
NICU (%)	9.0	11.6	0.19

NEJM 2009;361:1339-1348

Summary of Outcome & Interventional Studies

HAPO outcome by IADPSG criteria (all were significant)	ACHOIS	MFMU
C-section	↔	↓
Cord C-peptide >90th percentile	Not evaluated	↔
Increased infant body fat	Not evaluated	↓
Birth weight >90th percentile	↓	↓
Hyperbilirubinemia	Not evaluated	↔
Delivery <37 weeks	Not evaluated	↔
NICU	Not evaluated	↔
Preeclampsia	↓	↓
Neonatal hypoglycemia	↔	↔
Shoulder dystocia/birth injury	↔	↓

Is the use of the IADPSG protocol cost-effective?

- Two studies have addressed cost-effectiveness of IADPSG protocol

1. IADPSG is cost-effective when post-delivery care reduces likelihood of future diabetes
   - Werner, EF, et al. *Diabetes Care* 2012;35:529–535

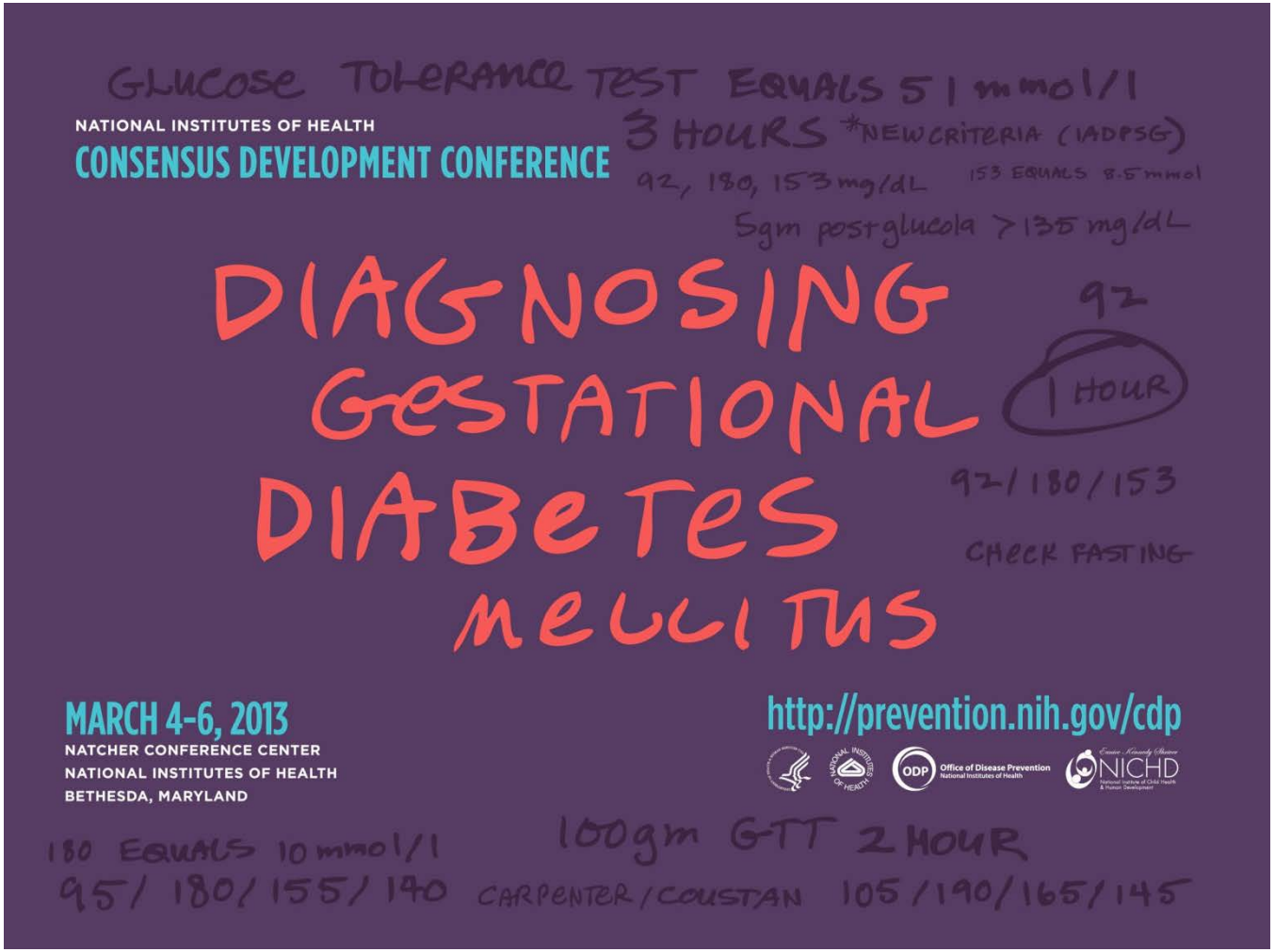
2. IADPSG screening is more expensive but is cost-effective in improving maternal and neonatal outcomes
   - Mission JF, et al. *AJOG* 2012;207:326.e1–9

IADPSG: Pros and Cons

Arguments in favor	Arguments against
• ACOG protocol not outcome-based	• OGTT has poor reproducibility, especially with minor degrees of glucose elevations
• Striking increase in obesity and type 2 diabetes in general population corresponds to GDM incidence of ~20%	• Even with strict cutoffs, a minority of fetal macrosomia will be identified
• Treatment of GDM improves outcomes	• Overdiagnosis of GDM will result in overtreatment
• Treatment of GDM is generally life-style modifications (diet, exercise) with insulin treatment needed in only ~10%	• Stricter OGTT criteria will result in increased workload
• Cost-effective	

AJOG in press (http://dx.doi.org/10.1016/j.ajog.2012.10.881)

Coming to Consensus



Laboratory Considerations

Which Protocol to Offer

- No consensus on which approach is best
- Get input of physicians
- May find it necessary to offer both

OGTT Management

- 4 OGTT protocols to manage
  - ADA for diabetes outside of pregnancy (75 g, fasting & 2 hour glucose)
  - ADA for GDM (75 g, fasting, 1, and 2 hour glucose)
  - ACOG GDM screening test (50 g, 1 hour glucose)
  - ACOG GDM diagnostic test (100 g, fasting, 1, 2, and 3 hour glucose)
- Test ordering errors
- Result reporting challenges
- Patient safety concerns

Measurement of Glucose

- Per IADPSG:
  - Measure measure plasma or serum glucose using an enzymatic method with high accuracy and precision
  - Requires proper sample collection and processing to minimize pre-analytic glycolysis
  - Capillary and plasma glucose concentrations are not interchangeable and conversion factors do not accurately estimate equivalent values

- In other words:
  - Don’t use a glucose meter
  - Be aware of pre-analytic sources of variation
  - Don’t use capillary samples (again, no glucose meters)

Alternative Approaches?

- Hb A1c
  - Evaluated in HAPO
  - Not a useful alternative to OGTT

- Jelly beans for GDM screening (AJOG 1999;181:1154–1157)
  - 50 g glucose beverage is intensely sweet
    - 15-20% of patients experience nausea and vomiting (voids test)
  - 28 Brach's No. 110 jelly beans = 50 g glucose
  - Poor sensitivity compared to beverage (40 vs. 80%, respectively)

Summary

- The incidence of GDM is steadily increasing
- Clear associations between maternal hyperglycemia and adverse outcomes
- Treatment of GDM improves maternal and fetal outcomes
- Three protocols for identifying GDM with current lack of consensus regarding ideal method