Aneuploidy – What are the outcomes?

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Objectives

Which aneuploidies?
What are the outcomes in utero?
What are the outcomes after delivery?
Common Aneuploidies Detected Prenatally

For an indication of an advanced maternal age

- Abnormal karyotypes
- 2/3 Trisomy 21, 18, 13 or 45 X
- 1/3 triploidy, unbalanced translocations, deletions/duplications

Three color FISH  Conventional karyotype  Chromosome Microarray (CMA)
Common Aneuploidies Detected Prenatally

Specific ultrasound findings associated with a higher risk of a specific aneuploidy

- AV canal and trisomy 21
- Cystic hygroma and 45, X
Trisomy 21 (Down Syndrome)

Trisomy 21
- Nondisjunction (95%)
- Unbalanced translocations (4%)
- Mosaicism (<1%)

47, XX, +21

46, XY, t(14p;21p)
Etiology – Trisomy 21

 Majority of nondisjunction 21 is maternal, specifically maternal meiosis 1

 ◦ Prolonged period of suspended meiosis in females
   ◦ Meiosis 1 initiated in fetal oocyte, completed just before ovulation (12 – 40 years)
 ◦ Prolonged meiosis 1 not present in males
Hypotheses for Trisomy 21

- Accumulated toxic effects of the environment
- Meiotic spindle degrades over time
- Diminished ovarian function and suboptimal hormonal signaling
- Degradation of the uterine environment

(Sherman, 2005)
Natural History of Trisomy 21 – Before Birth

At least half of first trimester miscarriages have a chromosome abnormality

- Trisomy the most common abnormality (62.1%)
  - Chromosome 16 21.8%
  - Chromosome 22 17.9%
  - Chromosome 21 10.0%

Among liveborns, trisomy 21 occurs 1 in 700 births

- 80% of trisomy 21 conceptions lost during pregnancy

(Hook 1983)
Natural History of Trisomy 21 – Before Birth

- How often is a trisomy 21 fetus lost between first trimester and term?
- Second trimester and term?
- Is loss associated with ultrasound features?
Prevalence Studies of Trisomy 21 – By Gestational Age

Rates of trisomy 21 at CVS, amniocentesis and delivery differ

- 40 yo at 11 wks: 1/40
- 16 weeks: 1/75
- Term: 1/100

(Morris, 2008)
Loss Rate by Gestational Age

<table>
<thead>
<tr>
<th></th>
<th>CVS</th>
<th>Amniocentesis</th>
<th>Stillbirth/neonatal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuckle, 1987,</td>
<td>30 – 48%</td>
<td>18 – 24%</td>
<td>7%</td>
</tr>
<tr>
<td>Macintosh, 1995,</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Halliday, 1995</td>
<td></td>
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</tbody>
</table>

(Morris, 2008)
## Influences on Loss Rate - Maternal Age?

<table>
<thead>
<tr>
<th>Method</th>
<th>All</th>
<th>Age 25</th>
<th>Age 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>32%</td>
<td>23%</td>
<td>44%</td>
</tr>
<tr>
<td>Amniocentesis</td>
<td>25%</td>
<td>19%</td>
<td>33%</td>
</tr>
</tbody>
</table>

(Sawa, 2006)
Influences on Loss Rate - Ultrasound Findings?

Images at 14 weeks gestation
Influences on Loss Rate - Ultrasound Findings?

**Increased nuchal lucency alone**
- Majority (5/6) resolved in 2nd trimester
- 1st trimester NT of 10, 7, 5, 5, 4, 8 mm
- Not associated with cardiac anomalies in these infants with trisomy 21
- Not predictive of spontaneous loss.

Images at 22 weeks gestation

(Pandya 1995)
Natural History of Trisomy 21 – Before Birth

- Overall risk of stillbirth about 10%
- Higher risk if congenital heart disease and/or IUGR

<table>
<thead>
<tr>
<th>Condition</th>
<th>Per Cent Loss</th>
<th>Absolute numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac anomaly</td>
<td>26.3%</td>
<td>5/19</td>
</tr>
<tr>
<td>Cardiac + IUGR</td>
<td>42.8%</td>
<td>3/7</td>
</tr>
<tr>
<td>IUGR</td>
<td>58.3%</td>
<td>7/12</td>
</tr>
</tbody>
</table>

(Wessels, 2003)
Pregnancies with intent to continue N=68

- Losses (5.9%)
- Fetal growth restriction (16.9%)
- Major anomalies (75.8%)
Specific Change in Fetal Surveillance Leading to Delivery

- Abnormal NST
- Abnormal BPP
- Abnormal dopplers
- Abnormal fluid
- Poor fetal growth
- Other

Legend:
- Term
- Preterm
Newborns with Trisomy 21

1/700 livebirths
Survival to one year of age – 87-95%
Most common cause of intellectual disability in North America
  - Degree of handicap can not be predicted for an individual

Health care concerns as children
  - Cardiac and GI conditions
  - Hypothyroidism
  - Leukemia
Down Syndrome in Adults

Health care concerns as adults – presenile dementia/Alzheimer-type disease (AD), adult-onset epilepsy, adult cataracts

- AD in < 50 year olds  10-25%
- AD in 60 year olds  50%
- AD in 70 year olds  75%

Average life span 49 year of age

(Menéndez, 2005, Young, 2006)
Trisomy 18

- Edward syndrome
- 2nd most common autosomal aneuploidy in prenatal diagnosis
- 1 in 5 - 7,000 livebirths
- Also due to maternal age nondisjunction
Natural History of Trisomy 18 – before birth

<table>
<thead>
<tr>
<th></th>
<th>Loss after amniocentesis</th>
<th>Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook, 1978</td>
<td>3 / 4 (75%)</td>
<td></td>
</tr>
<tr>
<td>Hook, 1989</td>
<td>27/40 (67.5%)</td>
<td>7/15 (47%) - between amniocentesis and results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3/15 (20%) – after results</td>
</tr>
<tr>
<td>Won, 2005</td>
<td>34/106 (32.1%)</td>
<td>no clustering by gestational age</td>
</tr>
</tbody>
</table>

(Morris, 2008)
Natural History of Trisomy 18 – After Birth

Survivals 50% at first week, 10% at one year
- 1 year survivorship range from 3% in a recent medical record registry to 42% from parent questionnaires

- Common causes of death
  - Sudden death from apnea
  - Cardiac failure from cardiovascular malformation
  - Respiratory insufficiency

(Vendola, 2009; Niedrist 2006)
Natural History of Trisomy 18 – After Birth

- Survivors exhibit failure to thrive, apnea, development delays, intellectual disabilities, complications of cardiac anomalies, renal abnormalities

- Survivors past 10 years of age have been reported
  - 1% survivorship to age 10

( Vendola, 2009; Niedrist 2006)
Natural History of Trisomy 18 – After Birth

Intensive neonatal and cardiac management increased median survival time and 1 year survival to 25%

° Mechanical ventilation, surgical correction of TEFs; cardiovascular medical management

° 5/24 infants were discharged from the hospital

° 3/5 were surviving at 1 year though 2 died shortly thereafter

° Profound developmental disability and multiorgan dysfunction present in all survivors at 6 months of age and onward

(Kosho, 2006; Kaneko, 2009)
Turner Syndrome (45, X)

Occurs in 1.5% of all conceptions
- Occurs in about 10% of miscarriages
- Only 2-3% survive to term

1 in 2000 girls

Not maternal age related

Absent sex chromosome is usually (75%) paternal
Turner Syndrome (45, X)

Due to a variety of X chromosome combinations / losses

- 50% 45,X
- 30% X rearrangements, deletions
- 20% mosaics
  - 46,XX/45,X
  - 46,XY/45,X
  - 47,XXX/45,X
  - 47,XXY/45,X
Natural History Fetal 45, X

Contrast between fetal presentation and relatively benign neonatal presentation

- 98% of 45,X conceptions do not survive
- 80% of 45,X fetuses at 10 weeks die before term

What influences possible survival?

- Mosaicism?
- Type of cardiac anomaly?
Cardiac Differences Between the Fetus and Newborn with 45, X

Among 53 fetuses with NT > 4.0 and 45, X
- 62.3% had cardiac anomalies
  - 45.3% coarctation
  - 13.2% HLHS
  - 3.7% other

In neonates with 45, X
- 15-30% with cardiac anomalies:
  - 14 - 19% bicuspid aortic valve
  - 4 - 7% coarctation of the aorta
  - 1 - 2% hypoplastic left heart 1-2%

(Surerus, 2003)
Mosaicism Differences Between the Fetus and Newborn with 45, X

Among 53 fetuses with NT > 4.0 and 45, X
- Only livebirths occurred in infants without cardiac anomalies and with mosaicism

Mosaicism
- Among fetuses with NT > 4.0
  - 45,X (92.5%); mosaics (7.5%); no rearrangements
- Among postnatal diagnoses
  - 45,X (58%); mosaics (35%); rearrangements (7%)

(Surerus, 2003)
Natural History for 45, X – Before Birth

45, X detected at amniocentesis for AMA and normal ultrasound
- Survival to livebirth higher

45, X detected for NL ≥ 4.0 mm
- Survival rate is lower
- Lowest if cardiac anomaly present and non-mosaic
Natural History of 45,X – Newborn

Normal intelligence is expected

Range of physical characteristics affected by mosaicism, rearrangements and by treatments
  ◦ Broad base to the neck
  ◦ Follow-up of cardiac, hypertension, hypothyroidism, diabetes
  ◦ Short stature (growth hormone treatments)
Natural History of 45,X – Fertility

Some will spontaneously conceive (mosaics)

Amenorrhea and infertility
- Use of donor eggs initially considered
- Increased risk of preeclampsia

2% risk of maternal mortality due to aortic disease
- Relative contraindication, absolute if aortic disease already present
- Gestational carrier recommended
Summary

The earlier the gestational age at diagnostic testing, the higher the rate of aneuploidies

- Each aneuploidy has associated spontaneous loss rate throughout pregnancy
- Most of the loss occurs in the first trimester
- Spontaneous loss can still occur after diagnostic studies
Summary

Predicting the natural history for an individual fetus either in utero or after delivery is difficult

- **Autosomal aneuploidies**
  - Increased 1\textsuperscript{st} trimester nuchal edema is transient and not a good predictor of fetal demise
  - Consider antepartum management with fetal surveillance in third trimester

- **Sex chromosome aneuploidy (45, X)**
  - Cardiac malformations, NL > 4.0 mm worsen in utero prognosis
  - Mosaicism benefits in utero survival
Thank you for your attention