Comparison of Two Screening Strategies for Gestational Diabetes (GDM^2) Trial: Design and Rationale

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Gestational Diabetes Mellitus (GDM)

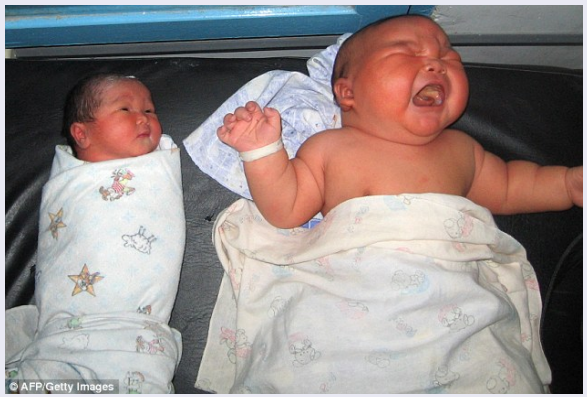
- A diabetes that occurs during pregnancy and affects approximately 5-7% of U.S. pregnancies annually. [3,7]
- Commonly diagnosed in US using a two-step screening and confirmatory diagnostic approach
- Typical therapy: dietary changes, blood glucose monitoring, and either insulin therapy or oral medications [3, 4]
- But if left untreated...

Maternal Complications

- Cesarean delivery (40%)
- Pre-eclampsia (17%)
- Shoulder dystocia (1.5%)
- Sever lacerations (2%)

Neonatal Complications

- Macrosomia (8%)
- Preterm birth (14%)
- NICU admission (12%)
- Hypoglycemia (11%)
- Hyperbilirubinemia (7%)
- RDS (4%)



Two-Step (CC) Approach

- Considered the gold standard
  1. screens pregnant women btw 24-28 weeks GA w/ non-fasting 1hr 50gm GCT
  2. If GCT $>$ 130 mg/dl $\Rightarrow$ women undergo a fasting 3 hr 100 gm OGTT test
  3. If $\geq$2 of the values are abnormal $\Rightarrow$ GDM diagnosis made

Carpenter Coustan criteria	
Fasting	≥ 95 mg/dl,
1hr	≥ 180 md/dl
2hr	≥ 155 mg/dl
3hr	≥ 140mg/dl
GDM dx: ≥ 2 values abnormal	

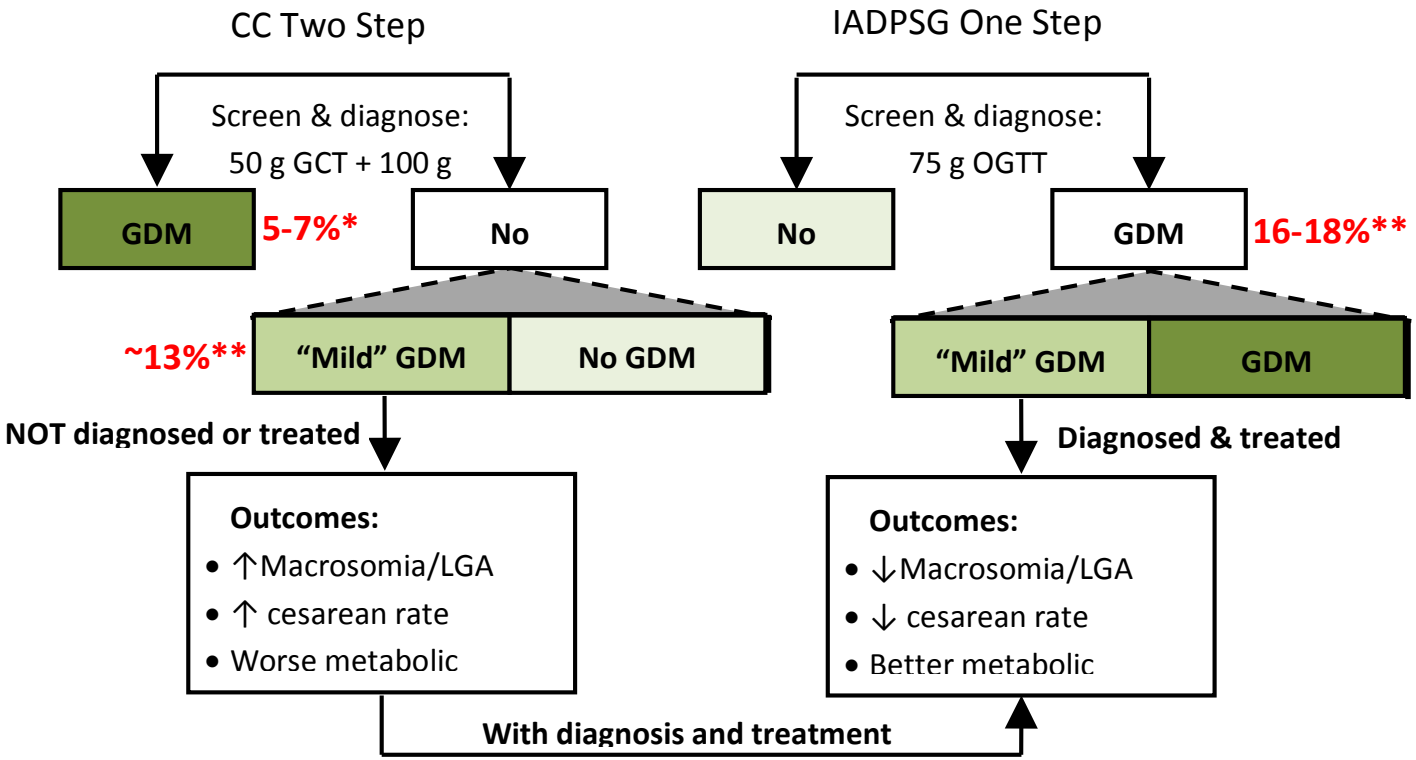
One-Step (IADPSG) Approach

- screens pregnant women btw 24-28 weeks GA with a fasting 2hr 75gm diagnostic test
  1. Eliminates non-fasting 1hr 50gm GCT
  2. If $\geq$1 of the values are abnormal $\Rightarrow$ GDM diagnosis made

IADPSG criteria	
Fasting	≥ 92 mg/dl
1hr	≥ 180 mg/dl
2hr	≥ 153 mg/dl
GDM dx: ≥ 1 value abnormal	

- In 2009, the International Association of Diabetes and Pregnancy Study (IADPSG) recommended replacing the current two-step approach with the one-step approach

Motivation for GDM^2 Trial



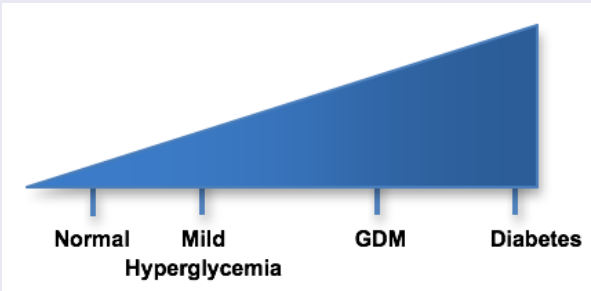
Hypothesis: Women with "mild" GDM would be diagnosed and treated in 1 step approach; consequently they will have better outcomes.
The GDM group in the 2 step approach would still be picked up in the 1 step approach, and thus diagnosed & treated.

*GDM prevalence

**estimated prevalence

Why not adopt the One-Step approach?

- Advantages:
  1. identification of GDM earlier in the disease spectrum
  2. improved perinatal outcome
  3. prevention of long-term metabolic dysfunction.

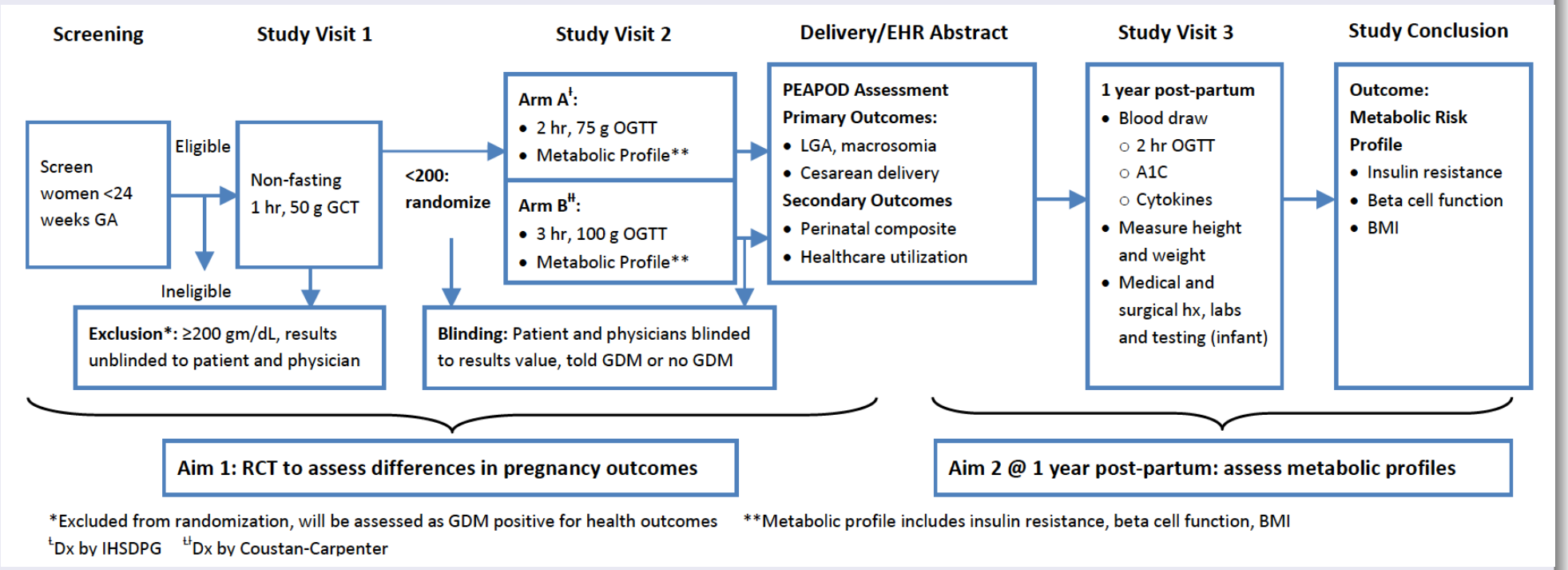


- Disadvantages:
  1. increased prevalence of GDM 2-3 fold to approximately 18%
  2. increased medical interventions
  3. increased risk of iatrogenic complications
  4. decreased patient adherence and increased cost.

Impetus for GDM^2

- In 2013, an NIH consensus conference was held to "...address controversial questions of public health importance when there may be discordance between clinical practice and the available evidence."
- To date, no RCT has directly compared the one-step and two-step approaches
- Overall recommendation: continue with the two-step approach until sufficient evidence on comparative detection, treatment, and outcomes is available.

- Parallel arm, comparative effectiveness trial comparing the rate of adverse perinatal outcomes between the one-step vs. two-step GDM screening strategies.



Inclusion Criteria

1. Ethnically and SES diverse women (18-45 yrs)
2. Singleton pregnancy between 18-24 weeks GA

Exclusion Criteria

1. Preexisting Type 1 or 2 DM
2. Diabetes diagnosed at $<$ 24 weeks GA
3. Multiple gestations (e.g twins)
4. Hypertension requiring medication
5. Corticosteroid (IM, oral or IV) use in the past 30 days
6. Major congenital anomaly w/ anticipated preterm delivery $<$ 28 wks GA
7. Inability to complete the glucose testing before 30 completed weeks GA
8. Advanced HIV (on mediations that cause hyperglycemia), severe liver disease, gastric bypass surgery or other illness/surgeries that preclude them from drinking the glucola solution.

Participants

Table 4: Overview of Data Collection and study visit

Description of Assessments	Phone Screen 18-24 weeks	Visit 1: Baseline 24-28 weeks	Visit 2: 25-32 weeks	Delivery	6-8 weeks post-partum	3 Months Post-partum	6 Months Post-partum	9 Months Post-partum	Visit 3: 1 y post-partum	Physician Input: ongoing
Screen for Eligibility	X									
Consent										
• Verbal	X									
• Written		X								
Questionnaires										
• Pt views			X						X	
• Demographics		X								
• Physician views					X					X
• Health			X						X	
• Dietary recall			X X						X X	
• Infant Feeding						X	X	X	X	
• Health Outcomes						X	X	X	X	
Lab Tests										
• 50 g GCT		X								
• 2 hr or 3 hr OGTT			X						X	
• Clinical and Cytokine			X						X	
• Cord Blood										
• Urine Pregnancy				X					X	
Anthropometric:										
• Weight		X							X[b]	
• Height		X							X[b]	
• Caliper measures									X[c]	
• Circumferences									X[c]	
PEAPOD Assessment				X						
EHR Data Abstraction										
• Delivery Data				X						
• Diabetes rescreening rates					X				X	
• Medical and surgical history, labs, and testing		X		X[a]	X[b]				X[c]	

[a]mother only [b]mother and infant [c]infant only

Primary Outcome

- LGA (large for gestational age), defined as >90th percentile for age by Alexanders curves[27]
- Assessed using birth weight and gestational age at delivery.
- Ascertained via an integrated electronic health record system.

Secondary Outcomes

Secondary Outcomes:	Measures	Data Source
Primary cesarean	Performed because of diagnosis of GDM or related complications	Delivery record; ICD9 procedure/ diagnostic codes
Fetal growth and composition	Fetal growth: Macrosomia= birthweight >=4000gm Fat mass and lean mass	measured weight and length at time of delivery and Peapod analyses
Maternal composite	Any of the following: 1) 3rd and 4th degree vaginal lacerations; 2) postpartum hemorrhage; 3) Pre-eclampsia/pregnancy induced Hypertension (defined according to ACOG definition	Obtained from delivery record and ICD 9 Dx and procedure codes.
Neonatal composite	Any of the following: 1) Hypoglycemia: blood glucose < 80mg/dl; 2) Hyperbilirubinemia: bilirubin 5 mg/dl over 24 hr, clinical jaundice; 3} hyperinsulinemia- measured with c-peptide level from venous cord blood, 4) still birth – absence of fetal heart tones before delivery, 5) birth trauma=Shoulder dystocia/ brachial plexus injuries;	-measured from heel stick for blood glucose and bilirubin within 1 hr after delivery (obtain from lab section of neonatal record) -obtained at delivery from cord
Participant views GDM testing	Items that assess knowledge, experience and preference for GDM testing	Questionnaire
Provider views GDM testing	Items that assess preference for GDM testing	Questionnaire

Objectives

- To determine differences in pregnancy outcome between two predominant GDM screening approaches using an "intention-to-screen" approach:
  1. Hypothesis 1: Women screened with the one-step approach will have lower rates of LGA, cesarean delivery, and adverse maternal and neonatal composite outcomes than those screened with the two-step approach.
  2. Hypothesis 2: Women classified as no GDM in the two-step approach will have higher rates of LGA and cesarean deliveries, and adverse maternal and neonatal outcomes compared to those classified as no GDM with the one step approach.

Sample Size for Hypothesis 1

- Assume rate of LGA in the two-step method (regardless of GDM diagnoses) to be approximately 15%.
- An absolute risk reduction of 7% (LGA rate of 8% in the one-step method) would be considered a small effect size.
- In order to achieve 80% power, necessary sample size is 460 women per arm, accounting for 15% attrition.

Sample Size for Hypothesis 2

- Assume "No GDM" prevalence to be approx 95% and 84% in the two-step (n=372) and one-step arms (n=329), respectively.
- Assume rate of LGA among "No GDM" women in the two-step method to be approximately 13%.
- Maintains 80% power to detect absolute risk reduction of 8.3%.

Statistical Analyses

- Using logistic regression, we will model the risk of LGA as a function of screening arm and clinic type.
- For Hyp 2, we will include covariates that cause imbalance at baseline.
- Each hypothesis tested at 2.5% significance level.

Strengths

- Unique co-primary hypothesis to determine if targeting earlier in disease spectrum results in reduced adverse perinatal outcomes.
- Lower sample size than typical "screening studies".
- Use of 1hr 50gm GCT on all women allow calculation of sensitivity/specificity of the one-step

Limitations

- Hypothesis 2 dependent on GDM diagnosis rates, which could be higher than expected $->$ reducing sample size of "No GDM" groups.
- Difficult to compare the "experience" of one-step versus two-step method.
- Generalizability

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Study Team

- PI: Dr. Esa M. Davis
- Co-I's: Drs. Abebe, Scifres, Simhan, Day, Catalano, Bodnar, Costacou
- Project Staff: Deanna Matthew, Steve Oriss, Jessica Duell,
- Data Center Staff: Diane Comer, Charlene Xie

THANK YOU

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Australian Carbohydrate Intolerance Study in Pregnancy Women (ACHOIS) Trial

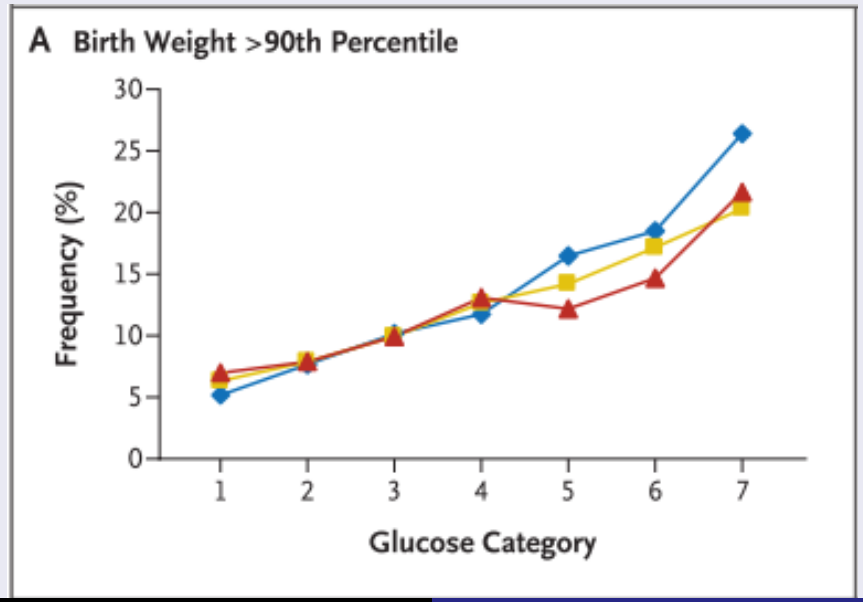
- 1000 women underwent a fasting 2hr 75gm; diagnosis was based on fasting glucose $<$140 and 2hr glucose 140-198 mg/dl
- Randomized to either
  1. treatment (dietary intervention, self-monitoring of blood glucose, and insulin therapy, if necessary) or
  2. control (routine care)

Table 4. Secondary Outcomes among the Infants.*

Outcome	Intervention Group (N=506)	Routine-Care Group (N=524)	Adjusted Treatment Effect (95% CI)†	Adjusted P Value†
Birth weight — g	3335±551	3482±660	−145 (−219 to −70)	<0.001
Large for gestational age — no. (%)‡	68 (13)	115 (22)	0.62 (0.47 to 0.81)	<0.001
Macrosomia (≥4 kg) — no. (%)	49 (10)	110 (21)	0.47 (0.34 to 0.64)	<0.001

Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study

- Over 25k pregnant women underwent 75gm OGTT at 24-32 weeks GA; excluded if fasting glucose >105 and 2-hr glucose >200
- Assessed for primary delivery outcomes such as LGA
- Increases in each of the fasting, 1-hr, and 2-hr plasma glucose levels resulted in increased odds of LGA (aOR of 1.38, 1.46, and 1.38, respectively)



Treatment for Mild Gestational Diabetes Trial (Landon)

- 958 women underwent the two-step method, but were diagnosed with broader criteria (same as CC criteria but with the added restriction that fasting $<$ 95 mg/dl)
- Similar arms as ACHOIS
- While no significant differences on primary outcome (composite of perinatal mortality & neonatal complications)...

Table 3. Secondary Neonatal Outcomes.*

Outcome Variable	Treatment Group (N=485)	Control Group (N=473)	Relative Risk (97% CI)	P Value
Birth weight — g	3302±502.4	3408±589.4		<0.001
Birth weight >4000 g — no./total no. (%)	28/477 (5.9)	65/454 (14.3)	0.41 (0.26–0.66)	<0.001
Large for gestational age — no./total no. (%)†	34/477 (7.1)	66/454 (14.5)	0.49 (0.32–0.76)	<0.001
Fat mass — g	427.0±197.9	464.3±222.3		0.003

- Parallel arm, comparative effectiveness trial comparing the rate of adverse perinatal outcomes between the one-step vs. two-step GDM screening strategies.
- 920 women between 24-28 weeks gestational age will receive a 1-hr 50gm screening test, and then be allocated to:
  1. fasting 2hr 75gm or
  2. fasting 3hr 100gm diagnostic test.
- Randomization will be done via eSYSDM; 1:1 ratio with randomly permuted blocks, stratified by clinic type.
- Blinding of a) participants, b) providers, and c) investigators unless warranted due to safety.
- Women & babies will be followed for up to 1 year postpartum to assess metabolic dysfunction and infant growth.