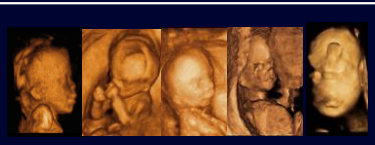
Common Chromosomal Syndromes in the Second Trimester



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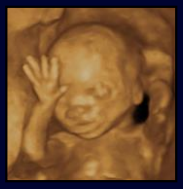
Diagnostic Ultrasound Associates

Disclosures

Bryann Bromley MD

Relevant Financial Relationships: None



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Learning Objectives

1. **Recognize the utility of the 2nd trimester sonogram as a screening tool for aneuploidy.**
2. **Describe the sonographic features of common aneuploidies.**
3. **Analyze and interpret markers for aneuploidy in the context of *a priori risk.***
4. **Understand the significance of markers after cell-free DNA screening.**
5. **Assess the risk of pregnancy loss associated with invasive diagnostic testing.**

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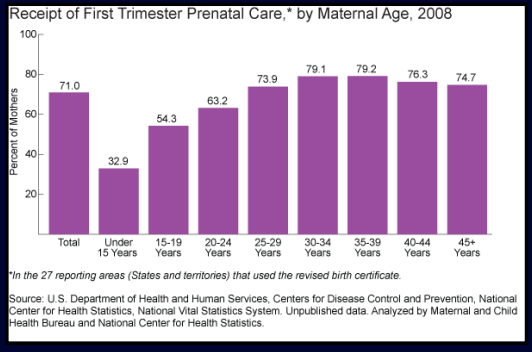

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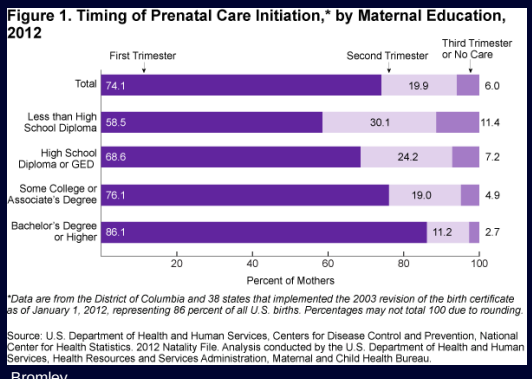

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Chromosomal Syndromes

The major chromosomal syndromes present with a relatively distinct constellation of findings.

- **Trisomy 21**
- **Trisomy 18**
- **Trisomy 13**
- **Triploidy**
- **45, X**

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Lecture Outline

1. Components of Genetic Sonography
2. Genetic Sonography for detection of T 21
   - Structural Malformations
   - Markers for Trisomy 21
   - Bayes Theorem to calculate revised risk
   - GS after first trimester risk assessment
   - Markers in the era of cell-free DNA
3. Trisomy 18
   - Structural Malformations
   - Markers for Trisomy 18
4. Trisomy 13
5. Triploidy and Monosomy X

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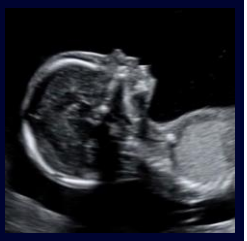
Detailed Obstetrical Ultrasound Genetic Sonography

Independent of MA & Serum Screening

- 16 - 20 weeks gestation
- Biometry (BPD, FL, HL, NB)
- Structural Anomalies
- Search for "markers"



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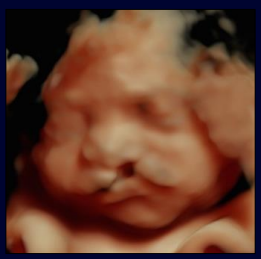
Structural Anomalies (SA)



Medical, surgical or cosmetic consequence regardless of karyotype.

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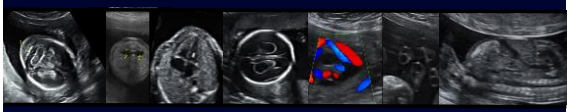
Markers

Sonographic features that are often normal and transient.



Higher prevalence **in the aneuploid population but most fetuses seen with a marker are euploid.**

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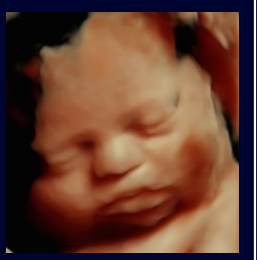
Trisomy 21



- Most common aneuploidy to result in a live birth.
- 1:504 second tri
- Sonographically elusive in the second trimester

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Egan et al. OG 2000

Anomalies T 21: 20-30% by prenatal US

Congenital Heart Defects

- Atrioventricular Canal
- Tetralogy of Fallot
- Atrial Septal Defects
- Ventricular Septal Defects

Gastrointestinal

- Duodenal atresia
- Esophageal atresia
- Tracheoesophageal Fistula
- Hirschsprung

Musculoskeletal, Genitourinary Tract, Ventriculomegaly *

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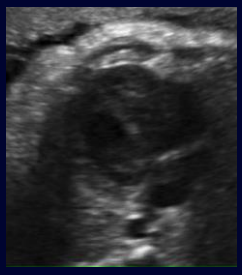
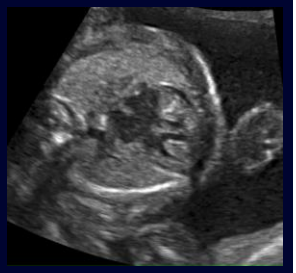
Stoll et al. Eur J Med Gen 2015

Cardiac Defects in T21





Atrioventricular Canal Defect

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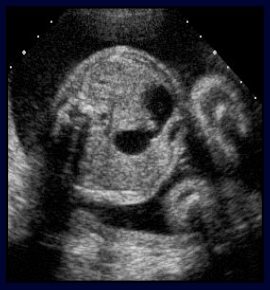
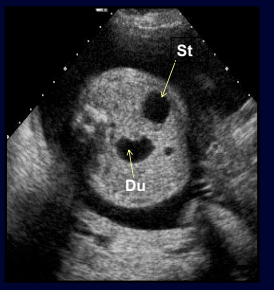
Duodenal Atresia





Double Bubble

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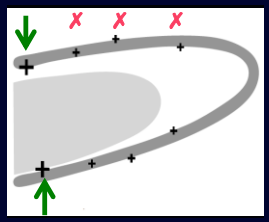
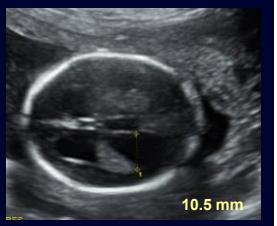
Mild Ventriculomegaly (10-15 mm) SA or Marker





Melchiorre et al . UOG 2009

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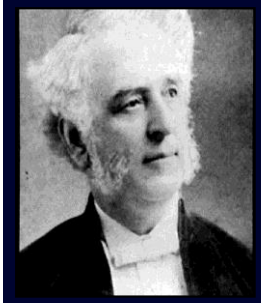
Dr. Langdon Down



" The face is flat and broad, destitute of prominence……skin is deficient in elasticity, giving the appearance of being too large for the body….the nose is small. "

London Hospital Reports 1866

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Commonly Used 'Markers' for T21

- Nuchal Skin Fold Thickness (NF)
- Short Femur / Humerus
- Urinary Tract Dilation (UTD)
- Hyperechoic Bowel (HEB)
- Echogenic Intracardiac Focus (EIF)
- Nasal Bone (NB)

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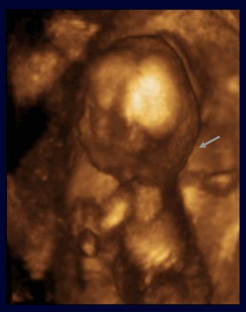
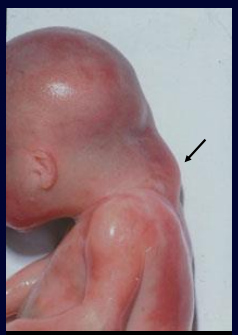
Nuchal Fold





Courtesy of Dr. Nyberg

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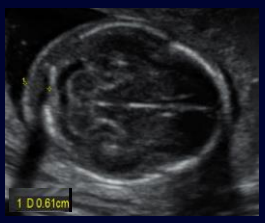
Nuchal Fold: 40-50% of T21



- Axial Scan: thalami, cerebral peduncles, cerebellum
- Measure: occipital bone to skin edge
- Overangling spuriously large measurement

Benacerraf et al. NEJM 1987

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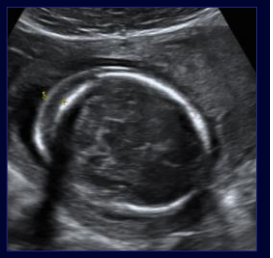
Nuchal Fold: Increases With Gestational Age

- ≥ 6 mm abnormal
- ≥ 5 mm 'borderline'
- MoM



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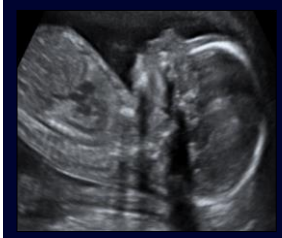
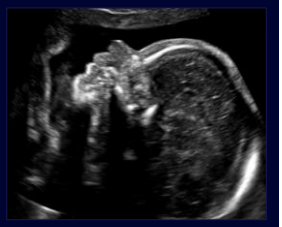
Absent (37%) or Hypoplastic* Nasal Bone (67%) 2nd tri. T 21





* Def. of hypoplastic NB not uniform among studies (< 2.5 mm , < .75 MoM, < 5%, BPD/NBL < 10)

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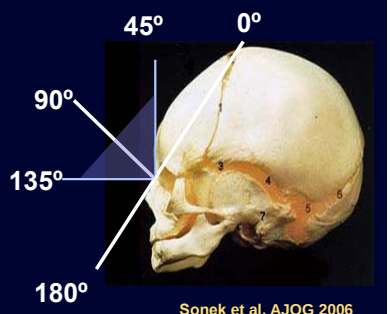
Technique for NB assessment

- Midsag profile
- Angle of insonation



Sonek et al. AJOG 2006

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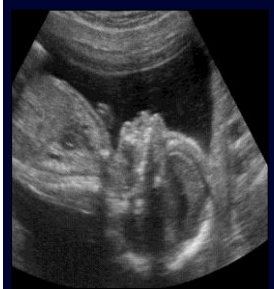
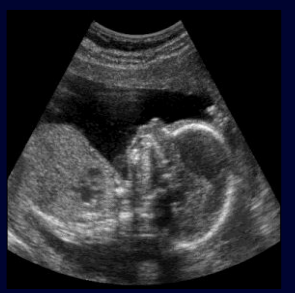
Wrong Angle of Insonation



Correct Angle of Insonation



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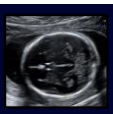
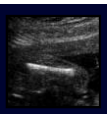
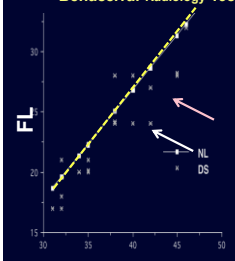


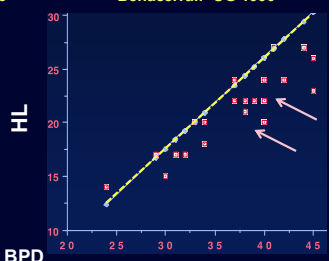
Short Femur/Humerus c/w BPD



Benacerraf Radiology 1989



Benacerraf. OG 1990



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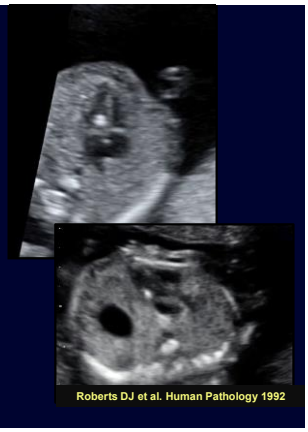
Echogenic Intracardiac Focus

- Discrete "dot" in the cardiac ventricle which is as bright as bone
- Most commonly in LV
- Pathologically represents a calcified papillary muscle



Roberts DJ et al. Human Pathology 1992

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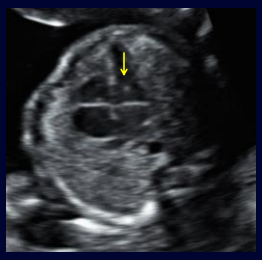
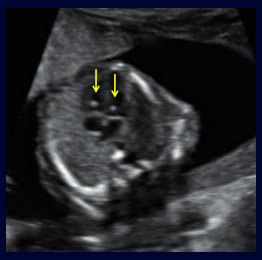
Not an EIF



Bilateral EIF



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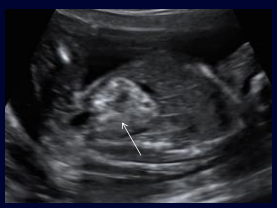
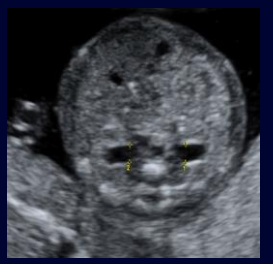
Hyperechoic Bowel



Echogenicity = Bone

Urinary Tract Dilation



AP pelvis ≥ 4mm

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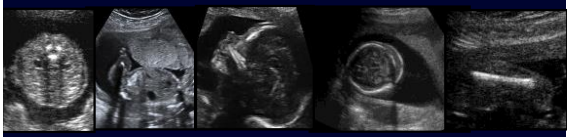
Ultrasound - Bayes Theorem



A Priori Risk x **LR Marker** = **Revised Risk**

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LR: Clusters of Markers

# Markers	Nyberg 2001	Bromley 2002	FaSTER 2009
0	0.4	0.2	0.46
1	2	1.9	3.1
2	10	6.2	21
≥ 3	115	80	170

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LR of Isolated Markers

I. Marker	Nyberg 2001	Smith-B. 2001	Bromley 2002
NF	11	17	NC
Humerus	5.2	7.5	5.8
HB	6.7	6.1	NC
Femur	1.5	2.7	1.2
UTD	1.5	1.9	1.5
EIF	1.8	2.8	1.4

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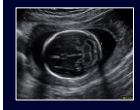
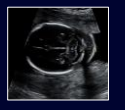
Risk Adjustment





A Priori Risk 1:1000

Normal GS (LR .2-.4)

Revised Risk = 1/1000 x 0.3

1/3333

GS: NF (LR 11-17)

Revised Risk = 1/1000 x 14

1/71

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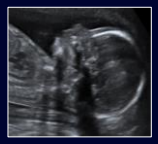
Genetic Sonography : T21

(1994-2002 – varying markers, no NB)

Detected: 60 - 85% of fetuses with Trisomy 21 with a FPR 5 -15%

< 2002: NB included



A/H NB: LR^+ 50.5
LR- 0.38

Increased detection rate by 7-14%

Vintzileos et al. OG 03
Cicero et al. UOG 03

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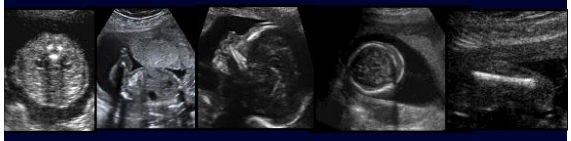
Statistically More Robust



A Priori Risk **x** +/-LR Each Marker **=** Revised Risk

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LR from Meta-Analysis

Marker	LR+	CI	LR-	CI
NF	23.3	14.35-37.83	0.80	0.74-0.85
NB (a/h)	23.27	14.23-38.06	0.46	0.36-0.58
EIF	5.83	5.02-6.77	0.80	0.75-0.86
HEB	11.44	9.05-14.47	0.90	0.86-0.94
Short F	3.72	2.79-4.97	0.80	0.73-0.88
Short H	4.81	3.49-6.62	0.74	0.63-0.88
UTD	7.63	6.11-9.51	0.92	0.89-0.96

Agathokleous et al. UOG 2013

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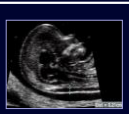
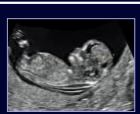
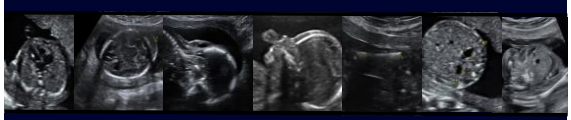
GS After 1st Trimester Screening



β-hCG
PAPP-A



NT and NF independent of each other



Can be used as a sequential screen

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DR (%) T21: 5% FP

Test	STD	pUS
GS alone	69	**
Quadruple	81	90
Combined	81	90
Integrated	93	98
Stepwise	97	98
Contingent	95	97

Aagaard-Tillery et al: OG 2009

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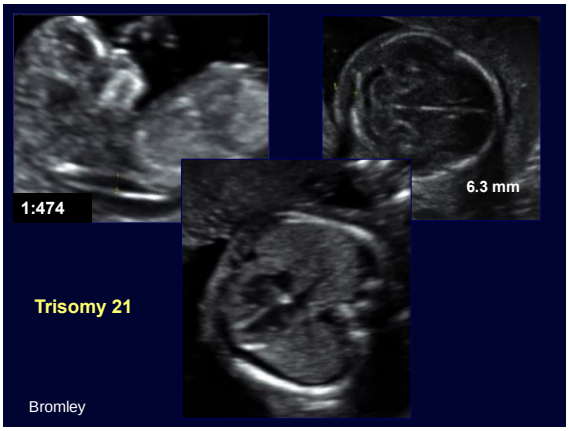

Trisomy 21

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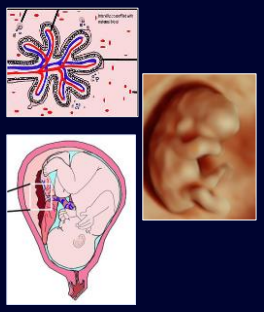
Cell free DNA- ≥ 10 wks GA



Abnl	Sens.	FPR
T21	99.2%	.09%
T18	96.3%	.13%
T13	91.0%	.13%
45X	90.3%	.23%
SCA	93.0%	.14%
X,Y	96.6%	1.1%

Gil et al. UOG 2015,

Bromley

Cell-free DNA: The implication of a "Positive" or "Negative" Result

	High Risk > 99% (+LR)	Low Risk < 1:10,000 (-LR)
T21	1240	100
T18	650	31
T13	460	13

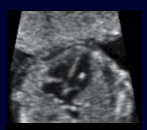
Chance of being affected depends on *a priori risk!!*

PerinatalQuality.org

Gratacós and Gil Fetal Diagn Ther 2014

Bromley

A Priori 1:500



EIF (LR 2)

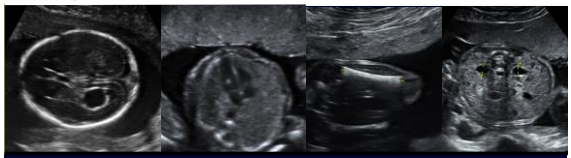
Neg. *cf* - DNA

Revised Risk = 1/500 x 2 1/250

Revised Risk = 1/250 x .01 1/25,000

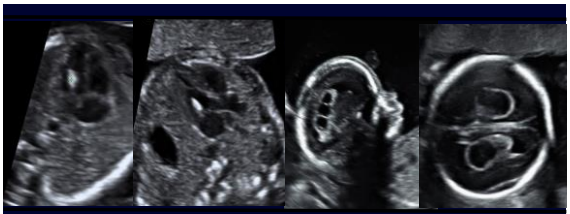
Bromley

Fetal imaging: Executive Summary of a Joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop *http://dx.doi.org/10.1016/j.ajog.2014.02.028*



"In women who have undergone …..cell free DNA testing…. the association of isolated soft markers and aneuploidy is generally no longer relevant."

Bromley



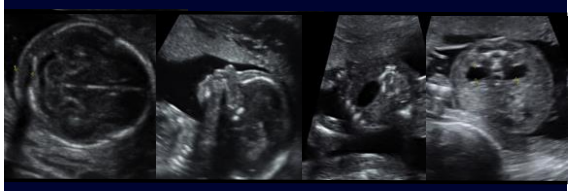
Isolated EIF (T21,T13) or CPC (T18) no longer relevant

No follow-up recommended after 'targeted scan'

Detailed Scan

Wax et al. JUM 2014

Bromley



- NF
- A/H NB
- HEB
- UTD
- Short Femur

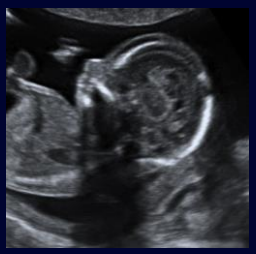
Possible association with other genetic abnormalities (aneuploidies, gene deletions, CF) or adverse outcome (infection, growth restriction, bowel abnormalities and UTD.

Bromley

Trisomy 18: Edward Syndrome

1:3000 births

- > 90% detected by US in 2nd tri
- 48% live-born
- Survival after birth: median 9 days; 1 yr 13 %, 10 yr 10%



Russo et al. Am J Med Genet Part A 2015

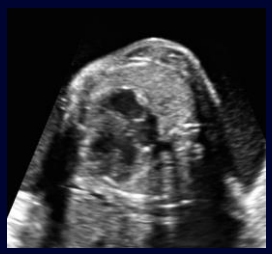
Nelson et al. JAMA 2016

Bromley

Trisomy 18: Edward Syndrome

Structural Anomalies

- Cardiac (87%)
- Abnl fingers (55%)
- Abnl feet (39%)
- Skeletal (39%)
- Craniofacial (32%)
- CNS* (23%)
- GI (16%) / GU (3%)

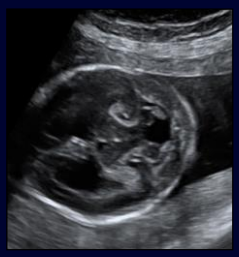


Lai et al. PD 2010

Bromley

CNS Abnormalities

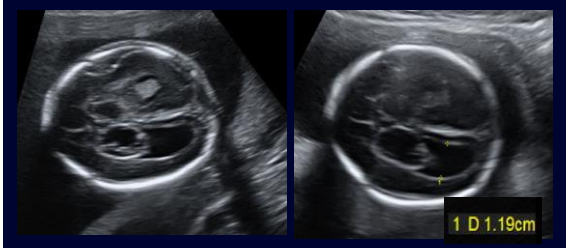
- Small CBL
- Posterior Fossa
- Neural Tube Defect
- Agenesis Corpus Callosum



Yeo et al. JUM 2003

Bromley

Mild Ventriculomegaly

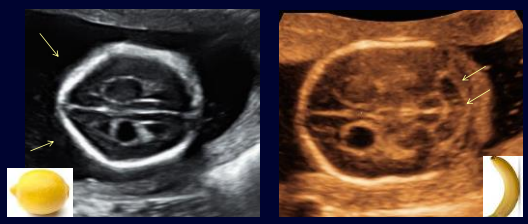


Bromley

Neural Tube Defect

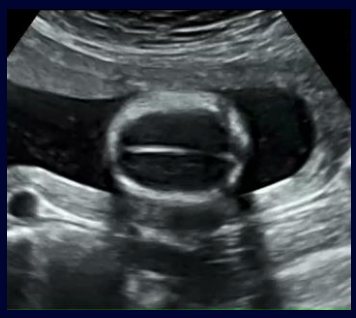
Lemon sign

Banana sign



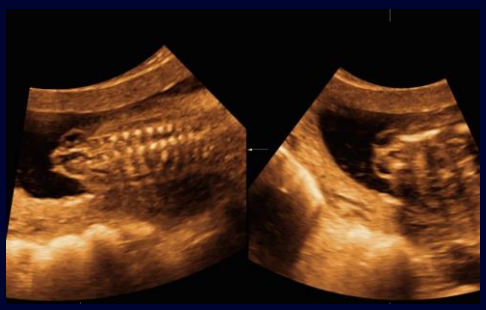
Bromley

Neural Tube Defect



Bromley

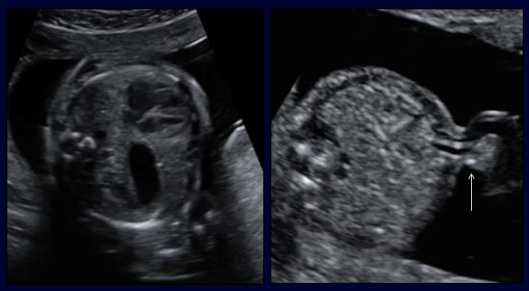
Neural Tube Defect



Bromley

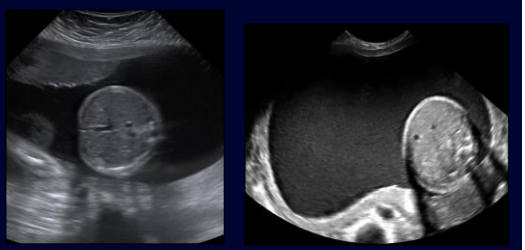
CDH

Omphalocele



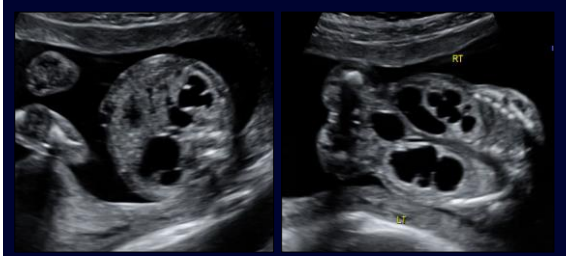
Bromley

Esophageal Atresia



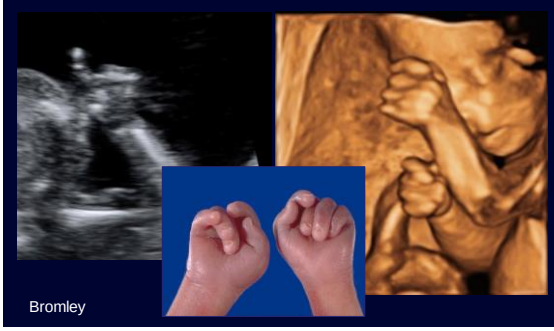
Bromley

Genitourinary Anomalies

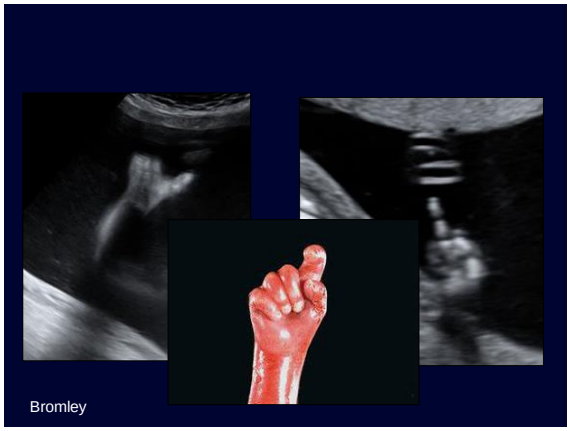


Bromley

Abnormal Clenched Hands
Abnormal Index Finger

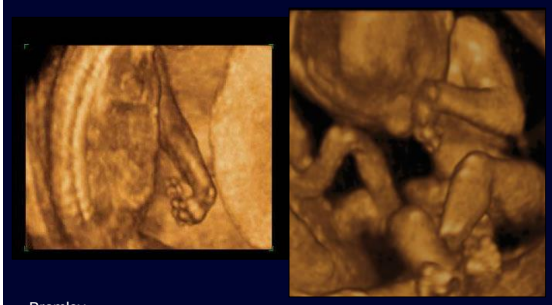


Bromley



Bromley

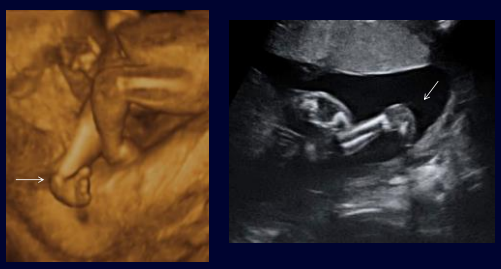
Radial Ray Defects
Abnormal Posturing of Hands



Bromley

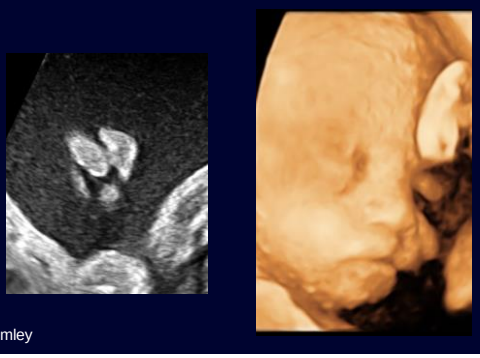
Abnormal Lower Extremities

Clubfoot **Rocker Bottom**



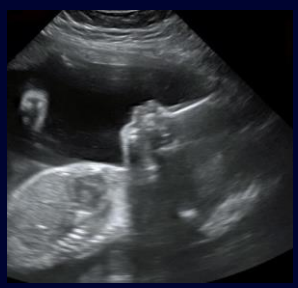
Bromley

Facial Cleft – Rare in T18



Bromley

Micrognathia

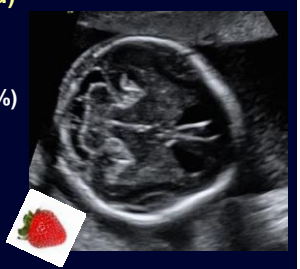


Bromley

Trisomy 18: Edward Syndrome

Markers (not isolated)

- CPC (50%)
- NF/CH (16%)
- Strawberry Skull (45%)
- ECM
- SUA
- UC cyst
- IUGR (89%)
  - * poly

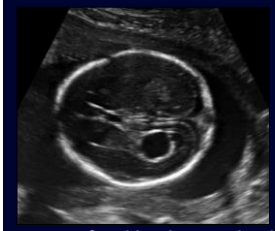


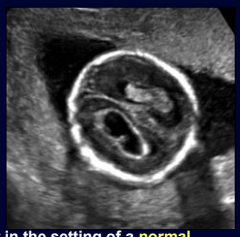
Lai et al. PD 2010

Bromley

CPC: 30-50% 2nd Tri T18

1-2% euploid fetuses

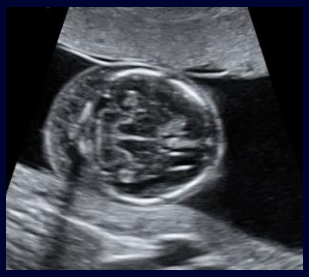




Considered a normal variant in the setting of a normal detailed fetal ultrasound and at low-risk for T 18 based on an accepted screening protocol.

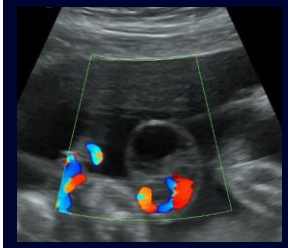
Bromley

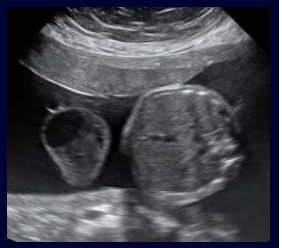
NF and Cystic Hygroma



Bromley

Umbilical Cord Cyst



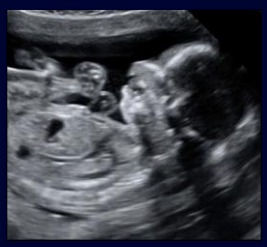


Bromley

Trisomy 13: Patau Syndrome

1:6000 births

- > 90% detected by US in 2nd tri
- 50% IUFD
- Median Survival 12 days; 20% 1 year; 13% 10 years



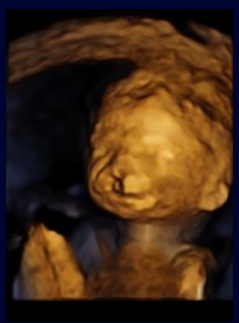
Barry et al. A J Med Gen Part A 2015
Nelson et al. JAMA 2016

Bromley

Trisomy 13: Patau Syndrome

Structural Anomalies

- CNS
  - Holoprosencephaly
  - Posterior Fossa
  - NTD
  - Microcephaly
- Midline Facial
  - Cleft
  - Hypotelorism
  - Proboscis

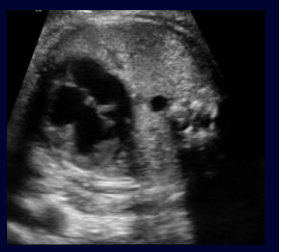


Bromley

Trisomy 13: Patau Syndrome

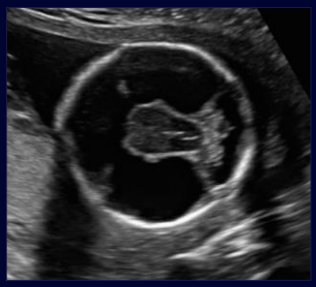
Structural Anomalies

- Cardiac Defects (80%)
- Oomphalocele
- CDH
- Renal Abnormalities
- Abnormal extremities
  - Postaxial Polydactyly
  - Club Feet

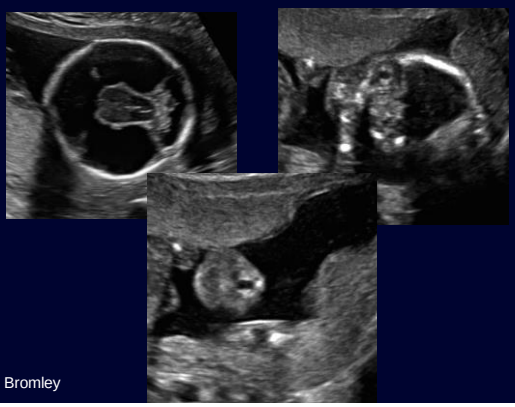


Bromley

Holoprosencephaly

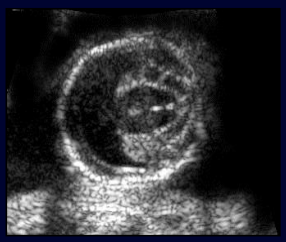


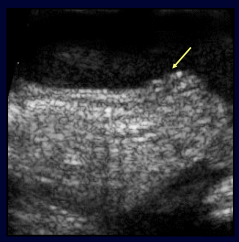
Bromley



Bromley

Holoprosencephaly and NTD



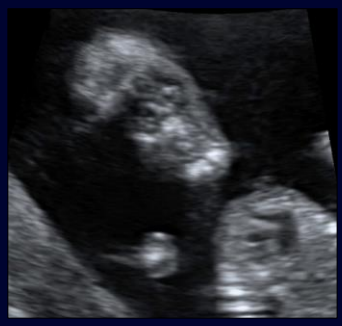


Holoprosencephaly

NTD

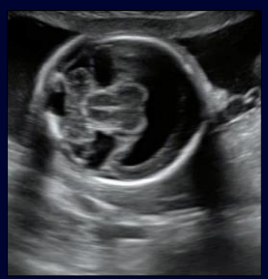
Bromley

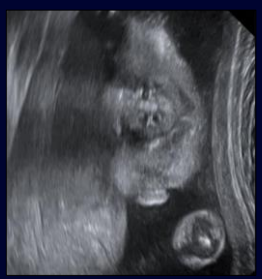
Hypotelorism



Bromley

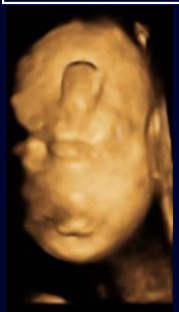
Trisomy 13

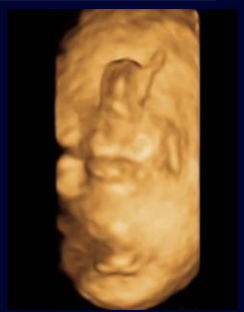




Bromley

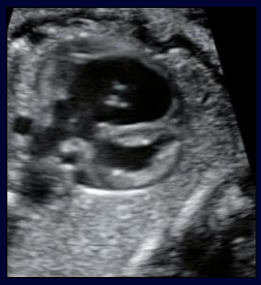
T13: Proboscis and Hypotelorism

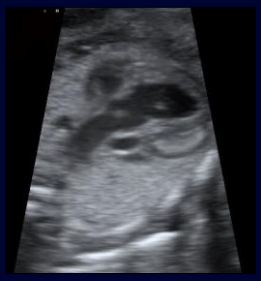




Bromley

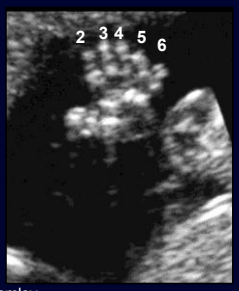
T13: Congenital Heart Defect

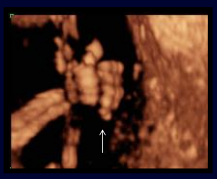




Bromley

T13: Postaxial Polydactyly

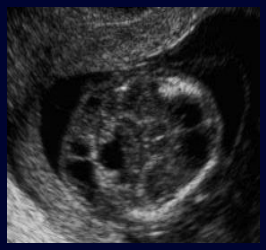




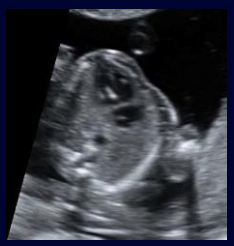
Bromley

Trisomy 13: Patau Syndrome

Markers: Not Isolated



Cystic Hygroma

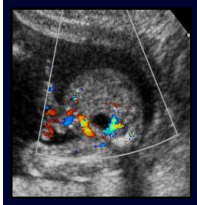


EIF (30%)

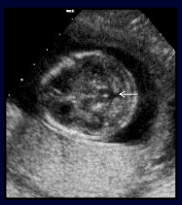
Bromley

Trisomy 13: Patau Syndrome

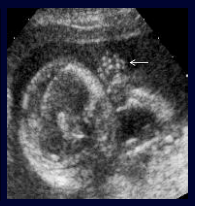
Markers: Not Isolated



SUA



Abnl PF

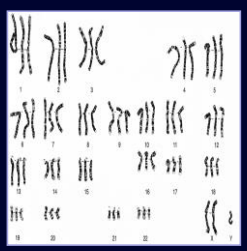


Polydactyly

Bromley

Triploidy: 1:5000 in second tri

69 Chromes



Paternal (dispermy /diandry)

Maternal

Not Maternal age related

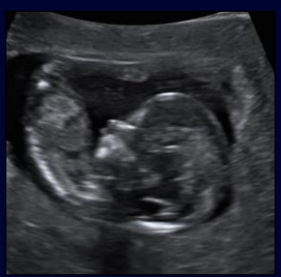
↑↑ **Sp. Ab.**

Jauniaux et al. OG 1996
Baumer et al. Eur. J Hum Gen 2000

Bromley

Triploidy

- Multiple anomalies
- Placental anomalies
- Asymmetric early growth restriction

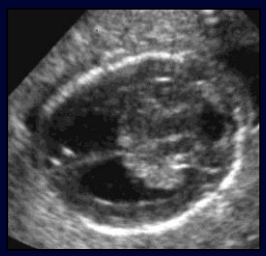


Bromley

Triploidy

Structural Anomalies (92%)

- CNS
  - Posterior Fossa
  - Ventriculomegaly (37%)
  - NTD
- Cardiac Defects (34%)
- Facial Defects
  - Hypertelorism
  - Micrognathia (26%)
- Abnormal Extremities
  - Syndactyly (52%)



Jauniaux et al. OG 1996

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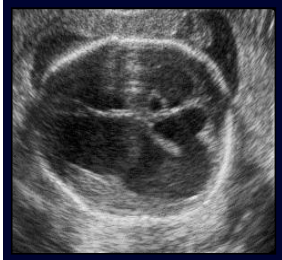
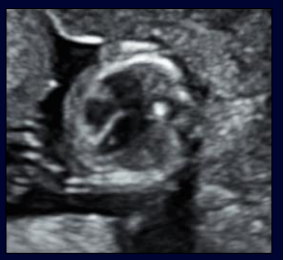
Ventriculomegaly



Cardiac Abnl



Jauniaux et al. OG 1996

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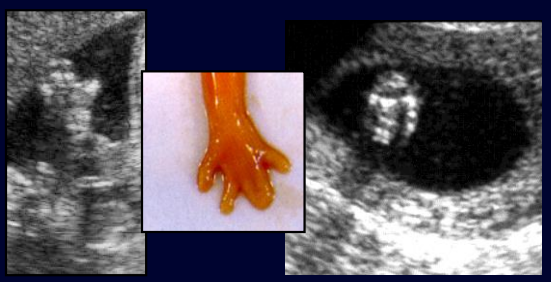
Syndactyly: 3-4 (52%)



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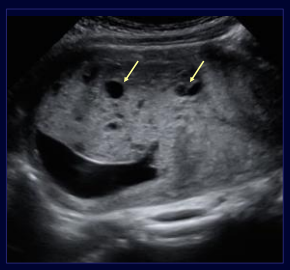
Placental Pathology (28.6%)

- Placental hydropic changes associated with extra haploid set of paternal origin
- Placentas are small with extra maternal haploid set



Jauniaux et al. OG 1996

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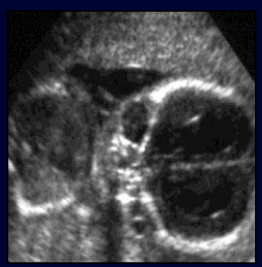
Triploidy: Head and Body Size Discrepancy

Oligohydramnios



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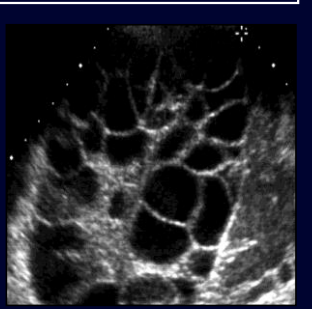
Perinatal Outcome: IUFD Most Common

Maternal

- Theca Lutein Cysts
- Hyperemesis
- Pre-eclampsia
- Trophoblastic Dz



Bromley

45,X Monosomy X (Turner)

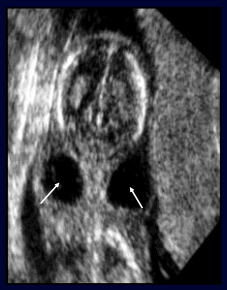
1:2500 Live Births

(- Paternal 78 %)

Not age related

45, X vs. Mosaic

↑↑ Spontaneous Ab



Papp et al. JUM 2006
Baena et al. Am J Med Gen Part A 2004

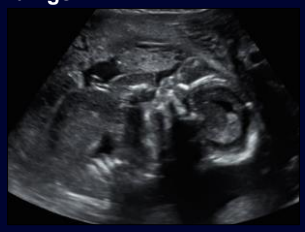
Bromley

45,X Monosomy X (Turner)

- 68 % overall US findings
- 92 % with 45,X

Large Septated
Cystic Hygromas

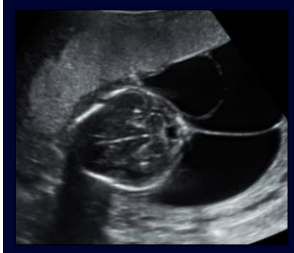
Female

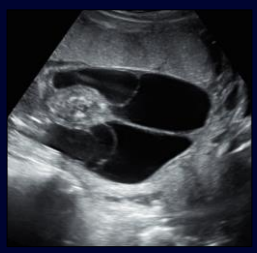


Papp et al. JUM 2006
Baena et al. Am J Med Gen Part A 2004

Bromley

45,X Monosomy X (Turner)





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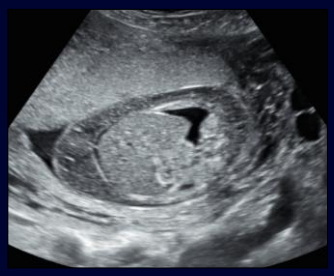
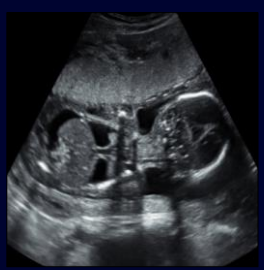
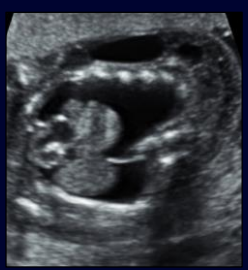
Skin Thickening



Bromley

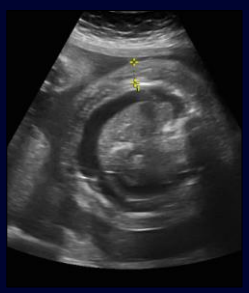
Fetal Hydrops

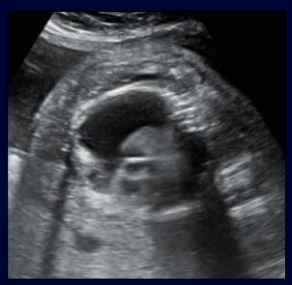




Bromley

Fetal Hydrops





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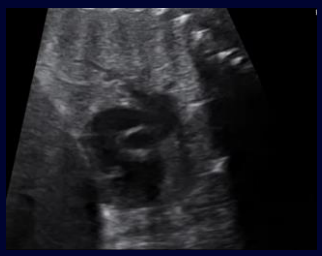
Cardiac Defects (13%)

- Left sided defects
- Coarctation Aorta
- Aortic Valve Anomalies

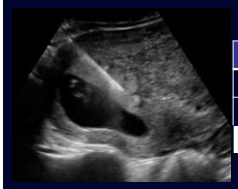


Papp et al. JUM 2006
Baena et al. Am J Med Gen Part A 2004

Bromley

Diagnostic Testing: Gold Standard

CVS **207 losses / 8899 CVS**



< 24 wks	% loss	95% CI
Miscarriage	2.18%	1.61-2.82
Background	1.79%	.61-3.58
PRL	**.22%**	**-0.71-1.16**

Akolekar et al. UOG 2015

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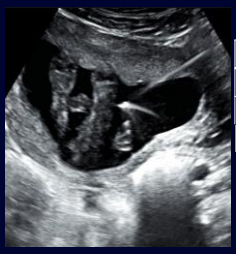
Diagnostic Testing: Gold Standard

Amniocentesis **324 losses / 42,716 A**



< 24 wks	% loss	95% CI
Miscarriage	.81%	0.58-1.08
Background	.67%	0.46-0.91
PRL	**.11%**	**-0.04-0.26**

Akolekar et al. UOG 2015

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Conclusions

- Each chromosomal aneuploidy has a relatively distinct constellation of findings in the 2nd tri
- GS detects 70% of fetuses with Trisomy 21 and 90+ % when including other screening methods
- Markers can be used to adjust the *a priori* risk of aneuploidy in the 2nd tri, including patients with 1st tri screening combined screening

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Conclusions

- GS detects 90% - 100% of those with Trisomy 18 and 13
- Isolated markers are not likely of clinical relevance with respect to aneuploidy after negative cell-free DNA screening –but carry a residual risk of other outcomes
- The procedure related risk of diagnostic testing is low

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Key References

Aagard-Tillery KM, Malone FD, Nyberg DA et al. Role of Second-Trimester Genetic Sonography after Down SyndromeScreening. Obstet Gynecol 2009: 114:1189-1196.

Agathokleous M, Chaveeva P, Poon LCY, et al. Meta analysis for second trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013; 41: 247-261.

Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;45:16-26.

Benacerraf B. Ultrasound of Fetal Syndromes. 2nd Edition. Elsevier. 2008

Bromley B, Lieberman E, Shipp TD, et al. The Genetic Sonogram: A method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002; 21: 1087-1096

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Key References

Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol. 2015;45:249-66

Reddy UM, Abuhamad AZ, Levine D, et al. Fetal Imaging Executive Summary. Obstetrics and Gynecology. 2014

Wax J, Minkoff H, Johnson A, Coleman B, Levine D, Helfgott A, et al. Consensus report on the detailed fetal anatomic ultrasound examination: indications, components, and qualifications. J Ultrasound Med. 2014;33:189-95.

OG: Obstet Gynecol UOG: Ultrasound Obstet Gynecol PD: Prenat Diagn
JUM: J Ultra Med

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