

Gestational Diabetes: A Risk Factor for Obesity & Diabetes in Later Life

ECO 2009 Satellite: Prevention of weight (re)gain

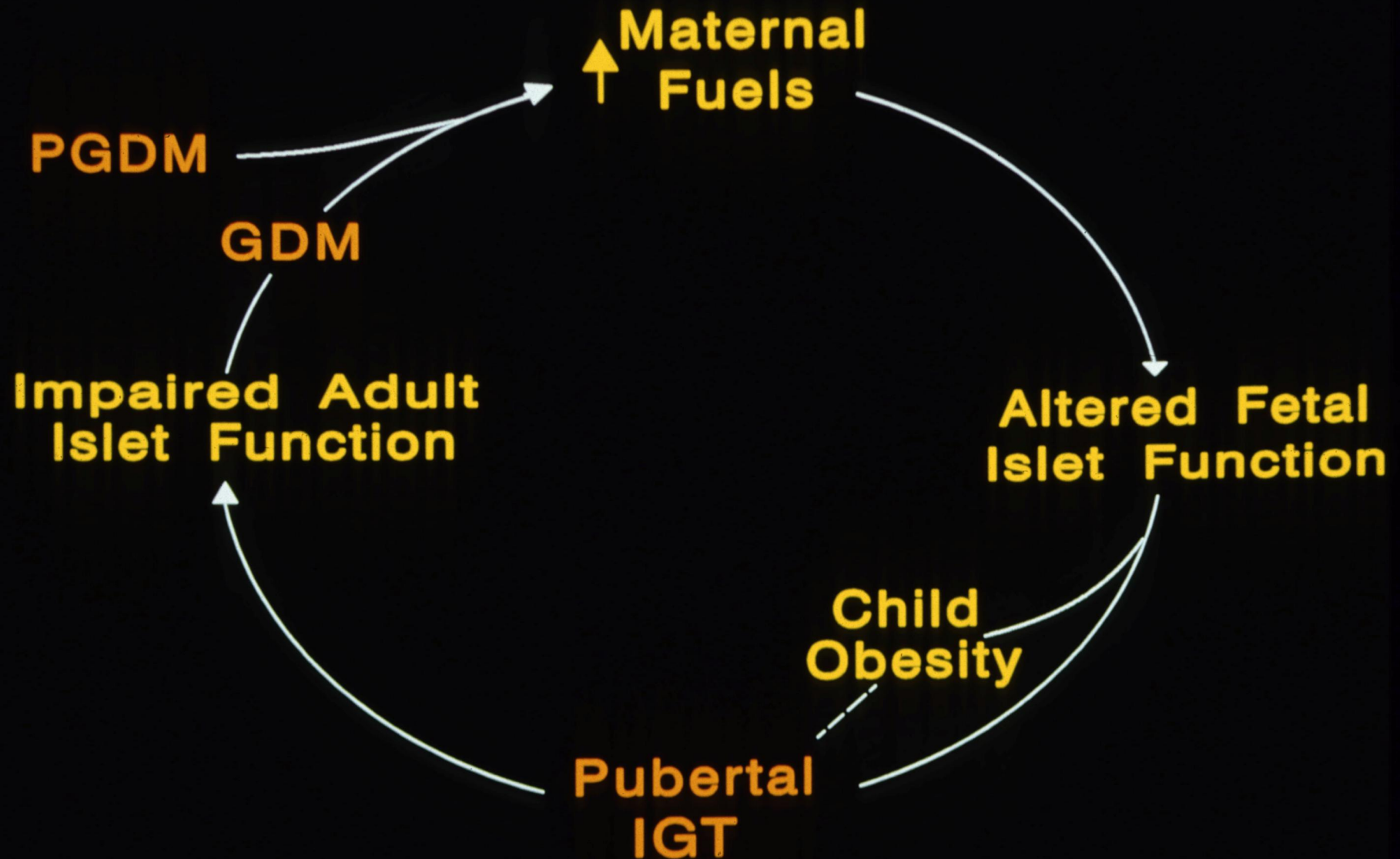
EC – US Workshop: Early life programming of obesity

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DIABETES BEGETS DIABETES



Diabetes Begets Diabetes: Animal Models

Maternal DM (genetic or chemical) **F₀**

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Intrauterine exposure to diabetes

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Size of fetus \pm ; insulin \acute{a} in pups **F₁**

ê

Nutrient exposure normal

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Adult: insulin resistant & obese (+/-)

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F₁ mated & develops GDM

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Intrauterine exposure to diabetes **F₂**

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Cycle repeats in **F₂** & beyond

Intrauterine Exposure To Maternal Diabetes

- U Many animal models
 - ⌘ Phenotype varies with severity of DM
 - ⌘ A “glucose infusion” model
- U **Studies in humans**
 - ⌘ None are randomized controlled clinical trials
 - ⌘ Key observational studies will be summarized
 - ✓ Reports from others provide support

Offspring Of Diabetic Mothers: Long-term Studies

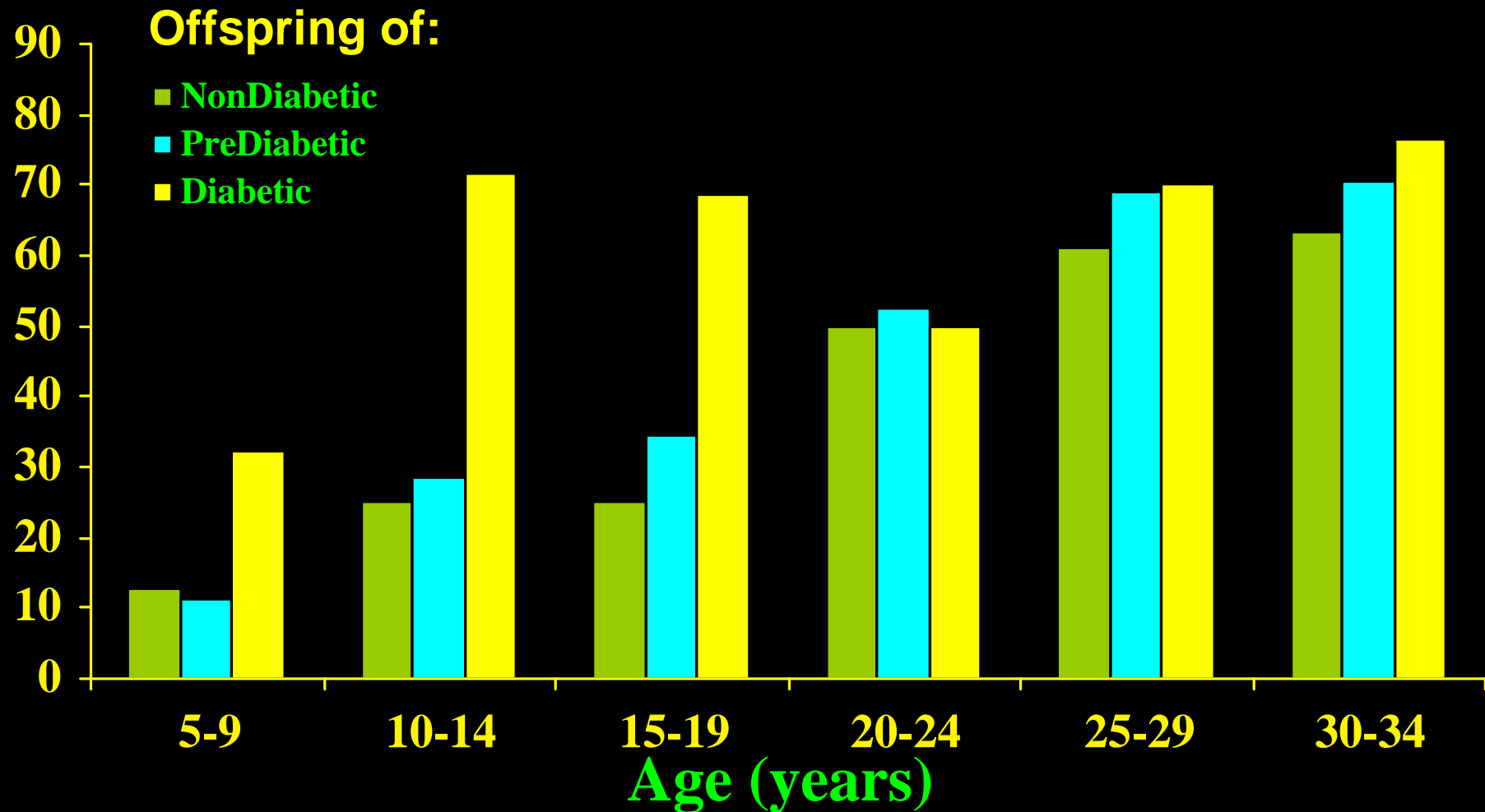
u **Pima Cohort**

- | OGTT biannually from 5 years of age
- | Anthropometrics

u **NU DPC Chicago Cohort**

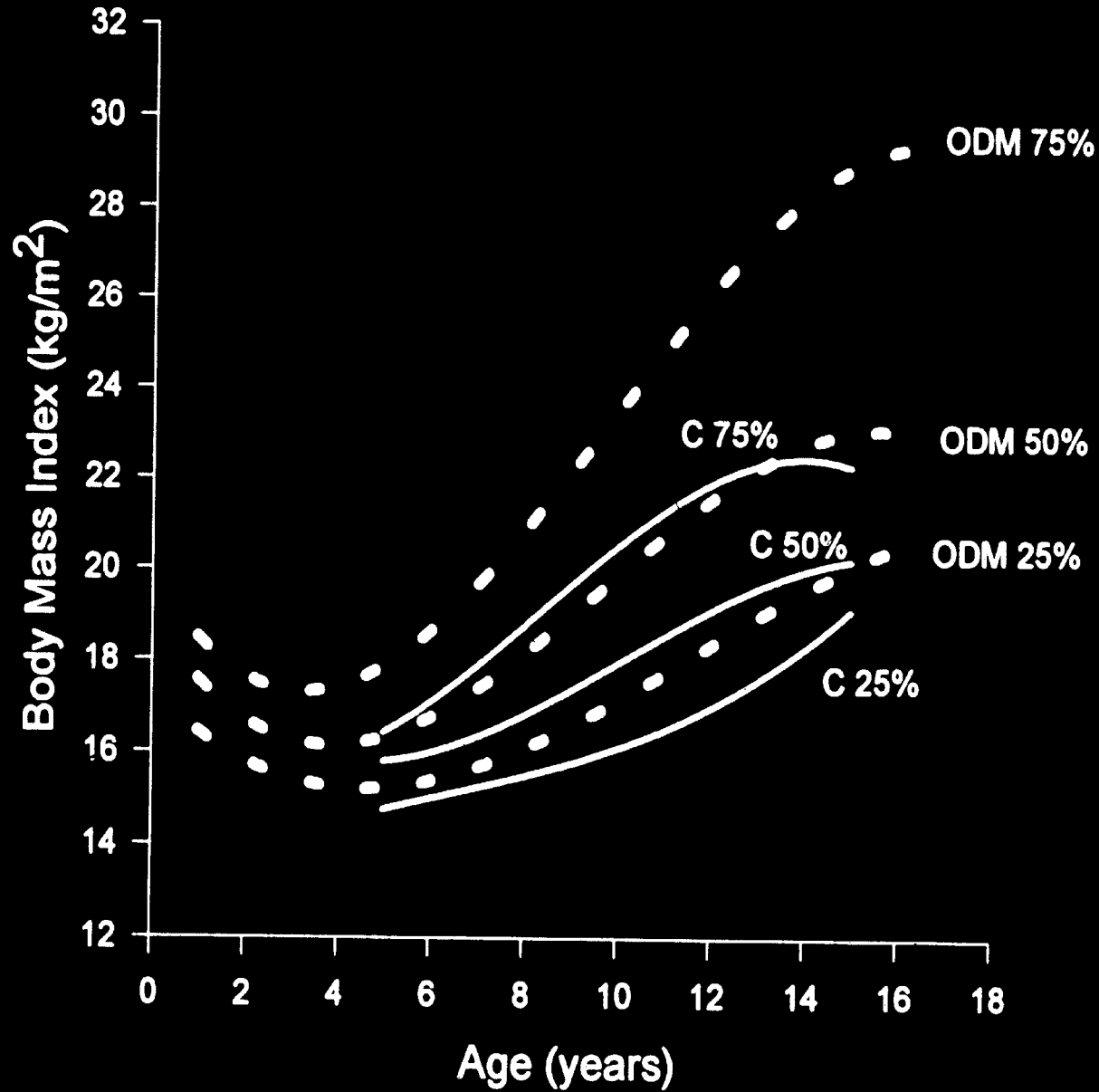
- | Enrolled for prenatal assessments
- | Age 2 yrs - adulthood: annual OGTT
- | Infancy - adulthood: anthropometrics

Prevalence Of Obesity* By Maternal Diabetes During Pregnancy

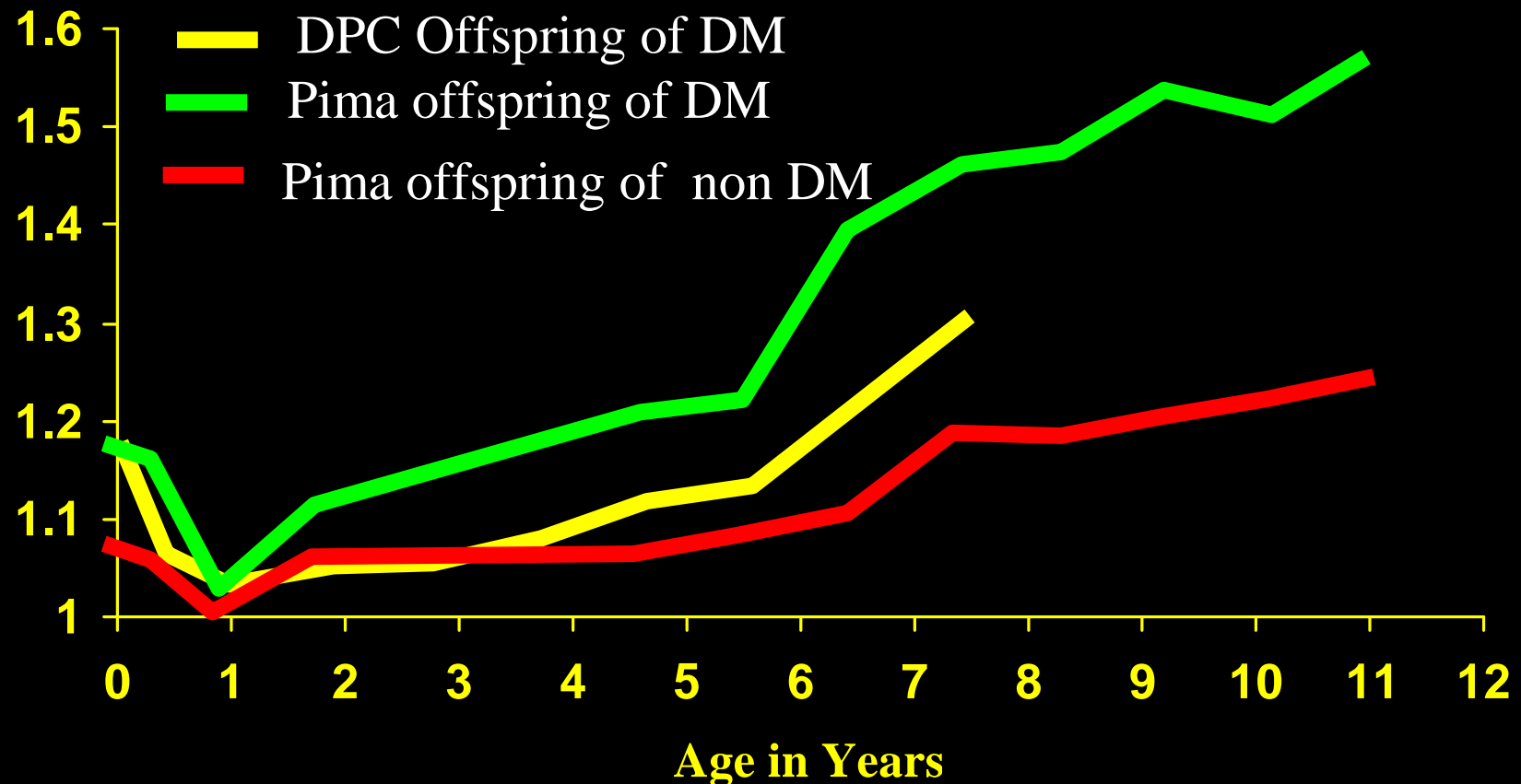


* ≥ 140 % standard

BODY MASS INDEX ODM vs. LOCAL CONTROLS

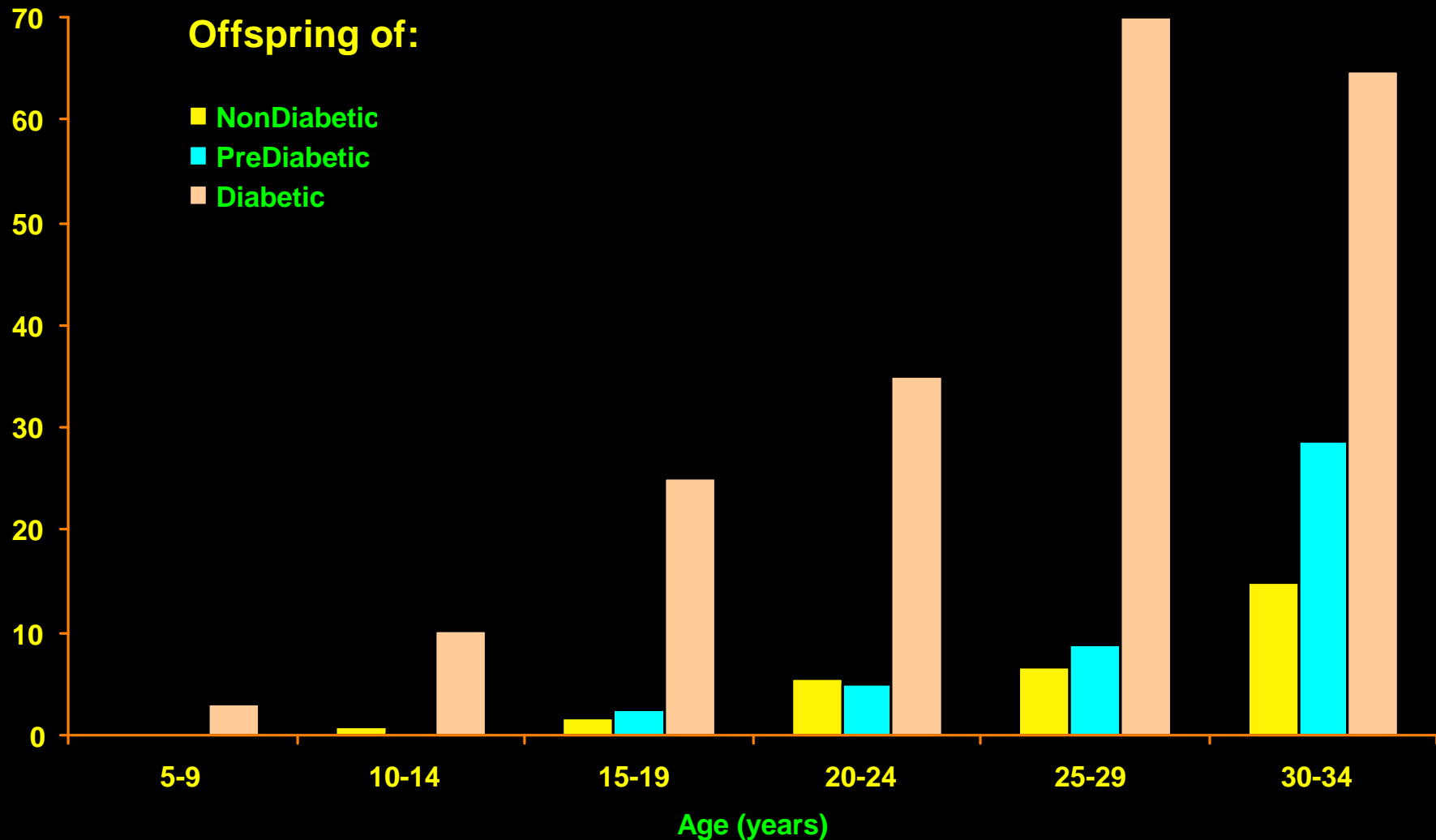


Symmetry Index In Offspring: The Diabetes In Pregnancy Center In Chicago & Pima Indians From Arizona*

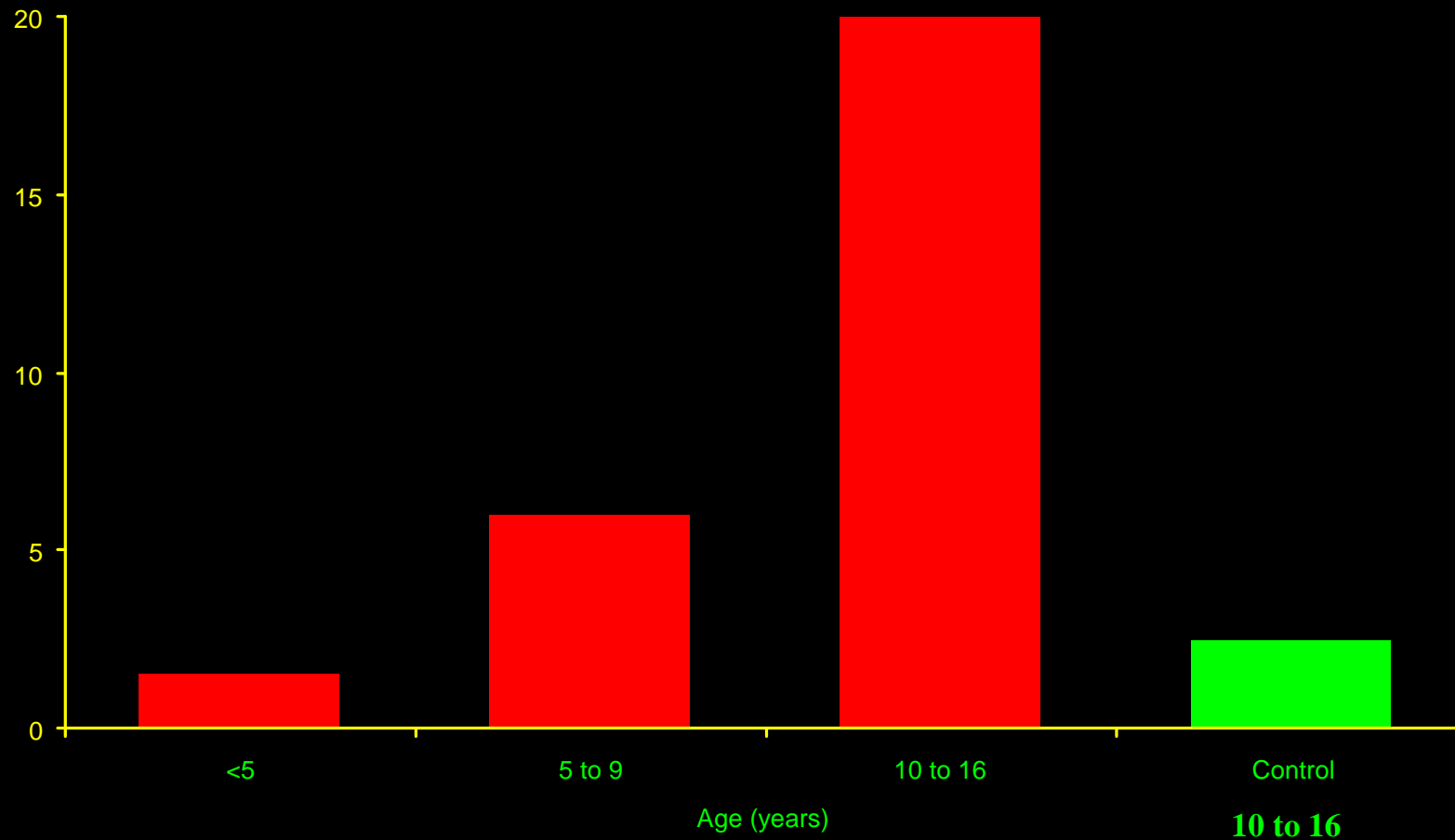


*Silverman et al. Diabetes 1991

Prevalence Of Diabetes By Maternal Diabetes During Pregnancy



Prevalence Of Impaired Glucose Tolerance: Offspring Of Diabetic Mothers (Diabetes in Pregnancy Center* Chicago)



* Silverman: Diabetes Care. 1995

Predisposition To Type 2 DM In Offspring Of Type 1 DM Mothers*

	<i>Mother (15)</i>	<i>Father (16)</i>	<i>p</i>
<i>IGT</i>	33%	0	0.02
<i>% body fat</i>	-	-	ns
<i>Ins sensitivity</i>	-	-	ns
<i>Ins secretion</i>	4.7 \pm 3.6	7.5 \pm 6.1	0.001

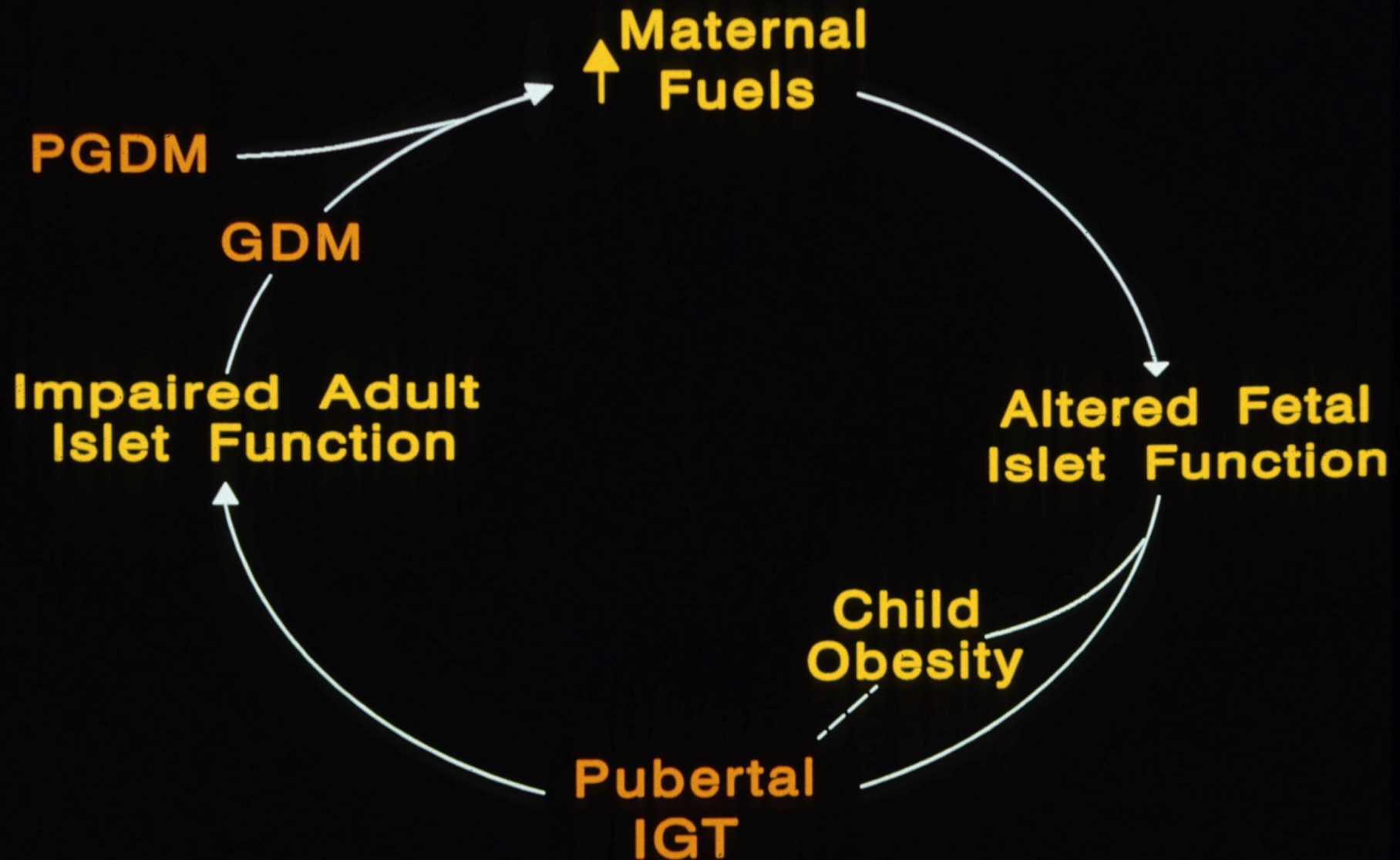
*E Sobngwi et al Diabetes 52: (Suppl 1) A32, 2003

Fetal Hyperinsulinism: A Clue To Long - Term Risks In ODM

- U Relative risk of adolescent obesity in ODM of NU DPC: **3.2 (CI 1.05-9.8) with elevated AFI***
- U Relative risk of adolescent IGT in ODM of NU DPC: **4.7 (CI 1.7-12.9) with elevated AFI***

* Adjusted for maternal BMI

DIABETES BEGETS DIABETES



HAP0 Study Rationale

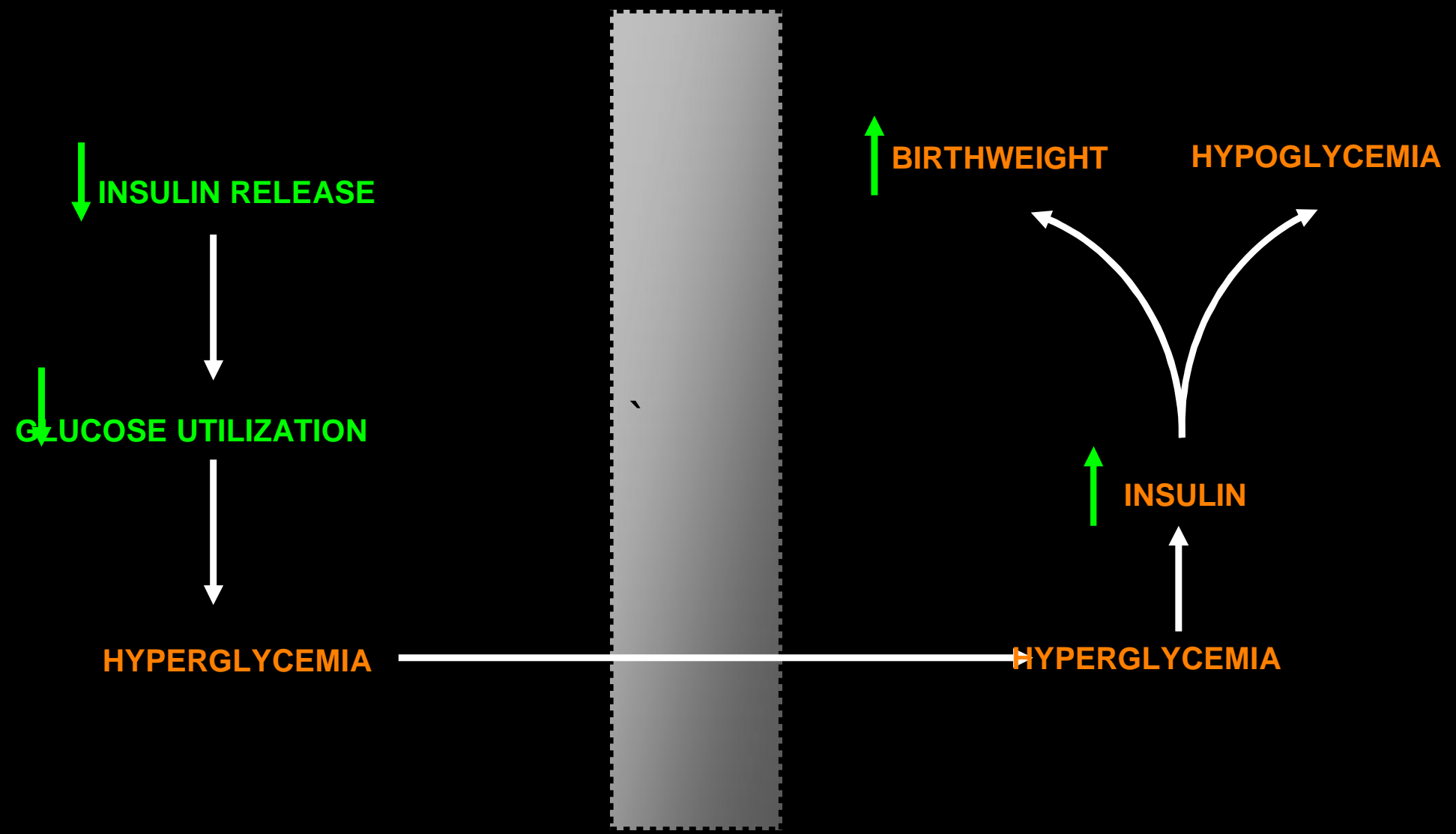
- U Overt diabetes clearly increases the risk of adverse pregnancy outcome.**
- U What level of glucose intolerance during pregnancy, short of diabetes, is associated with the risk of adverse outcome?**



MATERNAL

PLACENTA

FETAL



HAPO Protocol

75 OGTT 24-32 weeks

Fasting, 1 & 2 hr venous plasma

25,505

Unblinded at Field Center if
OGTT Fasting **>105/5.8** &/or 2 hr
>200/11.1
or random glucose **≥160/8.9** ~ 36 wks

746 (2.9%) unblinded for treatment or **<45/2.5** mg/dl **1,443** (5.7%) drop outs

23,316

Standard care for Field Center
Cord glucose & C-peptide
Neonatal glucose: 1-2 hrs of age
Anthropometrics by 72 hrs:
Length, head circ, weight, skin folds x3

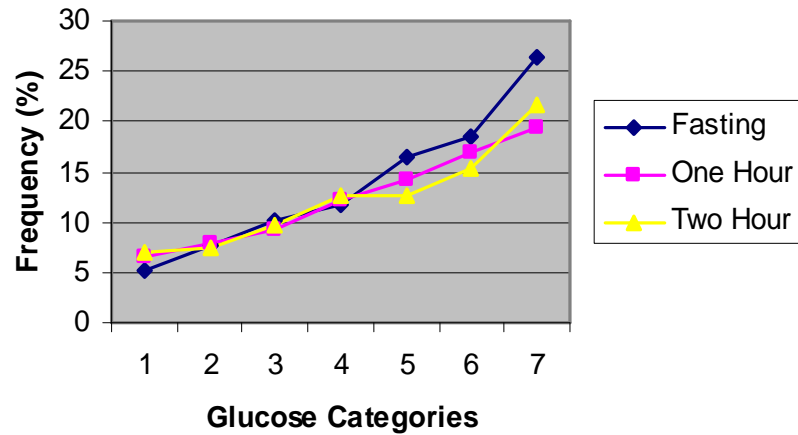
Primary Outcomes

- U Report associations of maternal glycemia with frequencies of :
 - q Infants with birth weight > 90th percentile
 - q Delivery by primary Cesarean section
 - q Clinical neonatal hypoglycemia
 - q Neonatal hyperinsulinemia (C-peptide concentration > 90 percentile value in the study population)

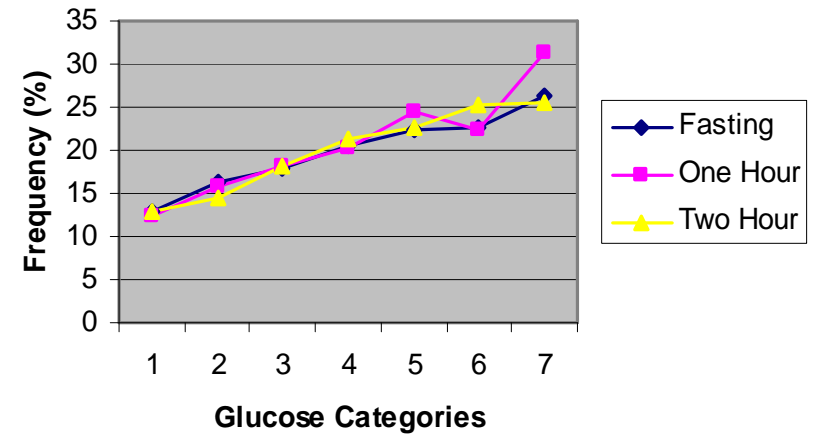


Associations of Glucose & 1^o Outcomes (NEJM 2008; 358:1991-2002)

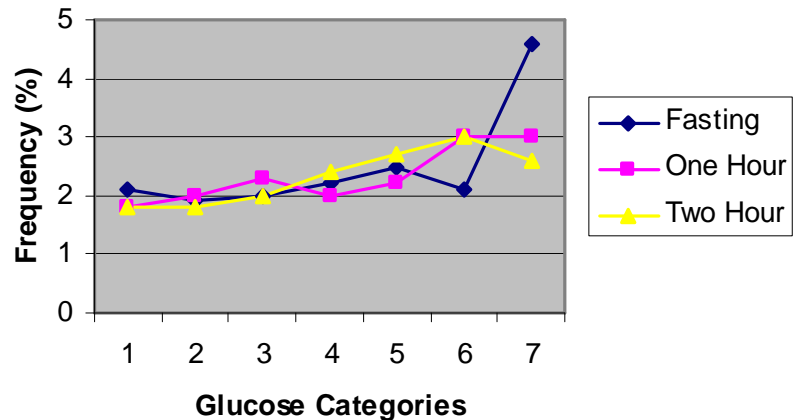
Birth Weight > 90th Percentile



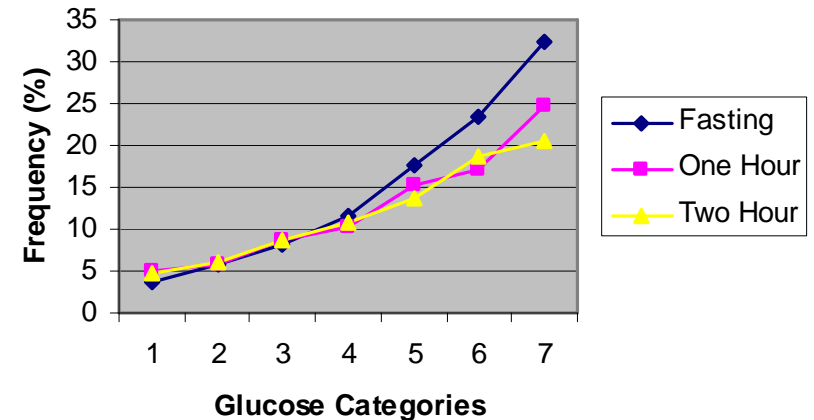
Primary C-Section



Clinical Hypoglycemia



Cord C-Peptide >90th Percentile



Birth Weight Models

90th percentile: definition based on gender, ethnicity, field center, gestational age, parity

Model I: adjusted for the above variables

Model II: adjusted for age, height, BMI at OGTT, smoking, drinking, 1st degree family history of diabetes, hospitalization pre-delivery, and mean arterial pressure and gestational age at OGTT

Adjusted Odds Ratios: Maternal Glycemia as Continuous Variable & Primary Outcomes

Outcome	Fasting	1-Hour	2-Hour
Birthweight >90%	1.38 (1.32-1.44)*	1.46 (1.39-1.53)	1.38 (1.32-1.44)
Primary C-section	1.11 (1.06-1.15)	1.10 (1.06-1.15)	1.08 (1.03-1.12)
Clinical Neo Hypo	1.08 [†] (0.98-1.19)	1.13 (1.03-1.26)	1.10 (1.00-1.12)
Cord serum C-Peptide >90%	1.55 (1.47-1.64)	1.46 (1.38-1.54)	1.37 (1.30-1.44)

*Odds ratios for glucose level \leq 1 SD (F = 6.9/.4; 1-hr = 30.9/1.7; 2-hr = 23.5/1.3 mg/dl)

[†]Quadratic (nonlinear association) p = 0.013

Adjusted Odds Ratios: Maternal Glycemia as Continuous Variable & Secondary Outcomes

Outcome	Fasting	1-Hour	2-Hour
Premature Delivery (<37 wks)	1.05 (0.99-1.11)*	1.18 (1.12-1.25)	1.16 (1.10-1.23)
Shoulder Dystocia/Birth	1.18 (1.04-1.33)	1.23 (1.09-1.38)	1.22 (1.09-1.37)
Intensive neonatal care	0.99 (0.94-1.05)	1.07 (1.02-1.13)	1.09 (1.03-1.14)
Hyperbilirubinemia	1.00 (0.95-1.05)	1.11 (1.05-1.17)	1.08 (1.02-1.13)
Preeclampsia	1.21 (1.13-1.29)	1.28 (1.20-1.37)	1.28 (1.20-1.37)

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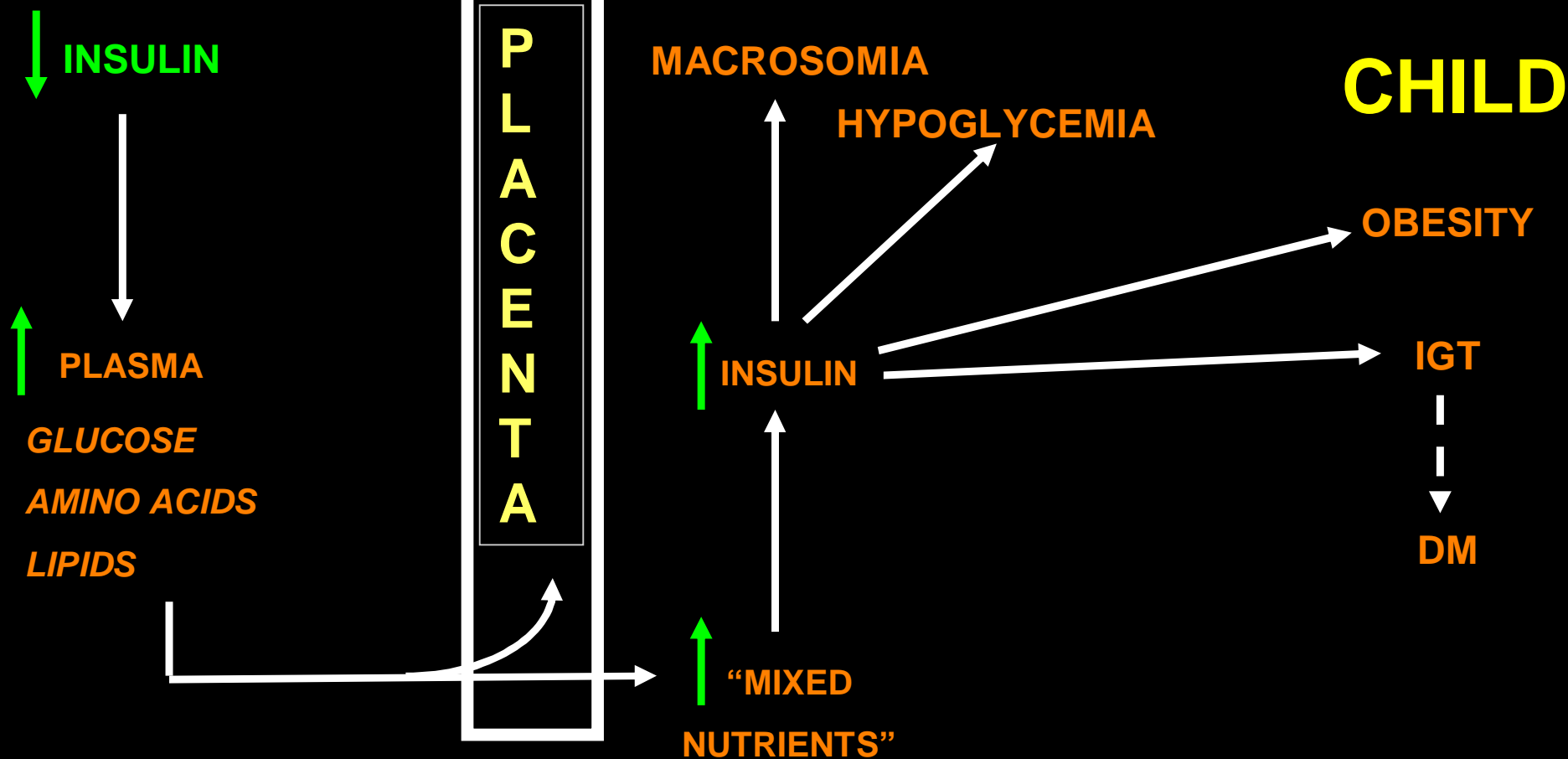
Impact of Potential Confounders

- u Adjustments for potential confounders including field center, ethnic group & BMI
 - q Small to moderate attenuation of most unadjusted associations****
- u Associations did not differ among centers**
- u The results are applicable to all centers**
- u Results can be used globally to develop “outcome based” criteria for classifying glucose metabolism in pregnancy**

PEDERSEN / FREINKEL HYPOTHESIS

MOTHER

FETUS NEONATE



DIABETES BEGETS DIABETES: THE MAGNITUDE OF PROBLEM?

- U Thirty years follow-up of Pima cohort*
 - I DM prevalence é 2 - 3 X in youth 10 - 19 yrs
 - I Concurrent increase in exposure to DM *in utero* and of obesity
 - I "Accounted for most of the increase in diabetes prevalence in Pima Indian children over the past 30 years"
- U Is this representative of other populations?

* Dabelea D et al.: Diabetologia 41:904, 1998.

Adjusted Odds Ratios: Maternal Glycemia as Continuous Variable & Primary Outcomes

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Hyperglycemia & Adverse Outcome: Childhood Obesity*

GCT (mg/dl)	Subjects (#)	Wt >85th %tile	Wt >95th %tile
43-94	1987	21.6 (ref)	10.3 (ref)
95-108	1953	23.6	12.0
109-121	1801	23.3	13.4
122-140	1868	25.7	13.2

*Hillier TA, et al. Diabetes Care 30:2287-92, 2007

Hyperglycemia & Adverse Outcome: Childhood Obesity*

OGGT Result	Subjects (#)	Wt >85th %tile	Wt >95th %tile
GCT (≤ 140)	7609	23.5 (ref)	12.2 (ref)
OGTT – NL	999	23.3	12.8
OGTT – 1 AV	288	26.7	15.3
GDM – CC	173	34.7	20.2
GDM – Rx	379	27.8	17.3

*Hillier TA, et al. Diabetes Care 30:2287-92, 2007

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