Aneuploidy – What are the outcomes ?

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Objectives

Which aneuploidies ?

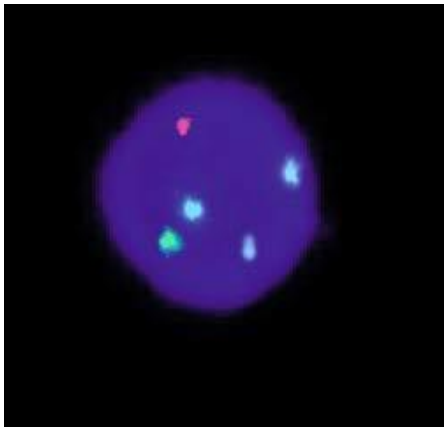
What are the outcomes in utero?

What are the outcomes after delivery?

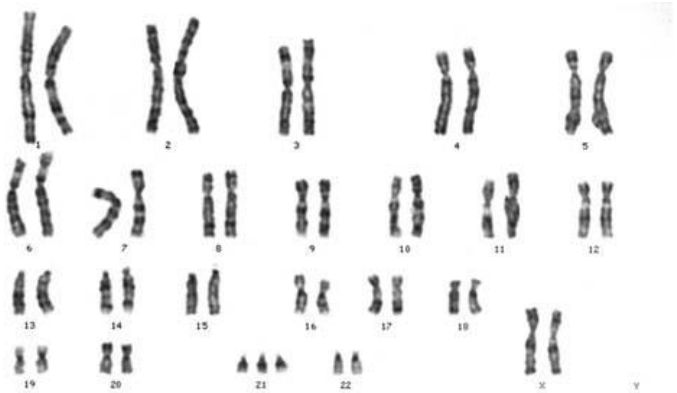
Common Aneuploidies Detected Prenatally

For an indication of an advanced maternal age

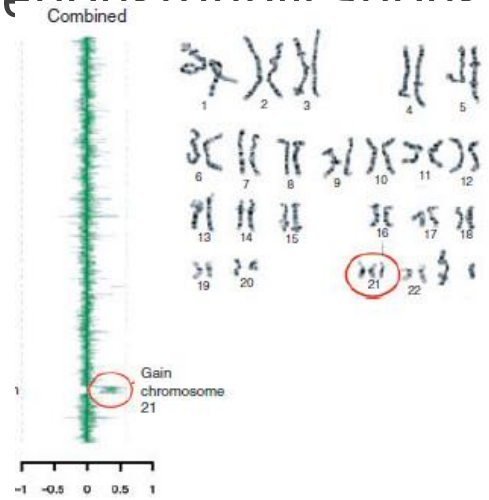
- Abnormal karyotypes
  - 2/3 Trisomy 21, 18, 13 or 45 X
  - 1/3 triploidy, unbalanced translocations, deletions/duplications



Three color FISH



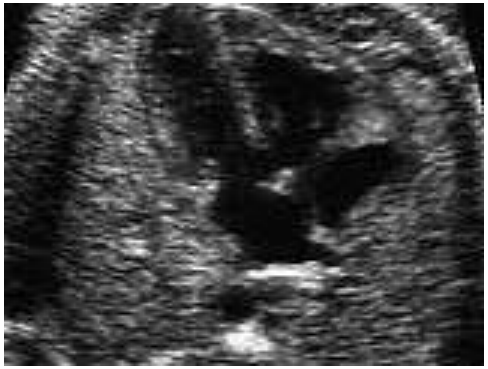
Conventional karyotype



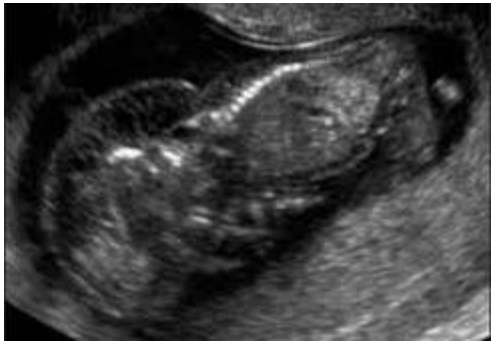
Chromosome Microarray (CMA)

Common Aneuploidies Detected Prenatally

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



AV canal and trisomy 21

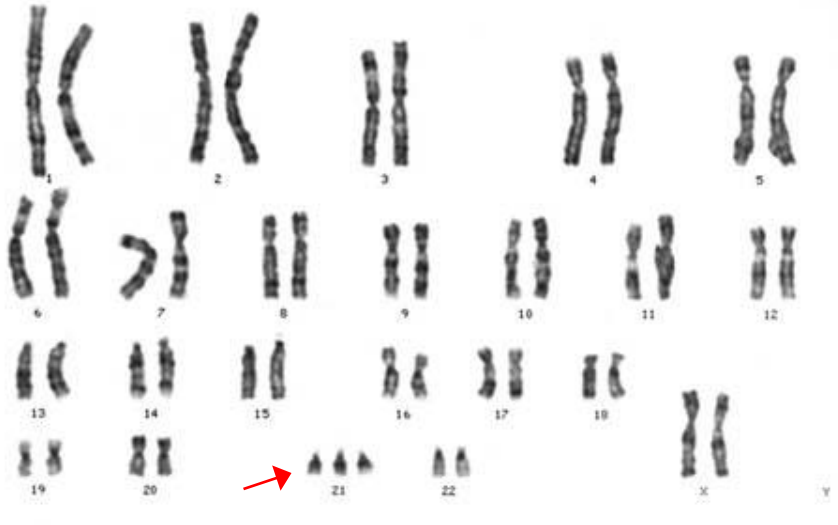


Cystic hygroma and 45, X

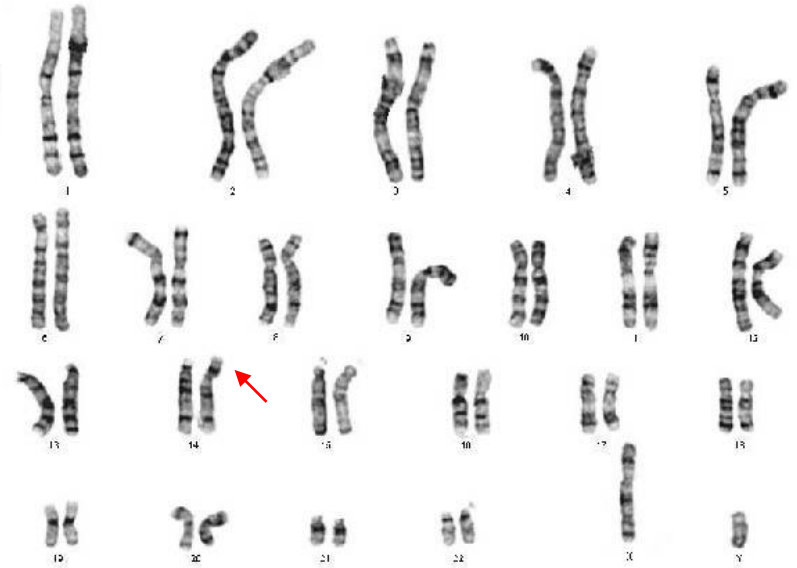
Trisomy 21 (Down Syndrome)

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

	CVS	Amniocentesis	Stillbirth/ neonatal death
Cuckle, 1987, Macintosh, 1995, Halliday, 1995	30 – 48%	18 – 24%	7 %

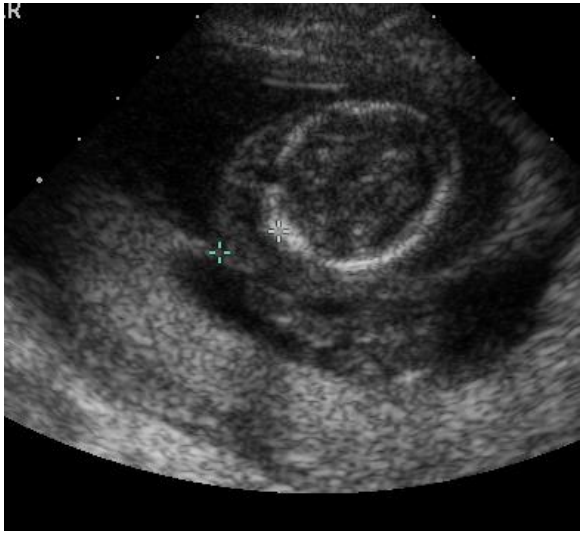
(Morris, 2008)

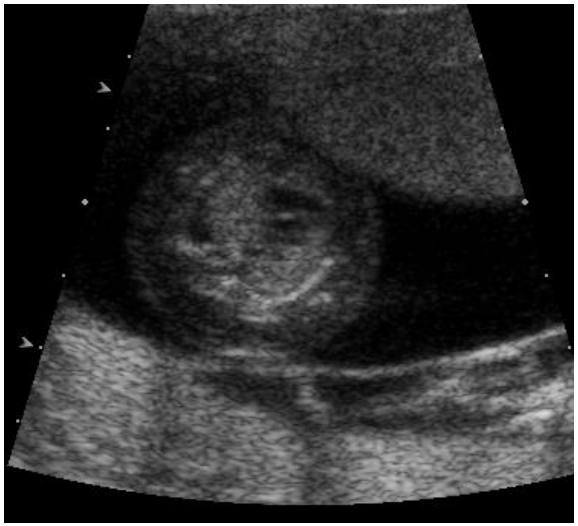
Influences on Loss Rate - Maternal Age?

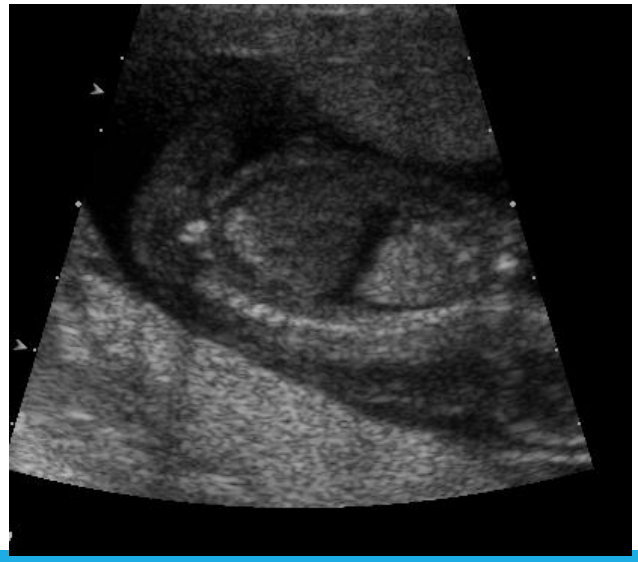
	All	Age 25	Age 40
CVS	32%	23%	44%
Amniocentesis	25%	19%	33%

(Sawa, 2006)

Influences on Loss Rate - Ultrasound Findings?

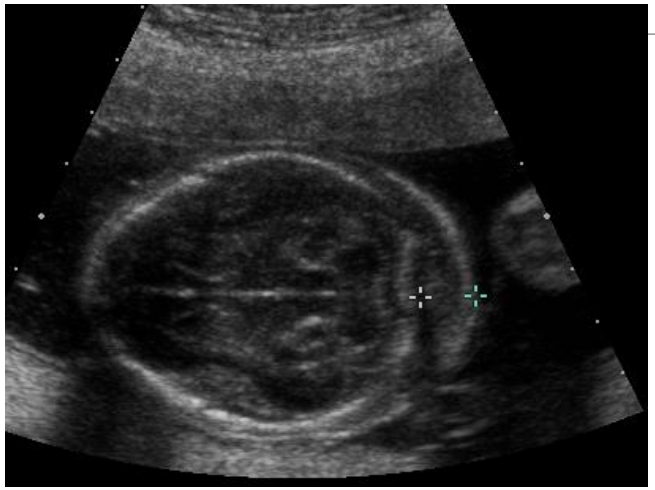


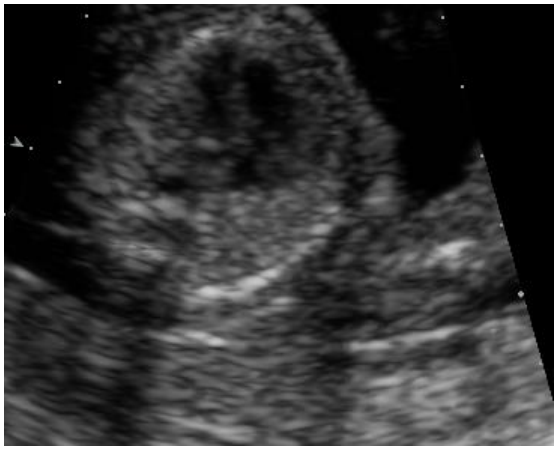




Images at 14 weeks gestation

Influences on Loss Rate - Ultrasound Findings?





Images at 22 weeks gestation

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

(Pandya 1995)

Natural History of Trisomy 21 – Before Birth

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

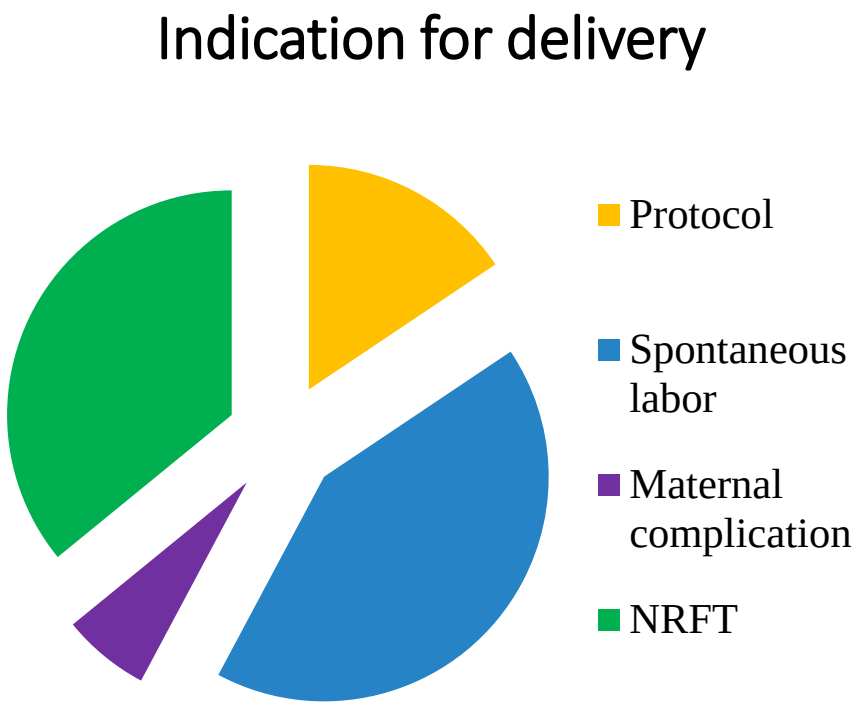
	Per Cent Loss	Absolute numbers
Cardiac anomaly	26.3%	5/19
Cardiac + IUGR	42.8%	3/7
IUGR	58.3%	7/12

(Wessels, 2003)

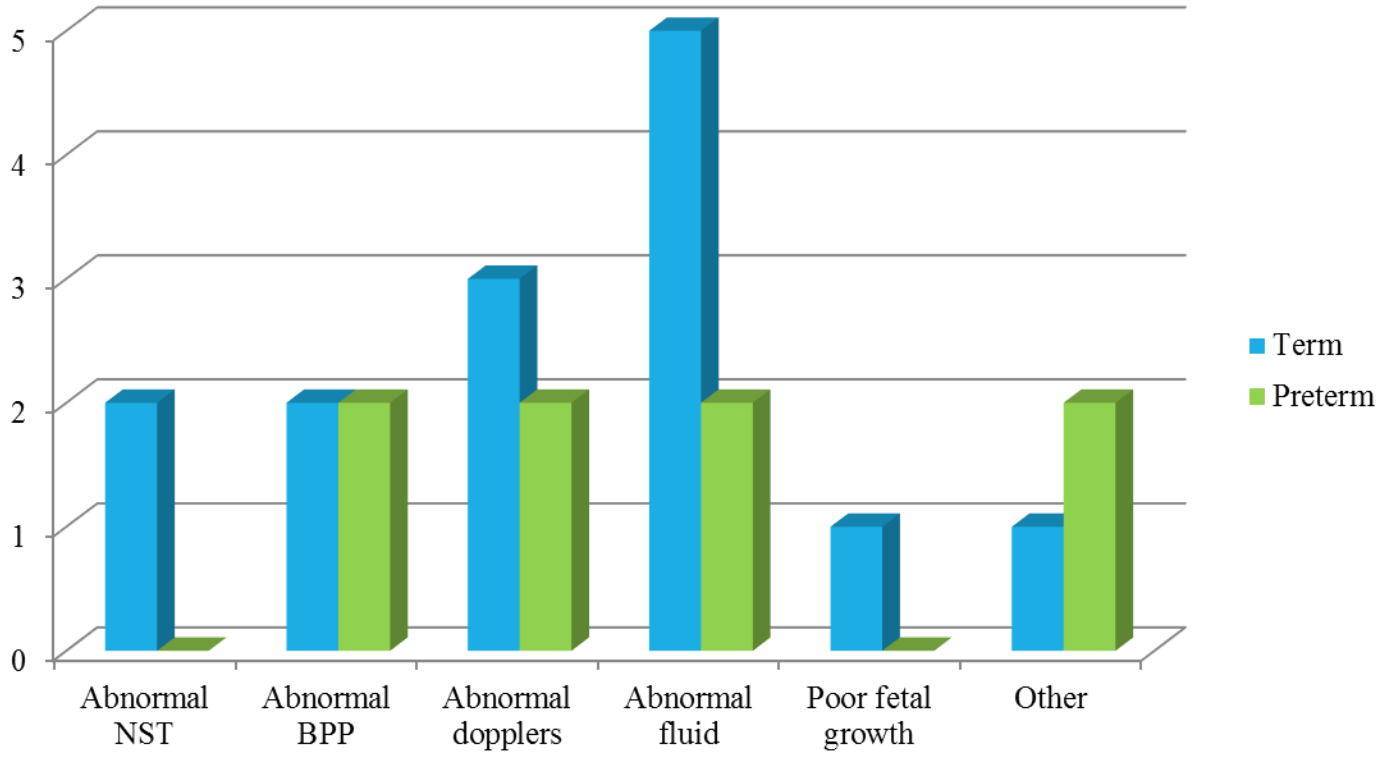
Natural History of Trisomy 21 – Before Birth

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



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

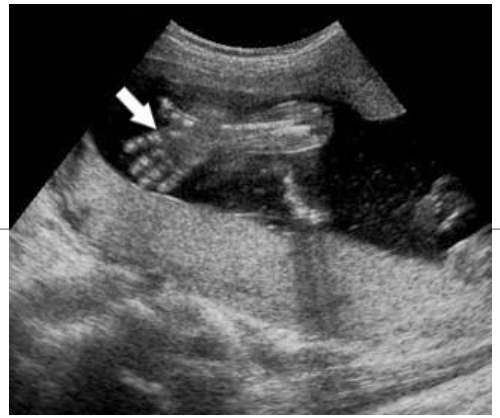
Health care concerns as adults – presenile dementia/Alzheimer-type disease (AD), adult-onset epilepsy, adult cataracts

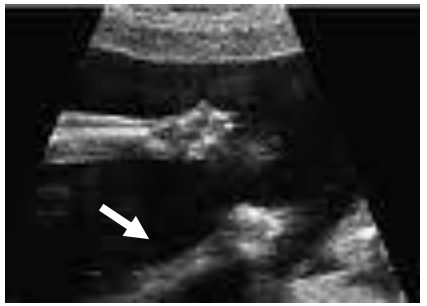
- AD in < 50 year olds 10-25%
- AD in 60 year olds 50%
- AD in 70 year olds 75%

Average life span 49 year of age

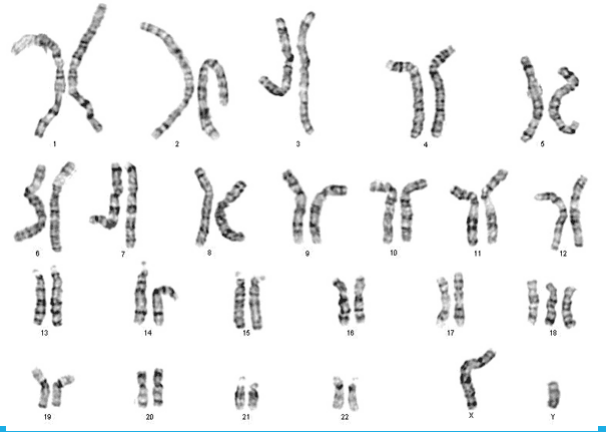
(Menéndez, 2005, Young, 2006)

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

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

(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

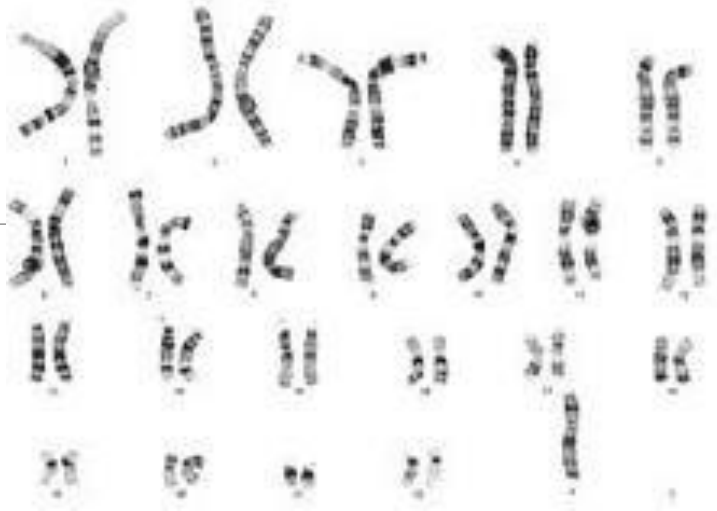
Not maternal age related

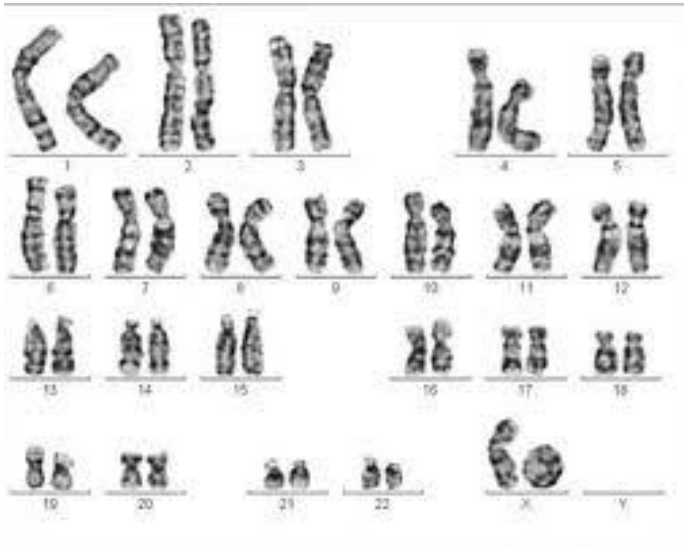
Absent sex chromosome is usually (75%) paternal

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





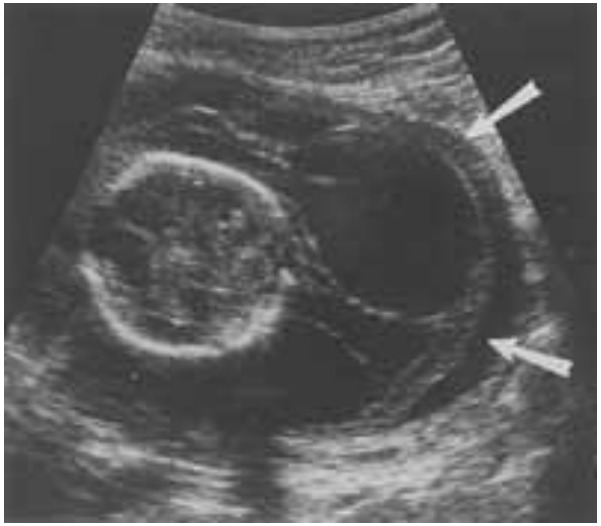
Natural History Fetal 45, X

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% hypolastic 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 $\geq$ 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 1st 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

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