Alterations in androgen metabolism, growth factors and insulin sensitivity in children: exposed to maternal diabetes in utero: A possible common mechancism and/or longitudinal relationship

Michelle Denburg
Mentor: Sharon Oberfield

A. Background

"Fuel-mediated teratogenesis"

It is suggested that concepts of teratogenesis should be expanded to include alterations occurring subsequent to organogenesis during the differentiation and proliferation of fetal cells. Such changes could cause long-range effects upon behavioral, anthropometric, and metabolic functions.[1]

B. Background

- Prior metabolic studies on long-term effects of IU exposure to maternal diabetes
- **Animal Models**
  - Streptozotocin-induced diabetic and glucose-infused hyperglycemic rats[2]

1st generation	Mild DM	Severe DM
2nd generation (in basal glc + insulin levels)	↓ β-cell response when stressed GDM	↑ β-cell response Insulin resistance GDM
3rd generation	IGT	IGT

  - Paternal intrauterine hx noncontributory to 3rd generation phenotype (excluding any genetic alteration casued by steptozotocin.
  - Same 3rd generation phenotype when 1st generation mothers rendered slightly hyperglycemic by glc infusion in last wk of gestation
  - Malformations of hypothalamic nuclei associated with hyperinsulinemia in offspring of rats with induced gestational diabetes (acquired dysplasia of VMN)
  - Prevention of VMN malformation in offspring of diabetic pregnant rats via pancreatic islet transplantation demonstrated.[3-4]
- **Studies in the Indians**
  - Longitudinal study among Pima Indians at least 5 yrs of age in the Gila River Indian Community of Arizona since 1965
  - Biennial exams: ht, wt, BP and 75g OGTT
  - OGTT during 3rd trimester of pregnancy

[1] Norbert Freinkel (Banting Lecture 1980. Of pregnancy and progeny)
[2] Aerts L et al.. 1990 Diabet Metab Rev 6:147-67
[3] Plageman A et al, 1999 Dev Neuorsci 21:58-67
[4] Harder T et al, 2001 Neurosci Lett 299:85-8.

- Maternal diabetes status: Type 2 DM, GDM, and impaired glucose tolerance (1GT) ↑ rate of obesity and abnormal glucose tolerance (AGT) in offspring of diabetic mothers (ODM) compared to offspring of pre- and non-diabetic mothers after accounting for maternal body size and offspring birth wt ↑ obesity and AGT in offspring of women with ACT vs n1GT
- At age 20-24, prevalence of T2 =45% in ODM (vs 8.6% and 1.4% in OPDM and ONM respectively) gp differences remained after accounting for paternal DM, parental age at onset and offspring body size
- In 5-19-year-old subjects, IU exposure to DM accounted for ~40% of T2 b/w 1987-96 (~2X attributable risk b/w 1967-76) *"vicious cycle" of diabetes in pregnancy*
- Greatest effects seen with pre-gestational DM
- In **siblings discordant for IU exposure** to DM, mean BMI and risk of DM higher in siblings born after vs before maternal DM developed but no difference b/w offspring born before and after paternal dx
- Lower insulin secretion in GT offspring of parents with early onset T2 and AIR lower in ODM than in offspring of mothers who had early onset DIM but post birth
- IU exposure to DM is risk factor for ↑ urinary albumin excretion in diabetic subjects, independent of other risk factors for nephropathy
- Except for those born before 1965, ↑ risk of obesity and DM and ODM not decreasing with time

- The Diabetes in Pregnancy Center at Northwestern University
  - Gravidas with diabetes recruited In 1977-1983 for longitudinal evaluation of maternal and offspring metabolism
  - Annual exams: ht, wt, VS, Tanner stage, lipid profile, modified OGTT (1.75g/kg with max of 75g; fasting and 2h post-load samples drawn)
  - Maternal diabetes status: Type 1, Type 2, GDM
  - ↑ childbood/adolescent obesity and GT in ODM **independent risks**
  - Excessive lU insulin secretion **reflected by API** = predictor of obesity and IGT in childhood/adolescence
  - Sig. correlations b/w AFI and obesity even after adjusting for maternal obesity and macrosomia
  - IGT not associated with birth wt, maternal DM type or White class
  - S_I by IVGTT ↓ in pubertal ODM with I GT but similar to nI adolescents in those with OGTT
  - ↑ systolic and mean arterial BP in ODM
  - ↓ fasting LDL and total cholesterol
  - Correlations of maternal FFA and β-OHB during pregnancy with offspring BP (diastolic and MAP)
  - ODM more sexually mature (exact stage of pubic hair and gonadal maturation not described)

Citation	**Disturbance in offspring wt and glucose tolerance**	**BP and lipid profle**
Pribylova H et al. 1996	Both ↑ in offspring of T1	↑ BP in ODM highest in those with IGT
Vohr BR et al. 1999	LGA ODM show ↑ body size and adiposity with age, similar pp glc b/w	Trend to ↑ BP at 6-7 yr when all ODM compared to controls

	ODM and controls (GDM)	
Weiss PAM et al. 2000	Both ↑ in offspring of T1 Correlated with AFI	↑ Cholesterol and LDL

- **Evidence vs long-term effect of diabetic IU environment: <u>MODY2 kindred</u>[5]**
  - Kindred divided into 4 gps based on presence or absence of glucokinase mutation in subjects (S) and mother (M)
  - Similar adult ht, wt, and BMI in all 4 gps
    MODY2 not associated with obesity
  - Similar BP, lipid profiles, insulin secretion and insulin sensitivity (HOMA) in adult non-diabetic M+S- and M-S- offspring.
  - Above variables and degree of hyperglycemia also similar in adult M+S+ and M-S+ MODY2 offspring
- In a study of 524 children whose mothers were screened for GDM, Witaker et al. 1998 found no difference in BMI or obesity b/w ODM and those whose mothers had a negative g1c screen. They concluded that IU exposure to mild, diet-treated GDM does not ↑ risk of childhood obesity
- **Pre-gestational Tpye 1 vs GDM[6]**
  - Similarly ↑↑ frequency of childhood IGT in both, but significant differences in OGT values
  - <u>Offspring of T1</u>
    - High-response of insulin and rising I/G ratio
      ⇓
    - ↑insulin resistance with age
  - <u>Offspring of ODM</u>
    - Low insulin response appears to develop
- **Prior studies in other populations at risk for insulin resistance and obesity premature adrenarche and PCOS**
  - In girls with PA:
    - ↑ risk for PCOS and its complications: infertility, IR, T2 DM, CVD
    - Hyperthydroenism, ↓ SHBG, insulin sensitivity, ↑ IGF and ↓ IGFBP- 1, dyslipidernia
    - ***↑free IGF-l levels compared to age-, sex and BMI-matched controls***
    - Considerably higher prevalence of T2 DM and IGT in I" degree relatives

C. Study Purpose

- To evaluate measures of insulin sensitivity, growth factors, androgen metabolism and lipid profiles in children exposed to diabetes in utero to further define the long-term risk characteristics of this population for development of IR and CVD (and S yndrome X?)
- To determine markers for risk that may fa cilitate development of interventions to reverse/arrest observed metabolic disturbance

D. Hypothesis and Primary Outcome

[5] Velho G, Hattesly AT, Froguel P, 2000 Diabetologia 43:1060-3
[6] Plagenmann A eet al 1997, Diabetologia 40: 1097-1100

- We propose that there is a relationship among measures of insulin sensitivity, growth factors, androgens and lipids associated with long-term metabolic risk in this population and that free IGF-1 may mediate and/or represent a marker for this risk.
- We hypothesize that serum levels of free IGF-1 will be elevated in these children compared to normal controls and perhaps to those siblings discordant for lU exposure to maternal DM

E. STUDY DESIGN

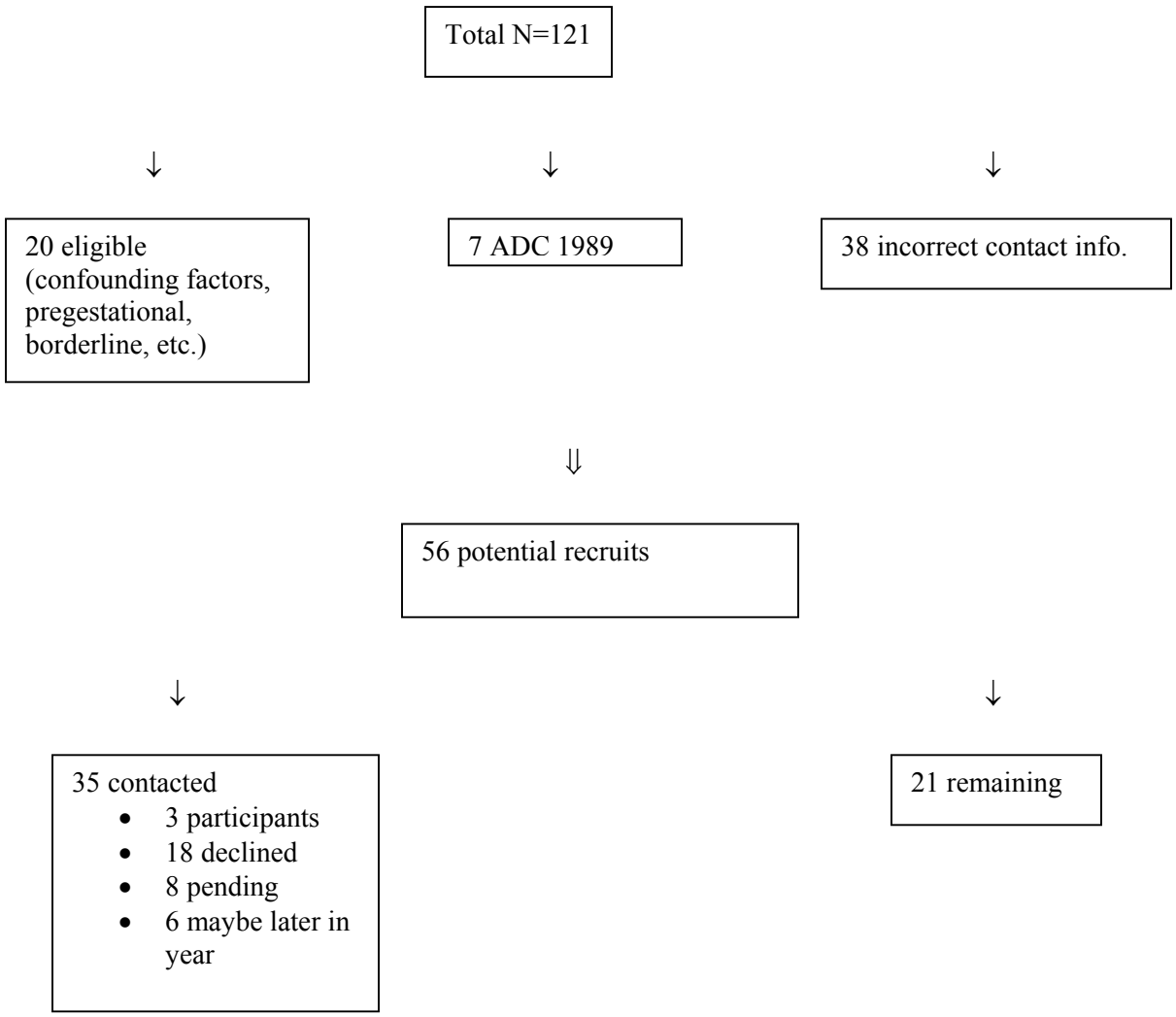
- Cross-sectional case-control
- 3 main subject groups
- Recruitment
    - Subjects and their sibling will be recruited from offspring of women with a history of gestational diabetes who were patients of Dr. Robin Goland
    - Controls will be recruited from friends of the subjects, from the practices of Dr. Sharon Oberfield, Dr. Lenore Levin and their colleagues in the Division of Pediatric Endocrinology and from the Rosetta body composition study at Luke's/Roosevelt
- Procedures
    - H&P *specifically for birth wt detailed FH of T2 DM and CVD, ht, wt, Tanner stage and acanthosis nigricans*
    - Fasting early AM blood for:
        - glucose, insulin, lipid profile and apolipoprotien A
        - testosterone, DHEA, DHEAS, 17-OHP, Δ4
        - IGF-1, IGFBP-I,***free IGF-I***
        - thyroid function tests
    - 1.75 g/kg of Glucola with blood draws at 30, 60, 90 and 120' for glucose and insulin
    - Pelvic US if female
- Free IGF-1 will be measured by immunoradiometric assay (DSL Webster, TX)
- Noncompetitive assay using sandwich b/w two antibodies
- Direct assay of dissociable fraction of serum for IGF-1
- **Inclusion criteria**
    - Children b/w 5 and 11 yrs of age whose mothers have a hx of GDM and who were exposed to maternal DM in utero
- Exclusion criteria
    - Evidence of adrenal enzyme defect or other endocrine problem (e.g. hypothyroidism, GH def.)
    - Serious medical conditions or chronic medications including corticosteroids which may interfere with lab values

***Note will be made of children known to have DM, the data will be separately analyzed and an 0TT will not be performed**

- **Safety Measures**
    - The study does not involve administration of any medications.
    - H&P and blood tests will be performed in the General Clinical Research Center
    - Nausea and less commonly, vomiting may occur after Glucola administration and subsides shortly. If a subject vomits within 30' of drinking the Glucola, the test will be ended.
- Sample Size
    - N = 30 subjects
    - Using transformation (free IGF-1)$^{1/4}$ and normal ranges for free IGF-1 by age and sex determined by Juul et al 1997
    - α=0.05 β=80% SD=0.14

- Effect size= $SD/[(n-1)/16]^{1/2}$
  - =0.014 with 1:1 ratio controls/subjects
  - =0.089 with 2:1 ratio controls/subjects
  - $(\text{free IGF-1})^{1/4}$ of $1.1 \rightarrow 1.19$
  - free IGF-1 of $1.46 \rightarrow 2$
  - Effect size of 0.54 or 37% for raw data

- **Progress Report**



F. References

Aerts L, Holemans K, Van Assche A. Matemal diabetes during pregnancy: consequences for the offspring, Diabetes Metab Rev 1990; 6(3): 147-67.

Cho NH, Silverman BL, Rizzo TA, Metzger BE. Correlations between the intrauterine metabolic environment and blood pressure in adolescent offspring of diabetic mothers. J Pediatr 2000; 136: 587-92.

Dabelea D, KnowIer WC, Pettit DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. J Matern-Fetal Med 2000-8:83-8.

Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ et al. Intrauterine exposure to diabetes conveys risks for Type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000 49: 2208-11.

Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH, Knowler WC. Birth weight, Type 2 diabetes, and insulin resistance in Pima Indian children and adults. Diabetes Care 1999; 22(6): 944-50

DiMartino-Nardi J. Premature adrenarche: findings in prepubertal African-Am and Caribbean-Hispanic girls. Acta Paediatr Suppi 1999; 433: 67-72.

Freinkel N. Banting Lecture 1980: of pregnancy and progeny. Diabetes 1980: 1023-35.

Gautier JF, Wilson C, Weye Mott D, Knowler WC et al. Low acute insulin secretory responses in adult offspring of people with early onset Type 2 diabetes. Diabetes 2001; 50:1828-33.

Harder T, Aerts L, Franke K, Van Bree R, Van he FA, Plagemann A. Pancreatic islet transplantation in diabetic pregnant rats prevents acquired malformation of the ventfornedial hypothalamic nucleus in their offspring. Neurosci Left 2001; 299: 85-8.

Ibaliez L at al, Increased prevalence of type 2 diabetes mellitus impaired glucose tolerance in first-degree relatives of girls with a history precocious pubarche. Clin Endocrmol 1999; 51, 395-401.

Ibanez L, Potau N, Chawn P, Pascual C, Carrascosa A. Hyperinsulin, dyslipaefta and cardiovascular risk in girls with a history of premature pubarche. Diabetologia 1998; 41: 1057-63.

Ibanez L, Potau N, Francois 1, DeZegher F. Precocious pubarche, hypertension and ovarian hyperandmilenism in girls: relation to reduced fetal growth. J Cli Endocrinol Metab 1998; 83: 3558-62.

Ibanez L, Potau N, Vudis R, Zampolli M, Terzi C, Gussinye M, Carrascosa A, Vi Calvet E. Postpubertal outcome in girls diagnosed of premature pubarche during childhood: increased frequency of functional ovarian hyperandrogenism. J Clin Endwinol Metab 1993: 76: 1599-1603.

Juul A, Holm K, Kastrup KW, Pederson SA, Michaeksen KF et al, Free insulin-like growth factor 1 serum levels in 1430 healthy children and adults, and its diagnostic value in patients suspected of growthh hormone deficiency. J Clin Endocrinol Metab 1997: 82: 2497-2502,

Lindsay RS, Hanson RL, Bennett PH,Krow WC. Secular trends in birth weight, BMI, and diabetes in the offspring of diabetic mothers. Diabetes Care 2000~ 23:1240,54.

Metzger BE, Silverman BL, Freinkel N, Dooley SIL, Ogata E and Green OC. Amniotic fluid insulin concentration as a predictor of obesity, Arch Dis 1990; 65: 1050-2.

Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. Diabetes 1998; 47:148

Oppenheimer E, Linder B, DiMartino-Nardi J. Decreased insulin sensitivity in prepubertal girls with premature adrenarche and acanthosis nigricans. J EndocrmolMetab 1995; 80:614-18.

Pettit DJ, Nelson RG, Saad MF Bennett WC. Long-tem effects of the intrauterine environment, birth weight, and breast-feeding in Pima Indians. Diabetes Cam 1998; 21(Suppl.) B138-BI41.

Pettitt DJ, Nelson RG, Seed MF, Bennett PH, Knowler WC. Diabetes and obes the offspring of Pima Indian woman with diabetes during pregnancy. Diabetes 1993; 1611): 310-14.

Pettift DJ, Bennett PH, Saad MF, Carles MA, Nelson RG, Knowler WC. Abnormal glucose tolerance during pregnancy in Pima Indian women: long-term effects on offspring. Diabetes 1991, 4(suppl 2): 126-30.

Pettitt DJ, Aleck KA, Baird HR, Canaher M , Bennett PH, Knowler WC. Congenital susceptibility to NIDDM: role of intrauterine envi mnt. Diabetes 1986; 37: 6228.

Pettilt DJ, Knowler WC, Bennett PH, Aleck KA, Baird HR. Obesity in offspring of diabetic Pima Indian woman despite normal birth weight. Diabetes Care. 1987; 10(1): 76-80.

Pettift DJ, Bennett PH, Knowler WC, Baird HR, Aleck KA. Gestational mellitus and impaired glucose tolerance during pregnancy: long-term e obesity and glucose tolerance in the offspring. Diabetes 1985; 34(suppl2):119-22.

Pettitt DJ, Baird HR, Aleck KA, Bermart: PH, Knowler WC. Excessive obesity offspring of Pima Indian women with diabetes during pregnancy. NEJM 1983; 308: 242-5.

Plagemann A, Harder T, Janert U, Rake A et al, Malformations of hypothalamic nuclei in hyperinsulinernic offspring of rats with gestational diabetes, Dev Neurosc 1 999:21: 58-67.

Plagemann A, Harder T, Kohlhoff R, Rohde W, Domer G. Glucose tolerance and insulin secretion in children of mothers with pregestational IDDM or gestational diabetas. Diabetologia 1997;40:1097-1100

Pribylova H, Dvorakova L. Long-term prognosis of infants of diabetic mothem: relationship between metabolic disorder in newborns and adult offspring, Acta Diabetol 1996; 33: 3034.

Silfen ME, Manibo AM, Ferin M, Levine LS, Oberfield SE. Free insulin-like growth factor (free IGF-1) is elevated in prepubatal girls with premature adrenarche (PA). LWPES/ESPE 6th Joint Meeting, Montreal, Canada, 2001.

Siffen ME, Manibo AM, McMahon DJ, Levine LS, Murphy AR, Oberfield SE. Comparison of simple measures of insulin senivity in young girls with premature adremarche: the fasting glucose to insulin ratio my be a simple and useful measure. J Clin Endocrinol Metab 2001: 86:2863-8.

Silverman BL, Rizzo TA, Cho NH, Metzger B. Long-term effects of the intrauterine environment: the Northwestern University Diabetes in Pregnancy Center, Diabetes Care 1998;21(Suppl.2):8142~9.

Silverman BL, Metzger BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism Diabetes Care 1995, 18(5): 611-7.

Silverman BL, Cho NH, Metzger BE. Impaired glucose tolerance (IGT) in adolescent offspring of diabetic mothers (ODM) does diabetes beget diabetes? [Abstract] Diabetes 1993; 42(suppl 2): 87A..

Silverman BL, Rizo T. Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metger BE. Long-term prospective evaluation of offspring of diabetic mothers. Diabetes 1991; 40(Suppl. 2):121-5.

Vohr BR, McGa y ST, Tucker R. Effects of maternal gestational diabetes on offspring adiposity at 4-7 years of age. Diabetes Cam 1999; 22: 1284:94.

Weiss PAM, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH. Long-term follow-up of infants of mothers; with Type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. Diabetes Care 2002; 23:905-11.

Whitaker RC, Pepe MS, Seidel KD, Wright JA, Knopp RH. Gestational diabetes and the risk of obesity. Pediatrics 1998; 101:e9.