Gender differences in the NICU: the disadvantaged ‘Y’

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Division of Neonatology and Developmental Biology
Outline

• Y chromosome
  – Ontogeny
  – Implications in the newborn
  – Implications in NICU
    • Prematurity/survival
    • Respiratory
    • Neurologic
    • Metabolic
    • Neuro-behavioral

• Review questions
“Over the course of time, the Y chromosome has degenerated and now contains only 50 genes compared to almost 3000 in the X chromosome. Therefore, the Y chromosome is highly repetitive and mostly non-functional (probably no surprise to half of the population without one).”

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• Review questions
Y chromosome

• Reduced by one third from original size and lost 97% genes (~45/1438 remaining)
• High mutation rate due to highly oxidative sperm/testis environment
• SRY (Sex-determining Region Y) gene
  – Primary sex determination gene
  – ‘Testis determining factor’
  – Found in all male mammals—130 million years old
Birds and reptiles
No SRY

Platypus
No SRY?

Kangaroo
SRY

Human
SRY

Mouse
Sry

Mole
vole
No Sry

SRY
Modified
30 Myr

80 Myr

130 Myr
SRY evolved

170 Myr

Y chromosome evolved

310 Myr

TRENDS in Genetics
SRY Is the Male Determination Factor

Cytogenetic localization of SRY region (after McLaren)


- Y chromosome of man
  - P pseudoautosomal pairing region with the X chromosome
  - Centromere
  - Yp
  - Yq
  - Sxr
  - Hy
  - Zfy
  - SRY

- HMG Transcription Factor Binds to sry element of Sertoli cell MIS/MRF gene (stimulates) & Leydig cell P450 aromatase gene (inhibits) [1993]

2. 14 kb DNA fragment

Sex Determination in Mammals Is a Process

Male

- XY chromosome with Y genes
- Sry (TDF)
- medulla
- testis
- MRF (Mullerian Regression Factor; Sertoli Cells)
- Testosterone (Leydig Cells)
- immature male genitalia
- external sex characteristics
- 5α-Dihydrotestosterone
- immature male genitalia
- external sex characteristics
- adult phenotype

Female

- XX chromosome
- Genetic, Gametic, Chromosomal Sex
- No Sry
- cortex
- ovary
- immature female genitalia
- external sex characteristics
- Estradiol + Progesterone
- Behavioral & Metabolic Sex
- adult phenotype

Gonadal Sex

Phenotypic Sex

Internal & External
• SRY transcribed as early as two-cell stage embryo

• Y chromosome results in accelerated early growth secondary to higher metabolic rate
  – Provides XY embryo with advantage for faster growth and development
  – XY embryos have better chance to develop testes before accumulation of estrogenic hormones

• Some researchers speculate that the Y chromosome might disappear completely in 100 million years—future male characteristics may only be special attribute found in women‡

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• Review questions
Implications in the newborn

- Sex ratio: dependent variables?
  - Birth order?
  - Parental age?
  - Social class?
  - Paternal occupation?
  - Season of birth?
  - Calendar period of delivery?
Implications in the newborn

- **Sex ratio:** dependent variables?
  - Birth order?
  - Parental age?
  - Social class?
  - Paternal occupation?
  - Season of birth?
  - Calendar period of delivery?

- **NO evidence that gender determination is anything other than a chance process†**
  - Sex ratio male vs female was 1.06 in population of 549,048 births

†Maconochie et al., *Sex ratios: are there natural variations within the human population?*, *Br J Obstet Gynaecol* 1997, 104: 1050-1053
• **Cesarean delivery**
  
  – **Overall Cesarean rates**
    - 13.2% in women carrying *male* fetuses
    - 9.2% in women carrying *female* fetuses
  
  – **Male fetuses**
    - Cesarean rate increased by 30% for FTP (vs. females)
    - Cesarean rate increased by 70% for fetal distress (vs. females)
    - When adjusted for GA and fetal size:
      – Male fetal sex DID NOT continue to predict risk of Cesarean delivery for FTP
      – Male fetal sex DID continue to predict risk of Cesarean delivery for fetal distress
  
  – **Emergency Cesarean rates**
    - 8.3% in women carrying male fetuses
    - 7.1% in women carrying female fetuses
    - May be due to increased bradycardia in males during last hour of labor as compared to females = different response to hypoxia?

*Lieberman et al., The association of fetal sex with the rate of Cesarean section, Am J Obstet Gynecol 1997, 176:667-671*
Outline

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• Review questions
Implications in the NICU

- Prematurity

Between 38-40 weeks GA, there was an excess of female newborns delivered.

From 41+ weeks there was again an excess of males.

‘the guys are either too early or too late!’

Gender + race

- Review of > 1.9 million births, 7.2% excess of males among white singleton preterm births compared to only 2.8% excess of comparable blacks*

* Mechanisms responsible for preterm birth rates in blacks are less dependent on fetal gender

Cooperstock et al., Excess males in preterm birth: interactions with gestational age, race, and multiple birth, Obstet Gynecol 1996;88:189-193
Generally believed that fetuses are involved in labor and male fetuses may promote onset of preterm birth

- One mechanism: action of androgen precursors involved in estrogen production, increased in males
- Second mechanism: induction of labor may be promoted by IL-1, exacerbated by lower levels of IL-1 receptor antagonist in amniotic fluid of preterm males → preterm labor*

Greater incidence of male births between 24-32 weeks GA (55% vs. 45%)

Neonatal mortality greater in males 24-32 weeks (9.1% vs. 5.6%) and even greater at 23-24 weeks (55% vs. 32%)

*Bry et al., Interleukin-1 receptor antagonist in the fetomaternal compartment, Acta Paediatrica 1995;84:233-236
• Respiratory
  
  – Male excess in neonatal mortality most prominent during first week of life
  – Mortality related to RDS is greatest in males with relative risk of 1.57
  – Mechanism may be due to slower lung maturation in males leading to higher incidence of RDS in male infants‡ (fewer alveolar type II cells and less surfactant)
  – Translates into a greater effect of betamethasone prophylaxis in female infants†
    • Although GR numbers are equal, male androgens may reduce tissue levels of GR mRNA and protein → inhibitory effect

†Weitzel et al., Clinical aspects of antenatal glucocorticoid treatment for prevention of neonatal respiratory distress syndrome, J Perinat Med 1987;15:441-446
- **Pulmonary function**
  
  - Studies have shown greater incidence in males of bronchopulmonary dysplasia and worse pulmonary function even after adjustment for birth weight.
  
  - Race also predicts pulmonary function with black females performing best and white males performing worst.

*Stocks et al., Influence of ethnicity and gender on airway function in preterm infants, AM J Respir Crit Care Med 1997;156:1855-1862*
Neurologic

- Extremely premature (and ELBW) male infants have a distinct disadvantage in outcomes for mortality, in-hospital morbidity, and neurodevelopment

- Both physical and mental developmental indices are worse in males than females <28 weeks GA
  - Moderate-severe CP (10.7% vs. 7.3%)
  - Bayley (mental index) < 70 (41.9% vs. 27.1%)
  - Psychomotor index < 70 (48.1% vs. 34.1%)

- Male gender remains as an independent risk factor for adverse neurodevelopmental outcome even after multivariate analyses accounting for illness severity, etc.

Hintz et al., Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birth weight infants, for NICHD Neonatal Research Network, Acta Paediatrica 2006;95:1239-1248
– **Mechanisms of neurologic injury?**

  • 1980s: hypothesis that increased incidence of IVH due to unstable cerebral blood flow and hemorrhage
  
  • Indomethacin introduced to ‘stabilize’ blood flow but large RCT showed no benefit
  
  • Re-analysis of nearly 20-year old data showed beneficial effect was gender specific (males)
  
  • Possibly due to innate gender differences in response to brain injury
    
    – Male and female cells may have divergent cell death pathways: deficiency in glutathione metabolism in male cells renders preterm oligodendrocytes more prone to death
  
  • Indomethacin protective action may be via anti-inflammatory effect to prevent cell death, leading to improved outcomes in males

*Edwards D., Brain protection for girls and boys, J Pediatrics 2004;145:723-4*
Are *cool* boys better than *cool* girls?

**Head**

**Whole body**

Stay tuned...
• Metabolic
  – It has been suggested that the higher metabolic rate in males may be sustained throughout life
    • Analysis of cord blood glucose at term showed males had higher mean levels compared to females (3.87 vs. 3.71 mmol/L)
    • No differences in blood glucose levels seen following planned Cesarean deliveries
    • Speculation is that differences in arterial cord blood glucose levels may be due to gender differences in response to labor stress
  – Females may be born lighter than boys due to greater insulin resistance* (?)

*Wilkin et al., The gender insulin hypothesis: why girls are born lighter than boys, and the implications for insulin resistance, Internat J of Obesity 2006;30:1056-1061
• Neuro-behavioral
  – Speech and language at 6.5 y follow up

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<th>A1. Information</th>
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<th>F/M sig.</th>
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No. of aspects, A1–A8, with a grade ≤3:

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<th>No. of scores, B4–B13, &lt; the 10% score of the controls</th>
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Digit recall (ITPA):

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<td>6</td>
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<td>1</td>
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PPVT (mean, SD, t-test):

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<th>F (Md, Min)</th>
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<th>F(C)/F sig.</th>
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<td>7.24 ± 1.7</td>
<td>7.6 ± 1.8</td>
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<td>6.52 ± 1.65</td>
<td>6.89 ± 1.82</td>
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<td>F &gt; F*</td>
<td>M(C) &gt; M*</td>
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Jennische et al., Gender differences in outcome after neonatal intensive care: speech and language skills are less influenced in boys than in girls at 6.5 years, Acta Paediatr 2003;92:364-378
Joint attention: an aspect of early communication emerging at 9-12 mos emanating from face-face interaction and interest in objects

At 1 y follow up, males were outperformed by females in all aspects of social communication even after correction for differences in birthweight

- It is suggested that females have an advantage in facial expression processing from infancy through adolescence
- It is likely that facial expression processing develops in concert with other non-verbal and early communicative skills

Olafsen et al., Joint attention in term and preterm infants at 12 months corrected age, Infant Behavior and Development 2006, 29:554-563
Pain

- Adult males generally believed to have higher pain threshold and tolerance—based on PET studies of premotor cortex activation
- Male newborns of all gestational ages expressed less facial features of pain compared to females

Guinsburg et al., Differences in pain expression between male and female newborn infants, Pain 2000;85:127-133
– Hearing: ‘Huh? What?’

• Males are less advanced in peripheral auditory development than females
• The human cochlea is fully functional as a mature sound transducer by 6 mo age
• Studies have shown that spontaneous otoacoustic emissions can be detected as early as 30 weeks GA
• Music stimulation (Brahms’ lullaby) significantly benefited premature females’ days to discharge

Morlet et al., Spontaneous otoacoustic emissions in preterm neonates: prevalence and gender effects, Hearing Research 1995;90:44-54
<table>
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<tr>
<th>Study</th>
<th>SOAE prevalence per subject</th>
<th>Higher SOAE prevalence in females?</th>
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<td>Adult</td>
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<td>Probst et al. (1991)</td>
<td>43%</td>
<td>yes</td>
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<tr>
<td>Burns et al. (1992)</td>
<td>62%</td>
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<td>Moulin et al. (1993)</td>
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<td>Children</td>
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<td>Strickland et al. (1985)</td>
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<td>Bonfils et al. (1989)</td>
<td>50–66% per ear</td>
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<td>Full-term neonate</td>
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<td>Burns et al. (1992)</td>
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<td>Kok et al. (1993)</td>
<td>93%</td>
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<td>Preterm neonate</td>
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<td>Morlet et al. (1993)</td>
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<td>In this study</td>
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– Sleep

• Sleep continuity and architecture are gender related

• One study showed preterm males (34 weeks GA) slept less (~25 min/day) with more wakefulness and active sleep and less quiet sleep than females

“Six hours for a man, seven hours for a woman, and eight for a fool.”

--Napoleon Bonaparte

_Bach et al., Gender-related sleep differences in neonates in the thermoneutral and cool environments, J Sleep Res 2000;9:249-254_
Review questions

1. Which of the following is necessary and sufficient to determine maleness in mammals?

a) Y chromosome
b) p arm of Y chromosome
c) SRY gene
d) Bilateral descended testes
1. Which of the following is necessary and sufficient to determine maleness in mammals?

a) Y chromosome

b) p arm of Y chromosome

c) SRY gene

d) Bilateral descended testes
2. SRY gene expression is seen at its earliest in which of the following:

a) Sperm cell
b) Ovum
c) Two cell fertilized embryo
d) Ovarian cortex
Answer

2. SRY gene expression is seen at its earliest in which of the following:
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   b) Ovum
   c) Two cell fertilized embryo
   d) Ovarian cortex
Question

3. Which of the following scenarios describes an advantage of the Y chromosome?

a) Faster growth of early embryo
b) Slower metabolism of early embryo
c) Increased facial expression of pain
d) There are no advantages of the Y
3. Which of the following scenarios describes an advantage of the Y chromosome?

a) Faster growth of early embryo
b) Slower metabolism of early embryo
c) Increased facial expression of pain
d) There are no advantages of the Y
4. For which of the following conditions is a male fetus NOT at greater risk for delivery via Cesarean?

a) Fetal distress
b) Failure to progress
c) Bradycardia
d) Hypoxia
4. For which of the following conditions is a male fetus NOT at greater risk for delivery via Cesarean?

a) Fetal distress
b) **Failure to progress**
c) Bradycardia
d) Hypoxia
5. Which of the following is TRUE regarding survival at 23-24 weeks GA?

a) Less than ½ of females survive
b) Less than ½ of males survive
c) Females do not develop BPD
d) Females have higher incidence of RDS
5. Which of the following is TRUE regarding survival at 23-24 weeks GA?

a) Less than $\frac{1}{2}$ of females survive
b) **Less than $\frac{1}{2}$ of males survive**
c) Females do not develop BPD
d) Females have higher incidence of RDS
THE FEMALE BRAIN

FOOTNOTE: The "Put Oil into the Car" and "The Quitne During the Game" glands are active only when a "SHINY THINGS AND DIAMOND OLFACTORY" gland has been satisfied or when there is a shoe sale.

THE MALE BRAIN

FOOTNOTE: the "Listening to children cry in the middle of the night" gland is not shown due to its small and underdeveloped nature. Best viewed under a microscope.
THANK YOU!