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Albert Einstein College of Medicine, Yeshiva University
Montefiore Medical Center

1) To describe the events that lead up to the female reproductive senescence
2) To discuss the differential roles of the ovary and neuroendocrine axis in female reproductive senescence
   - Human
   - Rodents
3) To describe the effect of aging on estrogen and IGF1 regulation of hypothalamic neurotransmission and function
The Female Reproductive Axis

Frequency and amplitude of GnRH pulses change with increasing reproductive age.

 Estradiol
 Folliculogenesis
 Progesterone

What brings about the menopausal transition?

What is the menopause?

A well-defined retrospective event

The ovarian senescence theory

- The greatest number of oocytes (6-7 million) are amassed in utero
- At birth this number is reduced to about 1 million
- 1st menses between 300,000-400,000 oocytes
- Accelerated follicular depletion in the mid 30’s precede menstrual changes
- At menopause less than 1000 oocytes remain

Broekmans et al., Endocrine Reviews 2009
Ovarian senescence theory

1) Decreased inhibin B
2) Primary decrease in gonadal steroids
   a) Increased FSH
   b) Frequent anovulation (longer menstrual cycles)
   c) Shortened follicular cycles (early oocyte development)

Hypoestrogenism does not characterize hormonal changes during the perimenopause

Theory of neuroendocrine axis senescence

1) Primary change in GnRH physiology and/or its regulators
   a) Monotropic FSH rise
   b) Abnormal LH surges patterns
2) Accelerated follicular depletion
Anovulatory cycles in perimenopausal women: A sign of neuroendocrine axis dysfunction

Reproductive cycles and estradiol feedback

Estradiol negative feedback

Estradiol positive feedback

Reduced responsiveness to E positive feedback and failed LH surge mechanisms

Pituitary vs. hypothalamic dysfunction?

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Presented at the 13th RCMI International Symposium on Health Disparities | December 9-13, 2012 | San Juan, Puerto Rico

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Objective
To determine if pituitary responsiveness to GnRH peptide is reduced in perimenopausal women

Inclusion Criteria

Young Women
Age = 18-34 yo
Euthyroid
Normal Prolactin
Non-smoker
Regular menstrual cycle
Day 1 FSH ≤ 1SD
Day 1 E2 ≤ 50 pg/ml
No hormonal therapy
Normal BMI

Perimenopausal Women
Age ≥ 45 yo
Euthyroid
Normal Prolactin
Non-smoker
Menstrual cycle (q 21-35 days)
Day 1 FSH ≥ 2SD
Day 1 E2 ≤ 50 pg/ml
No hormonal therapy
Normal BMI

Descriptive Data

<table>
<thead>
<tr>
<th></th>
<th>Young women (n=3)</th>
<th>Middle-aged women (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yr)</td>
<td>26±7.07</td>
<td>48±4.58*</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>22.8±5.51</td>
<td>28.2±4.16</td>
</tr>
<tr>
<td>Mean Estradiol (E2) (pg/ml)</td>
<td>238.5±12</td>
<td>241±86.5</td>
</tr>
<tr>
<td>Mean FSH (IU/ml)</td>
<td>5.6 ±0.5</td>
<td>17.5±3.2*</td>
</tr>
</tbody>
</table>
Methods

**ELIGIBLE PARTICIPANTS**

Daily Titration until E2 = 250-300 pg/ml

Day 1

Graded GnRH Challenge

P

• Admit to GCRC
• Blood sampling q5m i nx5h
• Serum LH measured

Day 5

**Pituitary response to GnRH in perimenopausal women**

**Summary**

1. Pituitary responsiveness to GnRH peptide does not account for age-related LH surge failure in women.
2. Age-related changes in LH release most likely reflects hypothalamic dysfunction.
Hypothalamic dysfunction and female reproductive senescence

What is known about female reproductive aging in rodents?

(Krajnak et al. Biol Reprod 2001)

Characteristically delayed onset and reduced peak amplitude of the preovulatory LH surge.


Estradiol and Progesterone

Excitatory

Glutamate

Kisspeptin

GABA

NE

Inhibitory

GABA

GnIH

Dynorphin

Dopamine

Opioid
Experimental design

Day 1
- Young
- Middle-aged
- O VX
- MPA cannula

Day 5-9
- JVC
- 2x E-2-oxoate x 2 days

Day 10
- Progesterone (P)
  1) Microdialysis
  2) Serum collection
  3) Hypothalamic dissection
  4) Immunoblots

Rodent Descriptive Data

<table>
<thead>
<tr>
<th></th>
<th>Y (n = 7)</th>
<th>M (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3-4 months</td>
<td>9-11 months</td>
</tr>
<tr>
<td>E (pg/ml)</td>
<td>27.1 ± 2.8</td>
<td>31.7 ± 2.5</td>
</tr>
<tr>
<td>P (ng/ml)</td>
<td>26.8 ± 3.5</td>
<td>22 ± 2.1</td>
</tr>
<tr>
<td>Weight (gm)</td>
<td>233.8 ± 8.7</td>
<td>352 ± 9.4*</td>
</tr>
</tbody>
</table>

*P<0.05 vs. Y

Young rats release more LH than middle-aged rats during the surge

75% of rats mount a LH surge

Neal-Perry, G. S. et al., Endocrinology 2005

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Objective
To determine the effect of age on pituitary responsiveness to GnRH peptide under E2 positive feedback conditions.

Middle-aged females exhibit normal pituitary responsiveness to GnRH peptide

Estradiol and Progesterone

Excitatory
- Glutamate
- Kisspeptin
- GABA
- Serotonin

Inhibitory
- GABA
- GABA
- Dynorphin
- Opioid

Gore AC. Hormones, 2010
Objective
To determine if age-related LH surge dysfunction results from impaired E2-dependent regulation of hypothalamic glutamate and/or GABA neurotransmission.

The LH surge in middle-aged rats is characterized by an imbalance of hypothalamic glutamate (↑) and GABA (↓) release patterns.

Do GnRH neurons remain responsive to increased excitation (Glu) and decreased (GABA) inhibition?

as published in: • Physiological & Biochemical Endocrinology 2008

Neal Perry et al. Biol Reprod 2008
Summary

1) GnRH neurons maintain responsiveness to excitatory input
2) Age-related LH surge dysfunction is linked to a failure of E to regulate
   $\uparrow$ Glu (VGlut2) and $\downarrow$ GABA (VGAT)
   neurotransmission in the hypothalamus

Why kisspeptin (Kiss-1)?

1) The most potent excitatory neuropeptide for GnRH neurons
2) Kiss-1 neurons and GPR54
3) $E_2$ modulates
   Kiss-1
   LH release
   Glutamate receptor activity
4) Kiss-1 modulates GABA receptor activity on GnRH neurons
5) Kiss-1 is critical for puberty
6) Altered Kiss-1 expression in aging primates.

Estradiol and Progesterone

- Excitatory
  Glutamate
  GABA
  Kisspeptin
- Inhibitory
  GABA
  Glutamate
  Dynorphin
  Enkephalin
  GABA
  GABA

Gore AK, Ben-Jonathan, 2010
Objectives

1. To determine if E regulation of Kiss-1 mRNA as well as the distribution and number of kisspeptin neurons is impaired in middle-aged females.

2. To determine if intra-hypothalamic kisspeptin infusion rescues the LH surge in middle-aged females.

3. To determine if intra-hypothalamic kisspeptin infusion modulates hypothalamic glutamate and/or GABA release.


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Middle-aged females have fewer kiss-1 positive cells in the AVPV under E-positive feedback conditions

Hypothesis
Age-related changes in the LH surge, (↓) Glu and (↑) GABA result from decreased hypothalamic kisspeptin

Intra-hypothalamic kisspeptin infusion rescues the LH surge in middle-aged females
Kisspeptin rescues the LH surge and restores the balance of Glu and GABA in middle-aged females.

Summary

1) Middle-aged females have reduced hypothalamic excitatory (kisspeptin, Glu) and increased inhibitory (GABA) input under E-positive feedback conditions.
2) GnRH neurons maintain responsiveness to excitatory input.
3) Kisspeptin rescues the LH surge and restores hypothalamic Glu and GABA release patterns.
4) Kisspeptin modulates the LH surge through activation of Glu receptors (NMDA).
Insulin Growth Factor-1 (IGF1) and Reproduction

1) GnRH neurons co-express IGF1 and IGF1-R
2) IGF1 is important for puberty and ↑ kiss-1 expression.
3) E ↑ IGF1, IGF1 binding protein and IGF1-R
4) IGF1-R signaling is necessary for the estrous cycle
5) Brain IGF1 but not IGFR is ↓ with aging

Hypothesis
Central IGF-1 deficiency contributes to age-related LH surge dysfunction

Objective
To determine if brain IGF-1 affects LH release in young and middle-aged females
Estradiol differentially affects serum IGF1 levels in young vs. middle-aged females

![Graph showing serum IGF1 levels](image)

- *P<0.01 vs. oil
- *P<0.001 vs. Y oil

Brain IGF1 potentiates and JB1 completely blocks LH release in middle-aged rats

![Graph showing LH release](image)

IGF1 and hypothalamic GnRH peptide content in middle-aged females

![Graph showing GnRH content](image)
**IGF-1 does not increase pituitary sensitivity to GnRH in middle-aged females**

**GnRH Challenge**

**GnRH Receptor Antagonism**

**IGF1 does not increase the percent of GnRH and c-fos co-localization in middle-age rats**

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**Objective**

To determine if IGF1 affects LH release by modulating kisspeptin and/or glutamatergic neurotransmission

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Todd et al, Endocrinology (2010): 151

Sun et al, Endocrinology 2011: 152 (11)
Experimental Protocol

Experimental Protocol

OVX
3V cannula
JVC
E x 2
P

Young and middle-aged Female SD cycling rats

Osmotic minipump:
- aCSF
- IGF1 (2ug/ml)
- JB1 (100ug/ml)

1) kisspeptin-10
3 or 30 nmol/kg
2) NMDA
15 or 30 mg/kg

1) Serum LH
2) IHC
3) Real-time PCR

IGF1 up-regulates estradiol induction of KISS1R and NMDAR subunits expression in middle-aged rats

IGF1 augments Kp10 induced LH release in middle-aged rats
IGF1 augments NMDA induced LH release in middle-aged rats

![Graph showing LH release with different treatments](image)

**Summary**

I. Age-related LH surge dysfunction reflects;
   1. Reduced hypothalamic responsiveness to E
   2. Reduced peripheral and central IGF1 synthesis and IGF1R signaling
      a) Reduced excitatory (glutamate and kisspeptin) and increased inhibitory (GABA) neurotransmission
      b) Reduced glutamate receptor subunit expression
      c) Reduced kisspeptin receptor expression
      d) Decreased GnRH peptide release but not synthesis
   II. IGF1 restores hypothalamic responsiveness to E
   III. Middle-aged females retain responsiveness to excitatory neurotransmitters

**Conclusion**

Female reproductive aging is a complex process that involves the failure of multiple estradiol dependent mechanisms which reflects a main effect of central IGF1 deficiency and reduced IGF1R signaling.
Clinical relevance and translational impact

- Develop non-hormonal therapy
  - Reduce risk for neoplasia related to unopposed estradiol exposure
  - Reduce risk for dysfunctional uterine bleeding
- Delay onset of age-related ovarian failure
  - Improve quality of life for aging women
  - Improve age-related fertility outcomes

Racial and Ethnic Disparities and the Menopause

Premature and Early Menopause

FSH and Estradiol

Address disparities in quality of life of women making the transition into menopause.

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Northwestern RIA core
UVA hormone assay core
Kisspeptin antibody
GnRH antibody

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IGF1R antagonisms delays and attenuates the LH surge in E-primed young females

Todd et al. Endocrinology (2010)

IGF1R antagonism in young females reduces LH release and cfos expression in GnRH neurons

Blockade of IGF1R reduces estradiol induced KISS1R and NMDAR subunits expression in young rats

* P < 0.01 vs. oil; † P < 0.001 vs. E; ‡ P < 0.0001 vs. oil
Blockade of IGF1R reduces Kp10 induced LH release in young rats

- 3nmol/kg Kp10: aCSF (red), JB1 (blue)
- 30nmol/kg Kp10: aCSF (red), JB1 (blue)
- Peak LH (ng/ml)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Peak LH (ng/ml)</th>
<th>AUC LH (ng/ml·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCSF</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>JB1</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

- P < 0.05 vs. aCSF group

Blockade of IGF1R reduces NMDA induced LH release in young rats

- NMDA 10 mg/kg: aCSF (red), JB1 (blue)
- 30 mg/kg: aCSF (red), JB1 (blue)
- Peak LH (ng/ml)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Peak LH (ng/ml)</th>
<th>AUC LH (ng/ml·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCSF</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>JB1</td>
<td>3.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

- P < 0.05 vs. aCSF

NMDA receptor antagonism blocks and the effects of kisspeptin on the LH surge

- MA (green)
- MA+K (purple)
- MA+K+MK801 (red)

- a = p<0.05 vs. MA+KiSS (Glu and GABA)
- b = p<0.05 vs. MA, vs. MA+KiSS (Glu), n= 5-6
Elevating IGF1 does not increase GnRH activation in middle-aged rats treated with Kp10 or NMDA

NMDA and IGF1/15mg/k 3nmol

IGF1R antagonism does not affect E2 induction of hypothalamic P receptors in young females
IGF-1 and aging

1. Aging is characterized by a decline in central and peripheral IGF1 levels
2. The responsiveness and expression of neuronal and glial IGF1R is maintained or even elevated in aged brains

CHANDRASEKHAR THOTA
Meharry Medical College
VITAMIN D REGULATES CONTRACTILE PROFILE VIA NFKB PATHWAY IN HUMAN MYOMETRIAL CELLS

Chandrasekhar Thota, Takeisha Farmer, R Juluri, Nahed Ismail and Ayman Al-Hendy

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2 Department of Ob & Gyn, University of Texas Medical Branch, Galveston TX 77555
3 Magee Woman’s Hospital, University of Pittsburgh Medical Center, Pittsburgh, PA. 15261

Grant support : RCMI -G12 RR03032

Introduction

Preterm birth is a major health disparity issue

Infection is the major etiology of preterm birth
(Borell LN et al J Dent Res. 2005; 84: 924)

Black women have lower serum Vitamin D levels and higher basal inflammation

Alberta MA et al Am J Cardiol 2003;93: 1238

Vitamin D has been reported to play a role in innate immunity
(Alberta MA et al Am J Cardiol 2009;93: 1238)

Serum 1,25(OH)2VITD(nM)

50 100 150 200 250 300

TERM PRETERM

0 20 40 60 80 100 120 140 160

1,25(OH)2VITD(pM) **

Caucasian African American

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Hypothesis

Vitamin D inhibits infection induced inflammatory cytokines and contractile associated proteins in myometrial cells through NFκB pathway

Objective

To assess the effects of Vitamin D on the expression of

- Chemokines and Cytokines,
- Steroid Hormone Receptors and its Co-activators,
- Contractile Associate Proteins and
- Members of NFκB pathway in myometrial smooth muscle cells co-cultured with THP1 cells

Methods

Cell culture

Immortalized human myometrial smooth muscle cells (UtSM cells; kind gift from Dr. Darlene Dixon, NIEHS) were cultured in SmBM medium (Lonza)

Co-culture

At 90% conflueny myometrial smooth muscle cells were co-cultured with THP1 (suspension cells; ATCC) cells in RPMI medium supplemented with 0.1% BSA.
Treatment

Myometrial and THP1 cell co-cultures were treated with different concentrations of vitamin D, and mRNA isolated after 24h from myometrial cells using Qiagen kit.

Quantitative Polymerase Chain Reaction

We measured chemokines, cytokines and contractile associated proteins mRNA expression by real time PCR using appropriate primers.

Western Analysis

Co-culture were also treated with different concentrations of 1,25(OH)2vitamin D3 for 24 and 48h. Whole cell lysates and nuclear fractions were isolated using standard technique.

We measured, progesterone receptor A and B, connxin 43, Cox-2 and IKBα and phospho IKB in whole cell lysate and estrogen receptor alpha and NFκB p50 and p65 in nuclear fractions.

RESULTS

1,25(OH)2Vitamin D3 inhibits chemokines and cytokines mRNA expression in myometrial cells.
1,25(OH)₂Vitamin D3 inhibits LPS induced chemokines and cytokines mRNA expression in myometrial cells.

a) IL-1β / GAPDH

b) IL-6 / GAPDH

c) TNFα / GAPDH

d) IL-13 / GAPDH

1,25(OH)₂Vitamin D3 antagonist ZK25922 reverses vitamin D effects on chemokines, cytokines, and oxytocin receptor mRNA expression in myometrial cells.
1,25(OH)₂Vitamin D reverses monocyte induced IL6, IL8 and TNFα mRNA expression in human myometrial cells

1,25(OH)₂Vitamin D reverses monocyte induced interleukin 13 mRNA expression in immortalized and primary human myometrial cells

1,25(OH)₂Vitamin D reverses monocyte induced oxytocin receptor and connexin-43 mRNA expression in myometrial cells
1,25(OH)₂ Vitamin D3 decreases cox-2 and connexin-43 expression in myometrial cells co-cultured with monocytes

Vitamin D causes a dose dependent decrease in progesterone receptors A to B ratio in human myometrial cells co-cultured with monocytes

Vitamin D3 decreases estrogen receptor α expression in human myometrial cells co-cultured with monocytes
1,25(OH)₂ Vitamin D3 decreases SRC3 expression in human myometrial cells co-cultured with monocytes.

1,25(OH)₂ Vitamin D3 decreases phospho IκBα and increases IκBα expression in myometrial cells co-cultured with monocytes.

1,25(OH)₂ Vitamin D3 decreases NFκB p50 and p65 expression in myometrial cells co-cultured with monocytes.
Conclusions

• Vitamin D decreases THP1 induced increases in the expression of inflammatory markers, contractile associated proteins, progesterone receptor A to B ratio and estrogen receptors in human myometrial cells.

• Vitamin D decreases NFκB activity and contractile associated proteins by increasing IκB levels in human myometrial cells.

Future Direction

• To assess if vitamin D prevents preterm birth induced by LPS and IL-1α in a mice model of vitamin D deficiency.

• To assess the effects of less calcemic vitamin D agonists on gestation length in vitamin D deficient mice treated with LPS and IL-1α.

• To assess the role of IL-13 on myometrial contractile protein profile using term primary myometrial cell lines stably transfected with IL-13.

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• Ms. Takeisha Farmer MS
• Ms. Archana Laknaur MS
• Dr. Sarbani Maitra MD
Gilbert’s Disease and Obesity in Pregnancy: Effects on Minority Health

By: Dr. Luc Rougée, PhD
John A Burns School of Medicine
University of Hawaii at Manoa
Honolulu, Hawaii
Obesity

- 30% of US adults are obese
- >70% in Native Hawaiian, Pacific Island, and African American women

Levi et al., 2010

Obesity increases the risk of developing other diseases including diabetes, metabolic syndrome, cardiovascular disease

Increases incidence of obstetric complications

Bilirubin

- Breakdown product of heme
- Antioxidant
- Metabolized solely by UDP glucuronosyltransferase (UGT) 1A1
Neonatal Bilirubin

- Immediately before birth fetal blood cells break down releasing high levels of bilirubin
- The elimination path for bilirubin (UGT1A1) is not active in neonates until days after birth, reaching full adult maturity in several months
- Neonatal hyperbilirubinemia is common

Hyperbilirubinemia

- Presence of excess bilirubin that results when the ability to uptake, store, conjugate or excrete bilirubin is compromised
- Kernicterus in neonates
  - Impaired neurological development

Causes of Hyperbilirubinemia

- Acquired conditions:
  - Biliary obstruction
  - Hormonal modulation
  - Drugs and poisons
  - Hepatocellular injury
- Genetic conditions:
  - Dubin-Johnson syndrome
  - Rotor syndrome
  - Gilbert-Meulengracht syndrome
  - Crigler-Najjar syndrome
Pilot Study

- Maternal serum samples:
  - 150 Non-Hispanic White
  - 150 Asian
  - 150 Native Hawaiian and Pacific Islanders (NHPI)
- Analyzed for total, direct (conjugated) and indirect (unconjugated) bilirubin levels
- Serum results analyzed with respect to clinical obstetric outcomes and Body Mass Index (BMI)

Obstetric and Neonatal Outcomes

- Gestational diabetes mellitus type 1 and 2
- Type 1 and 2 diabetes mellitus
- Intrauterine growth restriction
- Premature rupture of membranes
- Premature birth
- Pre-term labor
- Gestational hypertension
- Preeclampsia and eclampsia
- Hemolysis elevated liver enzymes low platelet count syndrome
- Pancreatitis
- Cholecystitis
- Neonatal malformation
- Small for gestational age
- Neonatal hyperbilirubinemia
- Apnea-bradycardia

Maternal Obesity

- Obesity Rates (Obese and Morbidly Obese)
  - Sample population – 23.8%
  - Asian – 5.7%
  - Non-Hispanic White – 11.5%
  - NHPI – 53.2%
- Combined Overweight and Obesity
  - Sample population – 45.9%
  - Asian – 22.0%
  - Non-Hispanic White – 32.0%
  - NHPI – 82.7%
Maternal BMI vs. Neonatal Size

- Positive correlation of maternal BMI and newborn height and weight

![Graph showing the correlation between maternal BMI and newborn height and weight.]

Elevated Maternal Serum Bilirubin

- General US population rate of elevated bilirubin between 3 to 10%
  - Clinically elevated bilirubin = Total bilirubin >0.5mg/dL with direct bilirubin < 20% of total and indirect bilirubin >0.4 mg/dL

- Average from sample population – 10%
  - 7.7% Non-Hispanic Whites
  - 10.3% Asian
  - 12.1% NHPI

Maternal Obesity Affects Neonatal Serum Bilirubin

- Significant correlation between maternal BMI and neonatal serum bilirubin levels

![Graphs showing the correlation between maternal BMI and neonatal serum bilirubin levels.]
Maternal Obesity Affects Obstetric Outcomes

- In the sample population, increasing obesity is associated with:
  - Gestational diabetes
  - Premature births
  - Neonatal malformation
  - Preeclampsia
  - Gestational hypertension

- These obstetric complications are associated with obesity, but do not significantly co-vary with maternal serum bilirubin levels.

Ethnicity and Obesity

- Obesity in NHPI population is associated with:
  - Cholecystitis
  - Gestational diabetes
  - Gestational hypertension
  - Premature rupture of membranes
  - Preeclampsia

- Combined elevated bilirubin and obesity is associated with:
  - Preeclampsia and gestational hypertension for Non-Hispanic White and NHPI
  - Premature rupture of membranes and premature births for NHPI

Discussion

- NHPI have:
  - Significantly higher obesity rates in pregnancy
  - The highest prevalence of maternal serum elevated bilirubin
  - Significantly higher incidence of elevated neonatal bilirubin that co-varies with obesity
  - In all ethnicities, obesity in pregnancy was associated with larger babies
  - Fetal overgrowth in utero has been associated with development of cardiovascular and other diseases later in life
Future Directions

• Power analysis has determined that 3000 individuals will be required to definitively assess covariance of maternal obesity, clinically elevated maternal/neonatal bilirubin and obstetric outcomes.

• Elevated bilirubin can be the result of several syndromes: Dubin-Johnson, Rotor, Gilbert’s or Crigler-Najjar. Of the four, Gilbert’s is most common inborn error of metabolism.

• Molecular confirmation of these syndromes will define the mechanism behind negative pregnancy outcomes related to obesity and clinically elevated bilirubin.

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Questions
Questions & Answers

Thank you for participating!