Timing is Critical: How to Optimize Prenatal Genetic Diagnostics in the Abnormal Fetus

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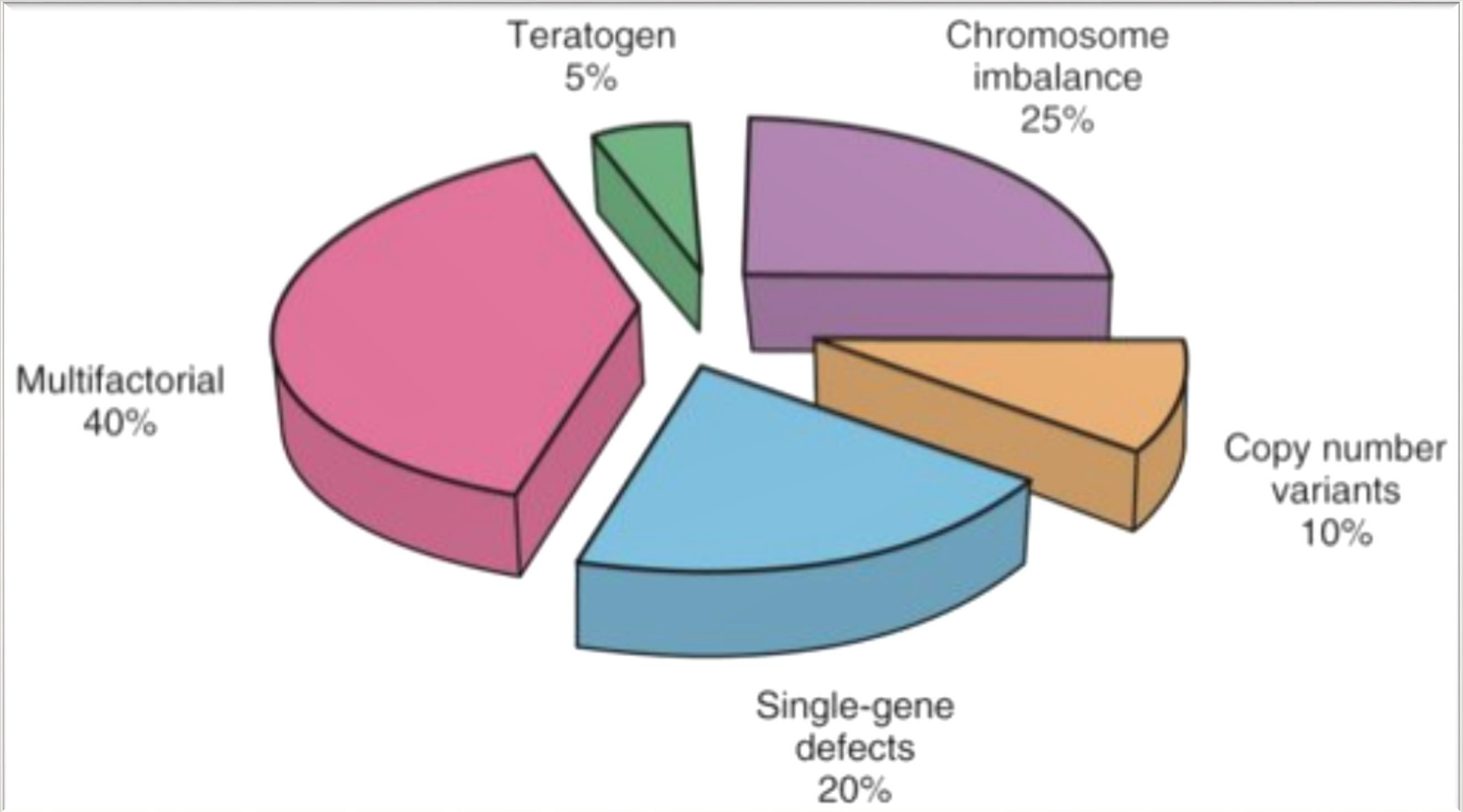
Disclosures

- We have no relevant financial disclosures

Fetal Anomalies

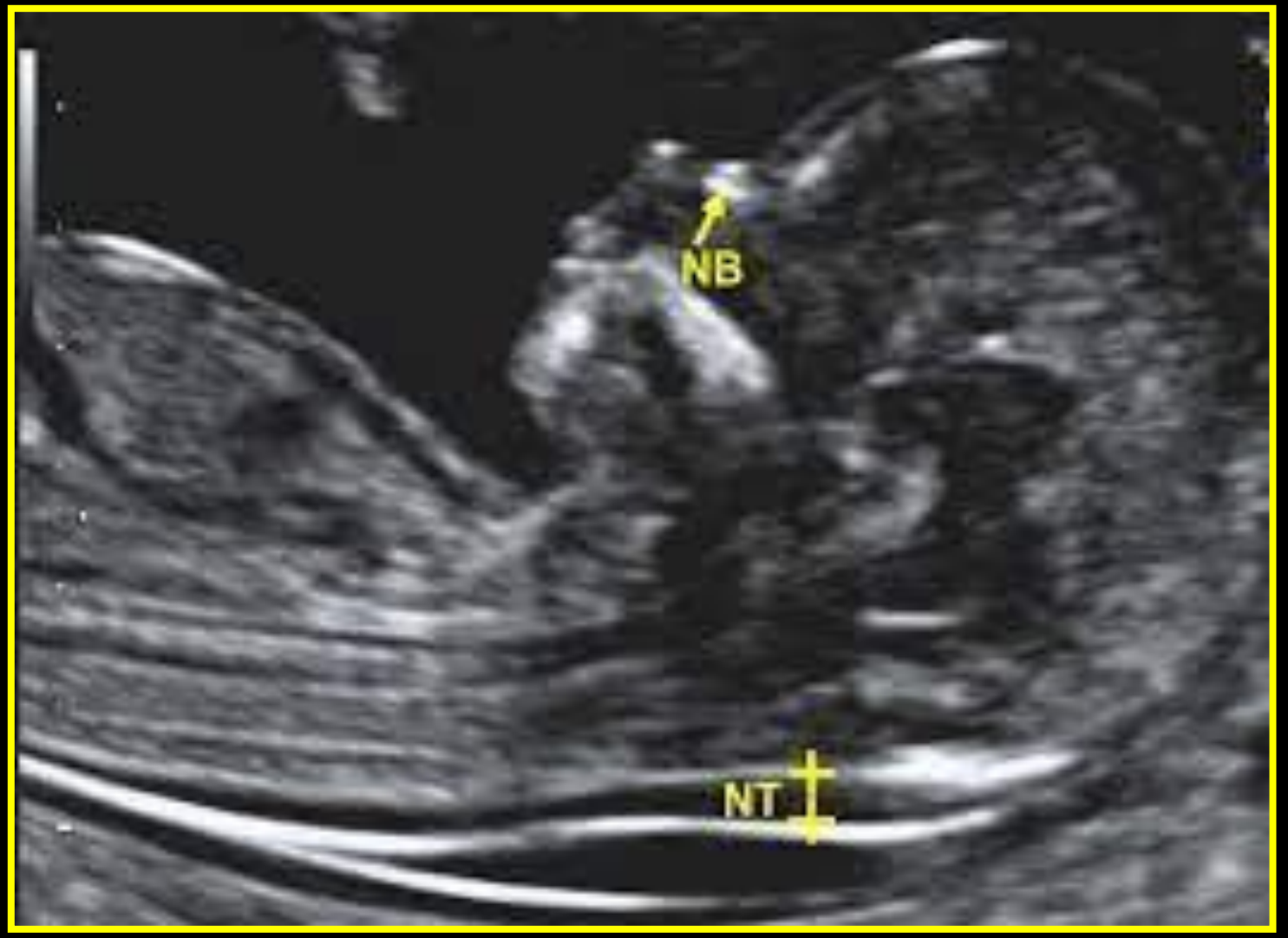
- 3-5% of live births have a congenital anomaly
- Most anomalies are detected on fetal anatomy scan
  - Anomalies may be identified on any ultrasound


Teratogen
5%
Chromosome
imbalance
25%
Multifactorial
40%
Copy number
variants
10%
Single-gene
defects
20%

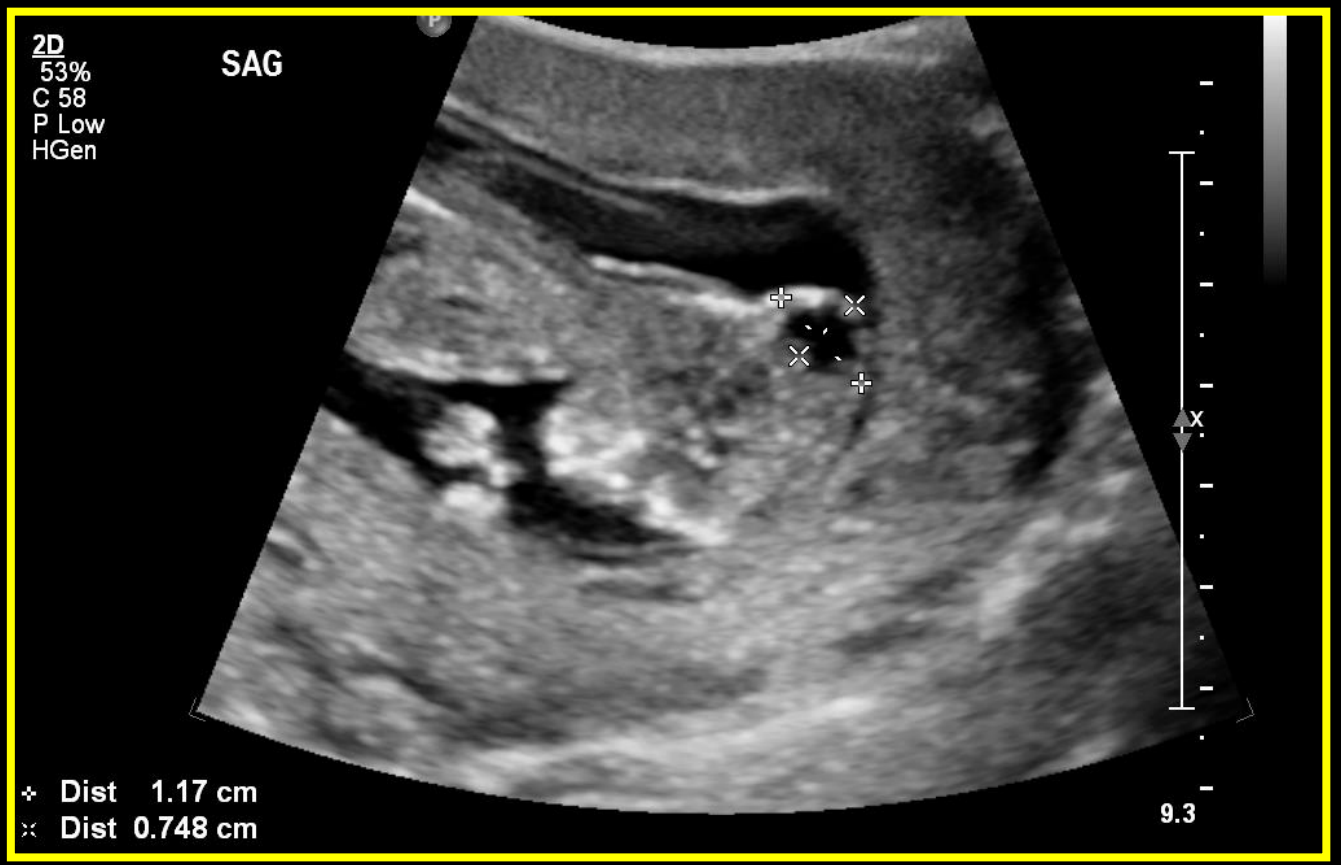
First Trimester Case

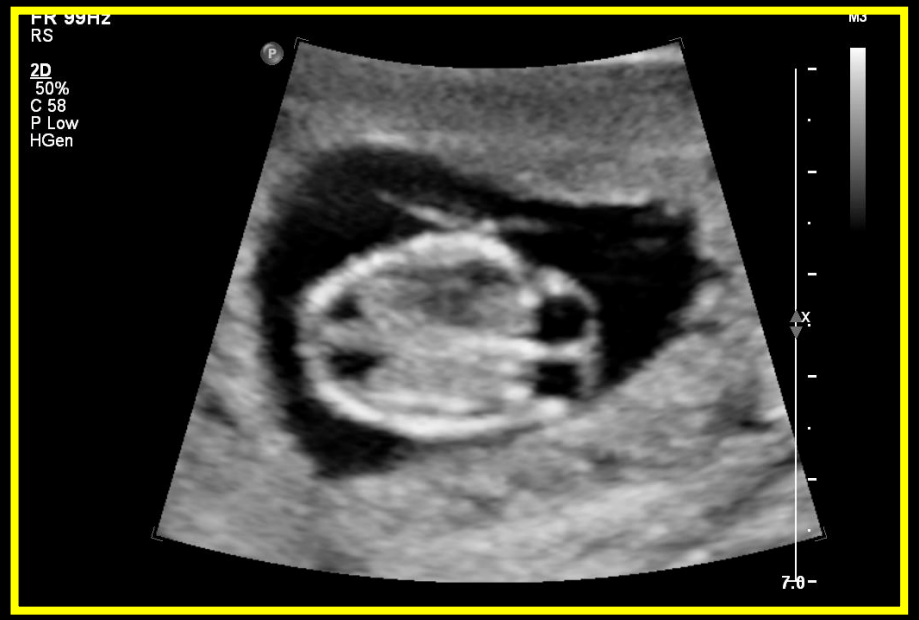
- 25 year old G1P0 at 13w0d
- First trimester ultrasound identified occipital encephalocele containing cerebrospinal fluid only

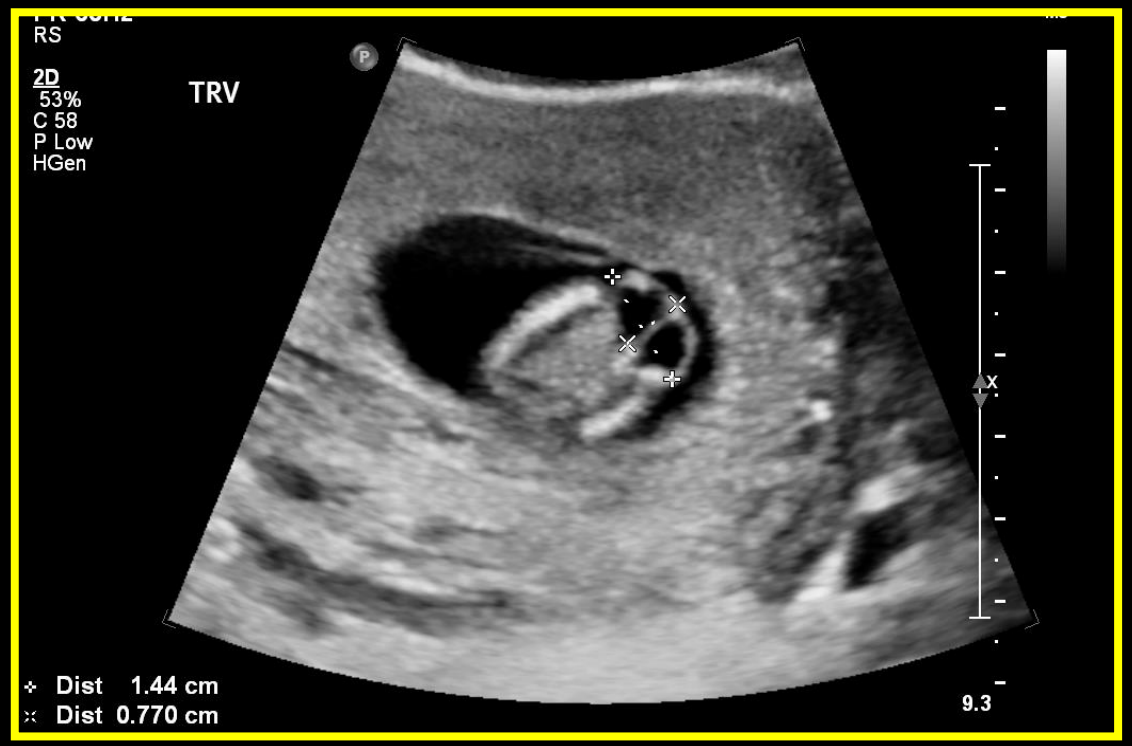
First Trimester Anatomic Evaluation - Normal NT



First Trimester Anatomic Evaluation







Genetic Counseling

- Discussed with patient that isolated neural tube defects are typically multifactorial
  - Some caused by chromosome abnormalities or single gene conditions
  - Limited phenotypic information in first trimester
- Patient elected for chorionic villus sampling (CVS)

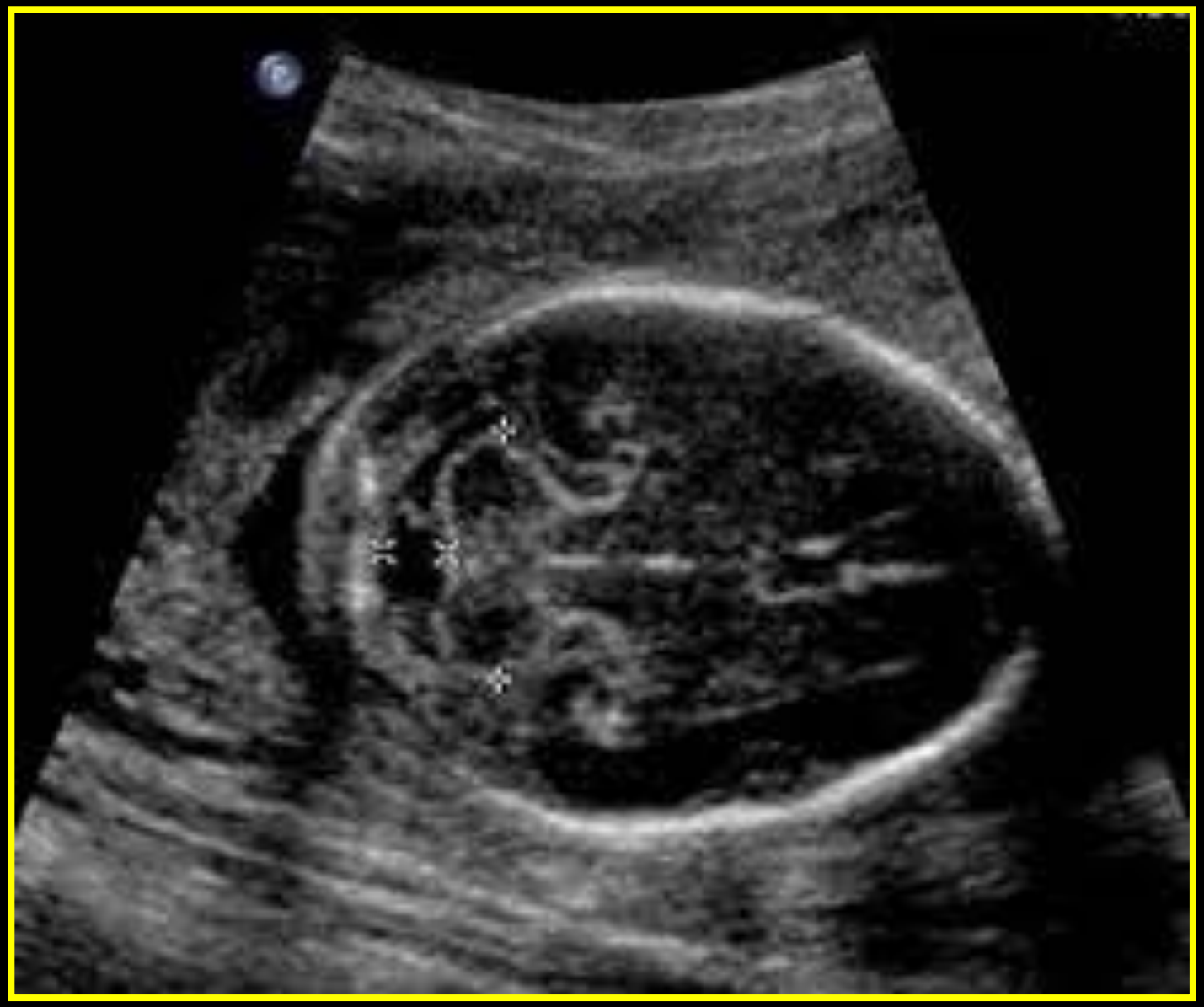
CVS Results

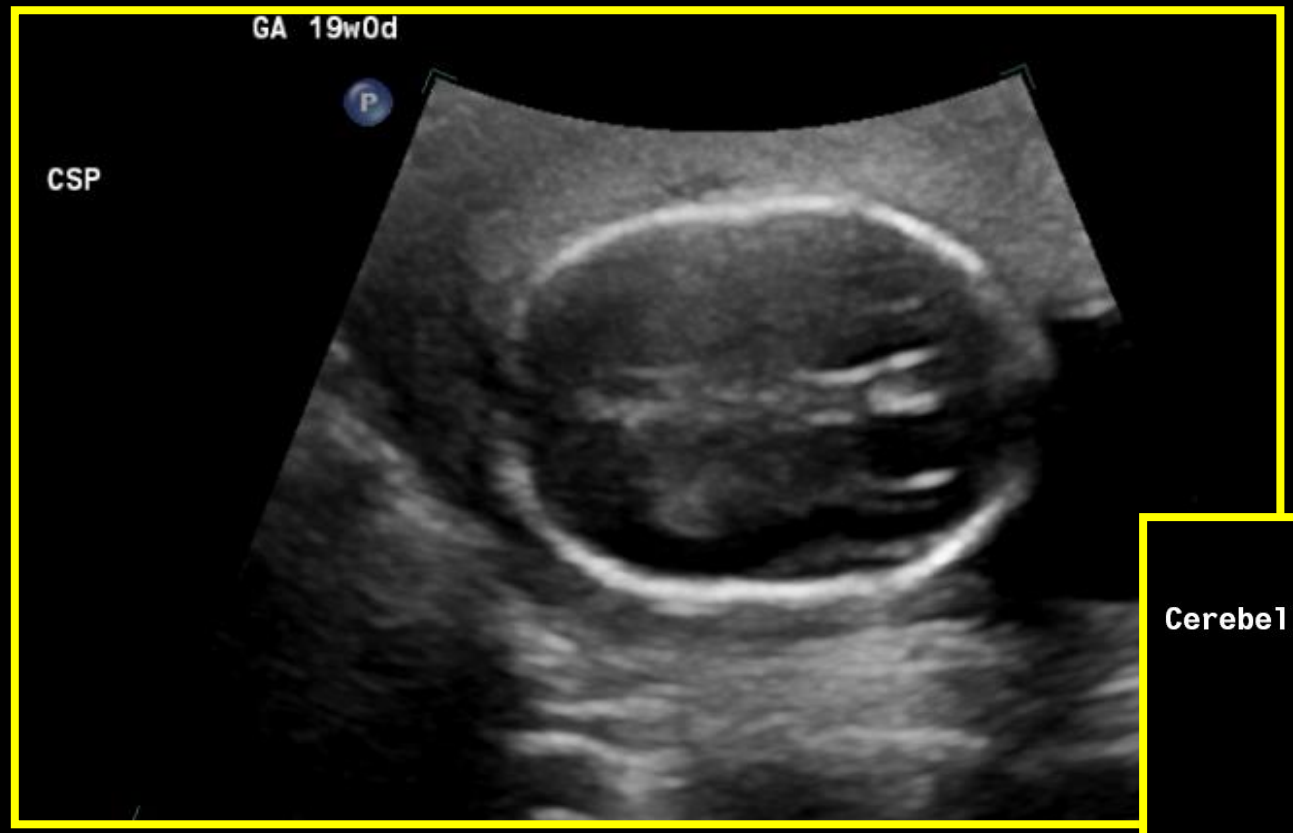
- Karyotype: 92, XXXX (tetraploidy)
- Prognosis changed from uncertain to lethal
- Recurrence risk: not increased

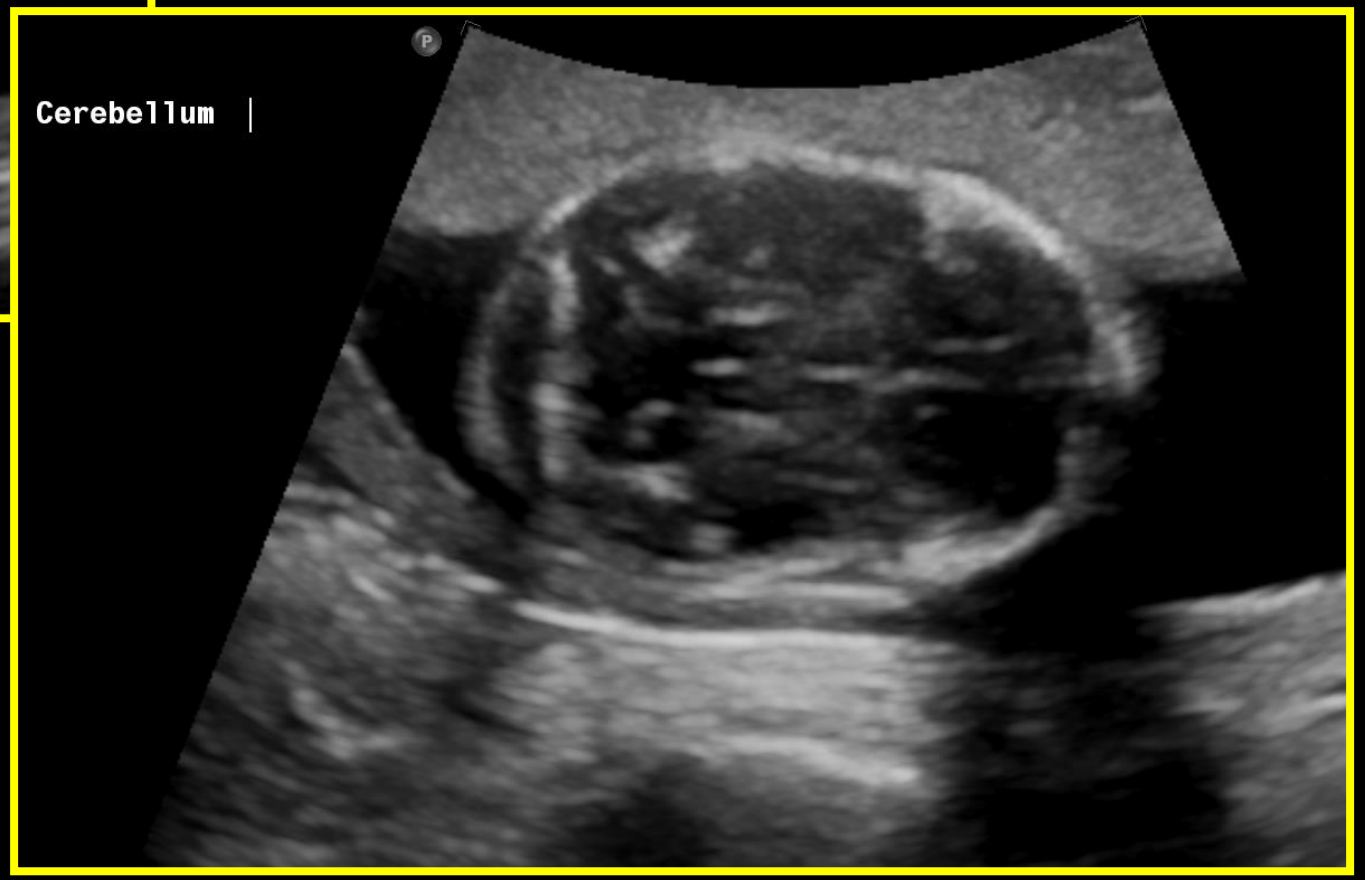
Second Trimester Case

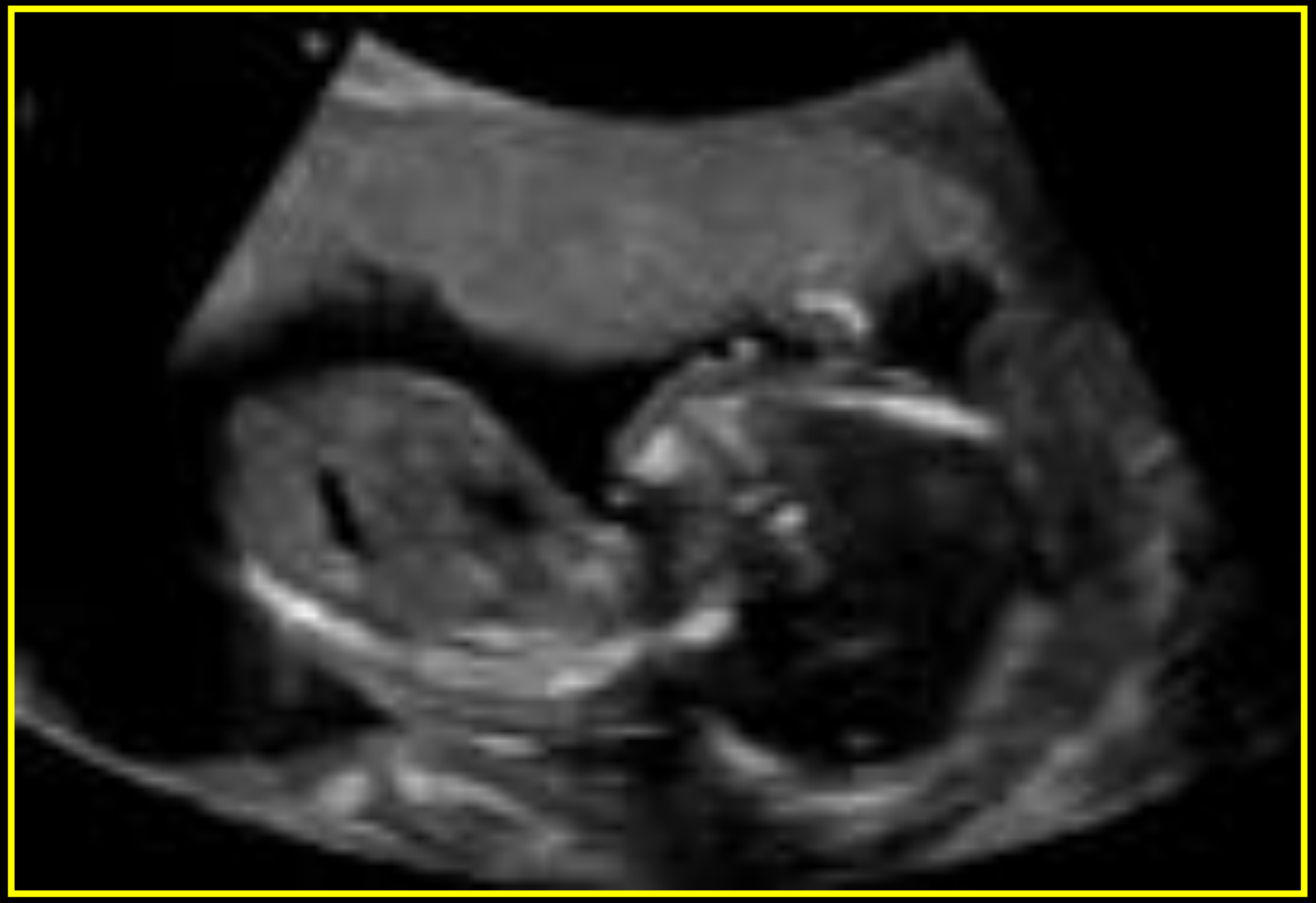
- 26 year old G1P0 at 19w0d
- Multiple anomalies including:
  - single umbilical artery
  - complex cardiac defect
  - vermian hypoplasia
  - Polydactyly
  - Clubfeet
  - flattened facial profile
- No previous genetic screening

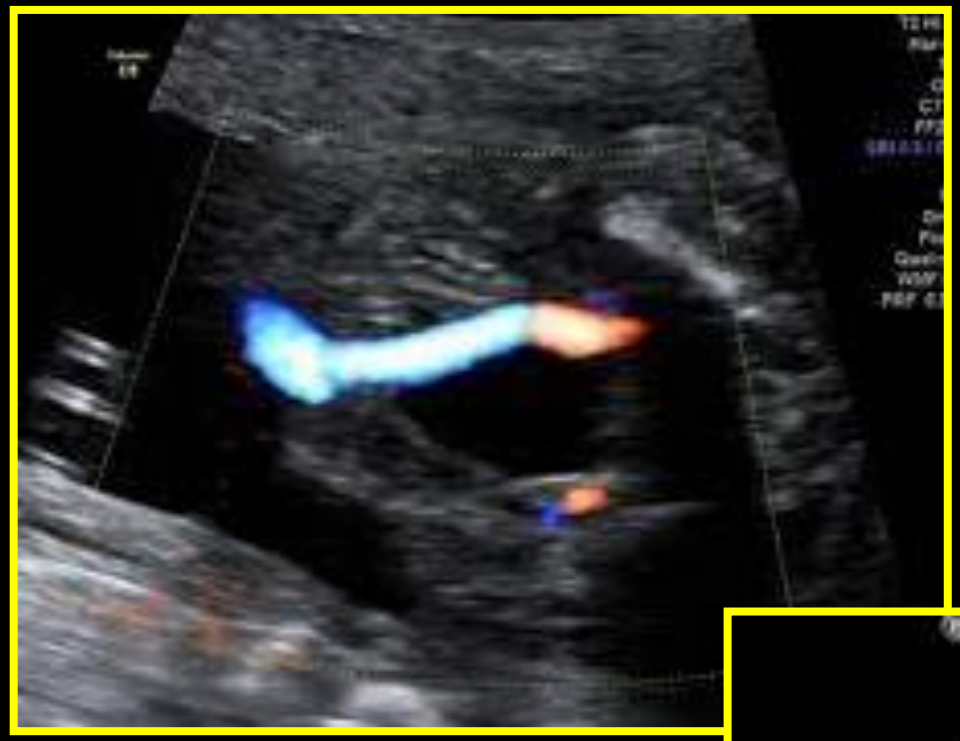
Fetal Neuroanatomy - Normal

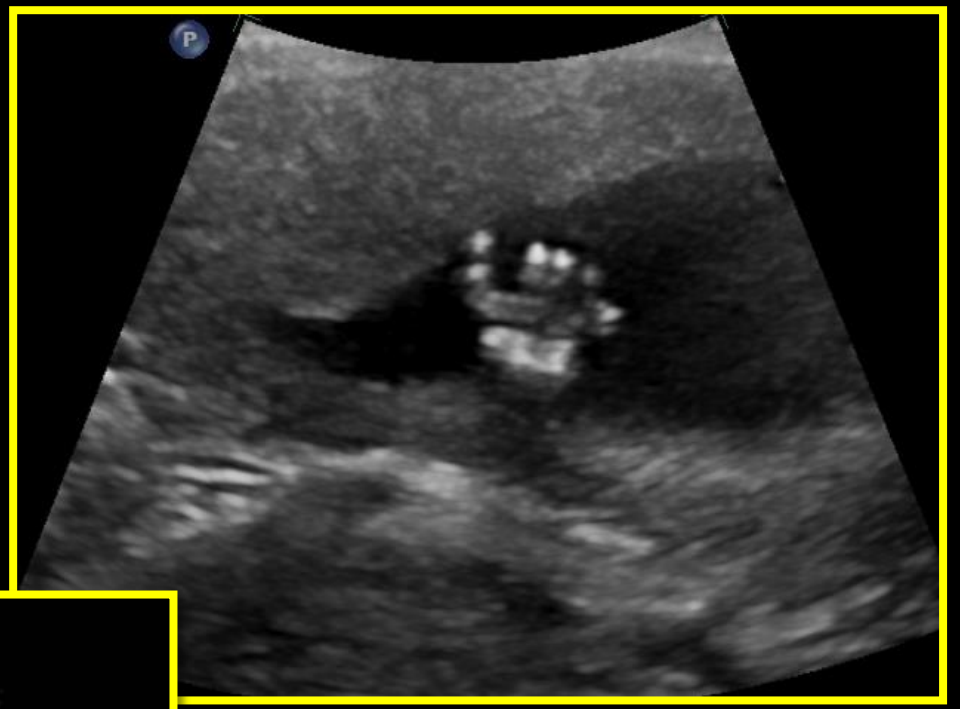


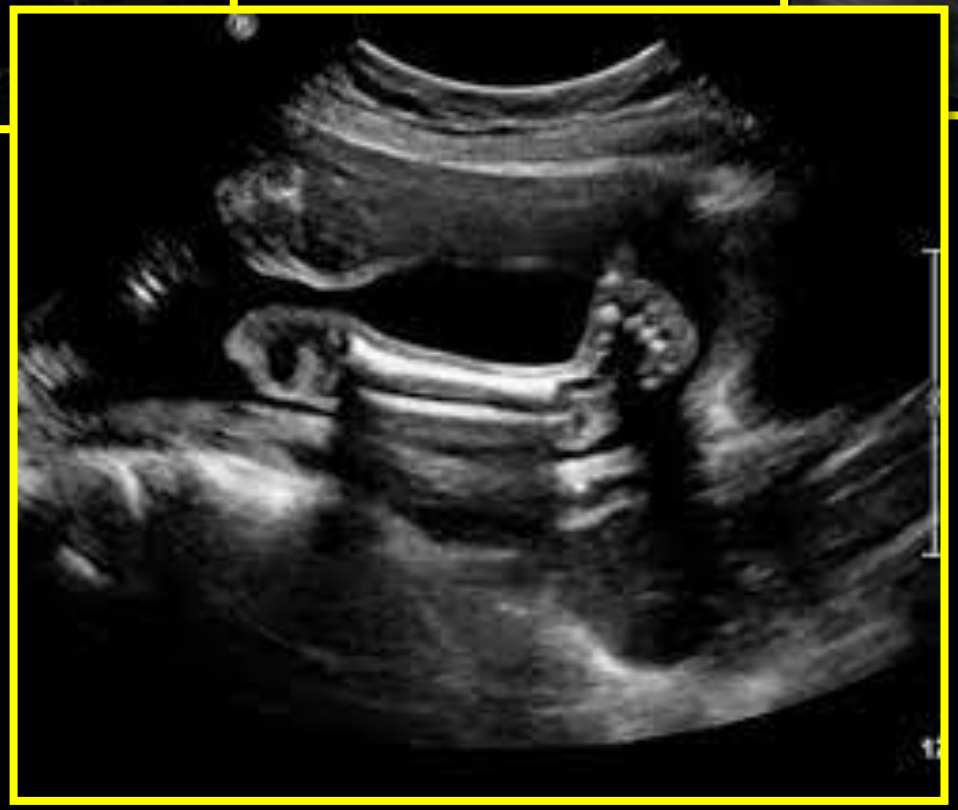

GA 19w0d
CSP


Cerebellum









Genetic Counseling

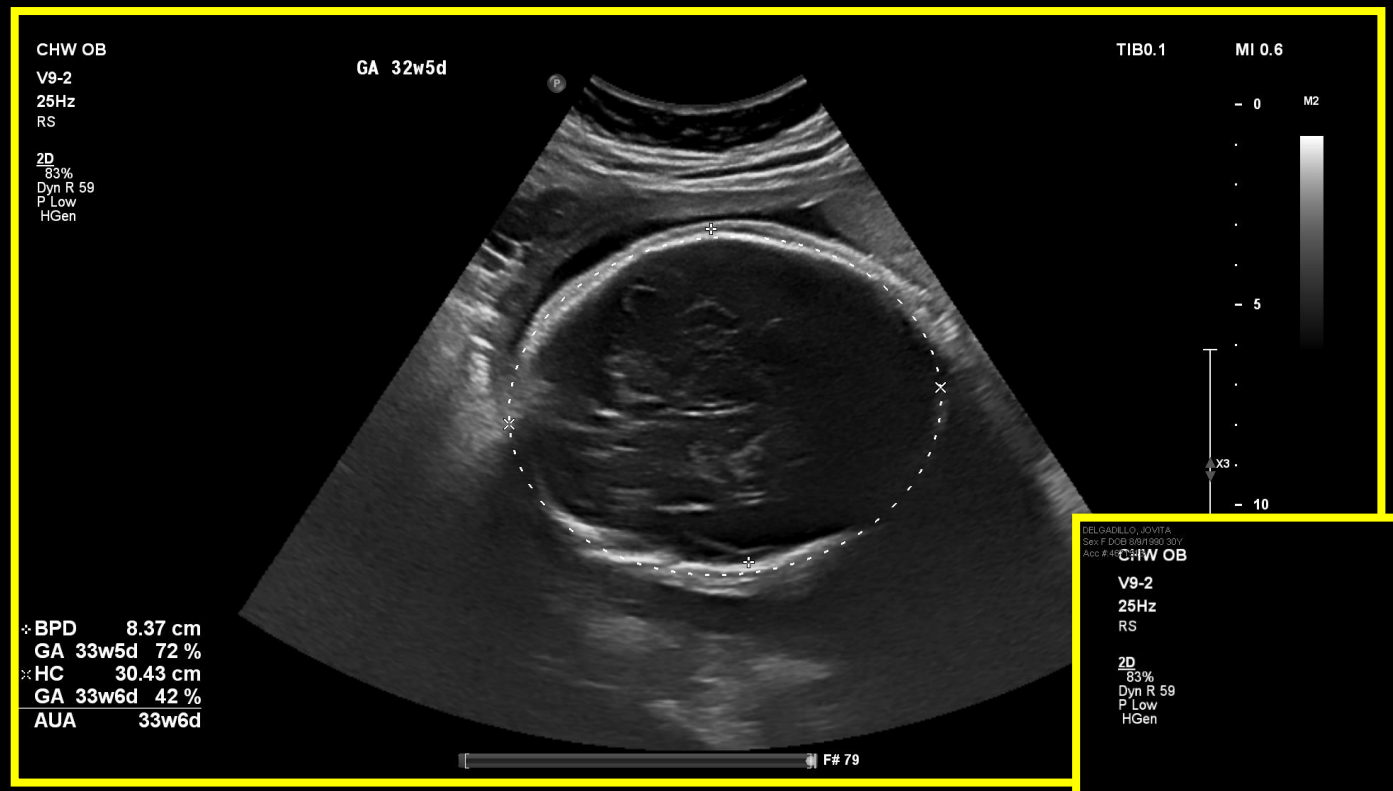
- Patient counseled regarding high risk for genetic syndrome
  - Trisomy 13 and trisomy 18 high on differential
- Patient likely considering termination of pregnancy due to ultrasound findings
  - Highly concerned regarding recurrence risk
- Counseled about recommendation for amniocentesis for these reasons

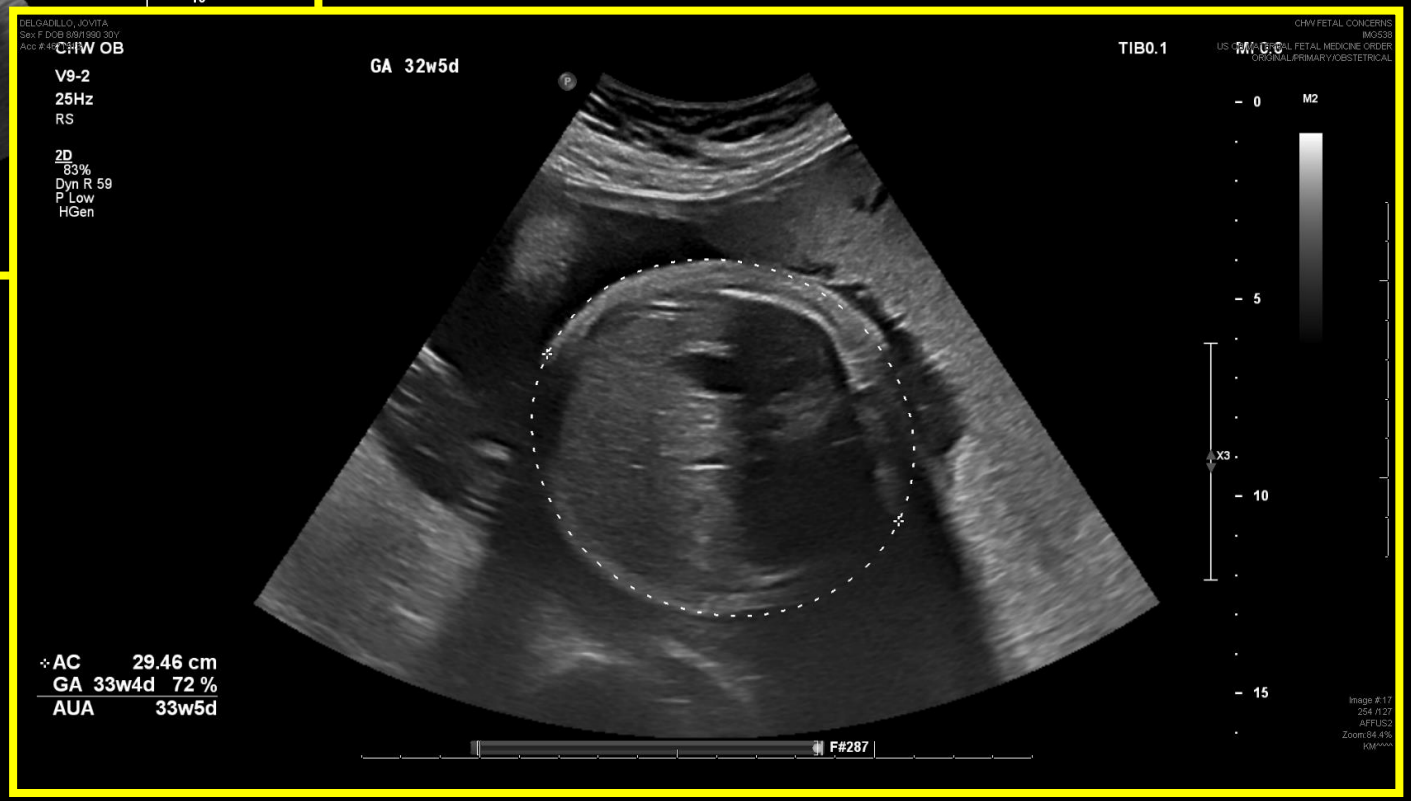
Amniocentesis Results

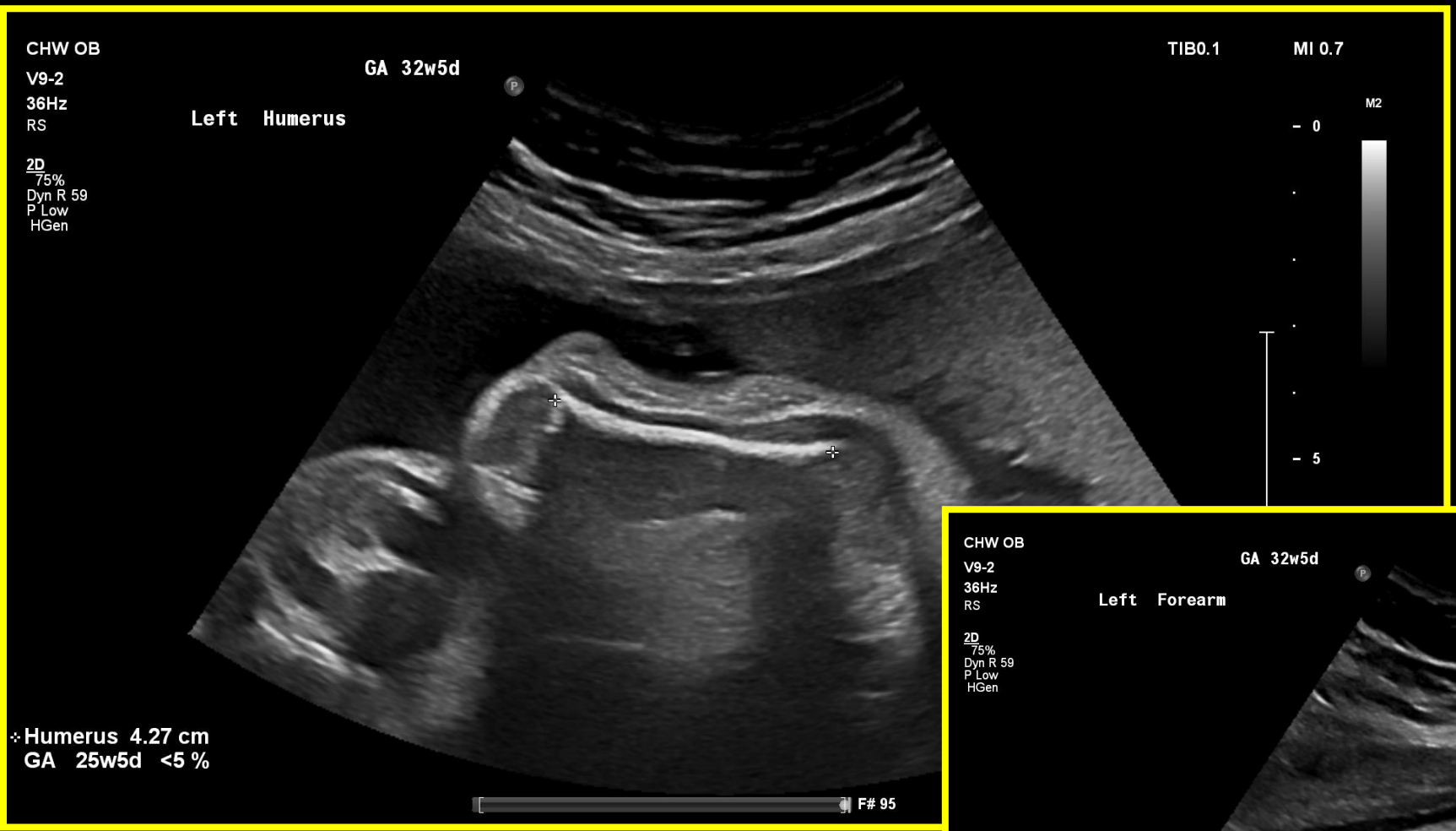
- 46, XY, der(13;14)(q10;q10),+13
  - Consistent with trisomy 13 due to an unbalanced translocation
- Parental karyotypes:
  - Mom: 45,XX,der(13;14)(q10;10)
  - Dad: 46,XY

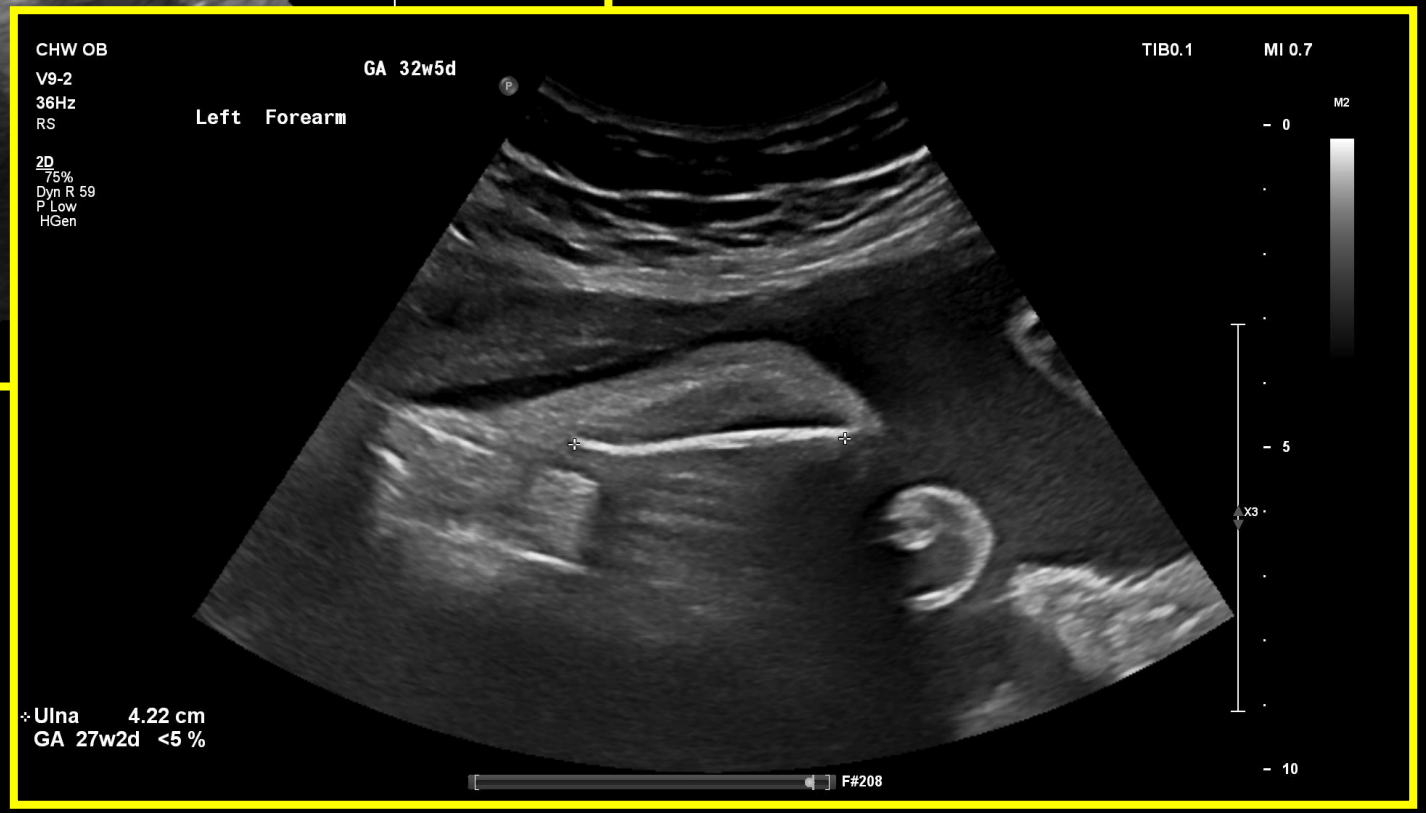
Third Trimester Case

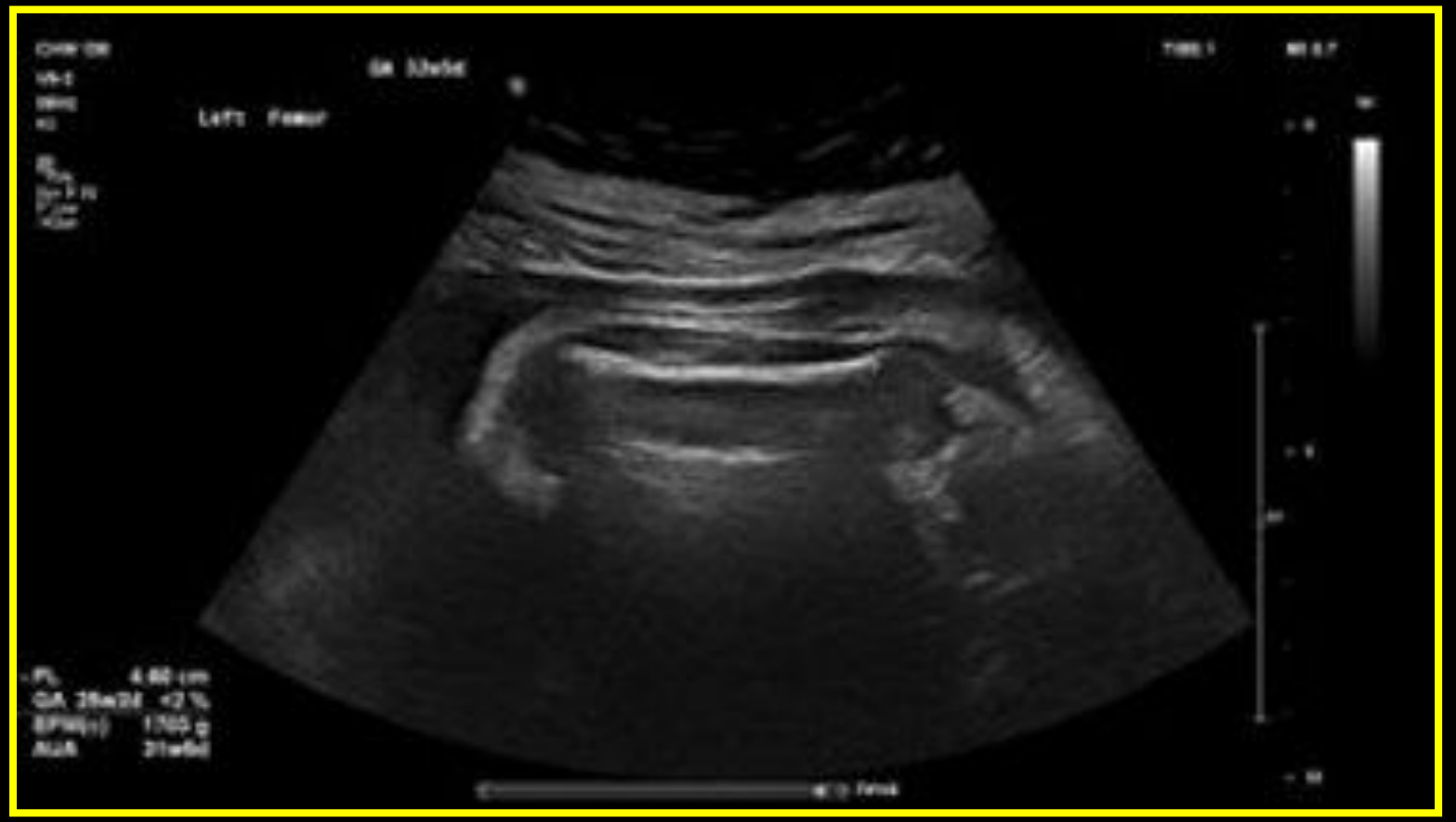
- 30 year old G3P1011 at 32w5d
- Third trimester growth ultrasound identified multiple findings consistent with a non-lethal skeletal dysplasia
  - Short long bones (7 weeks behind)
  - Abnormal chest shape
  - Frontal bossing
- Referred from outside institution
  - Question of delivery location

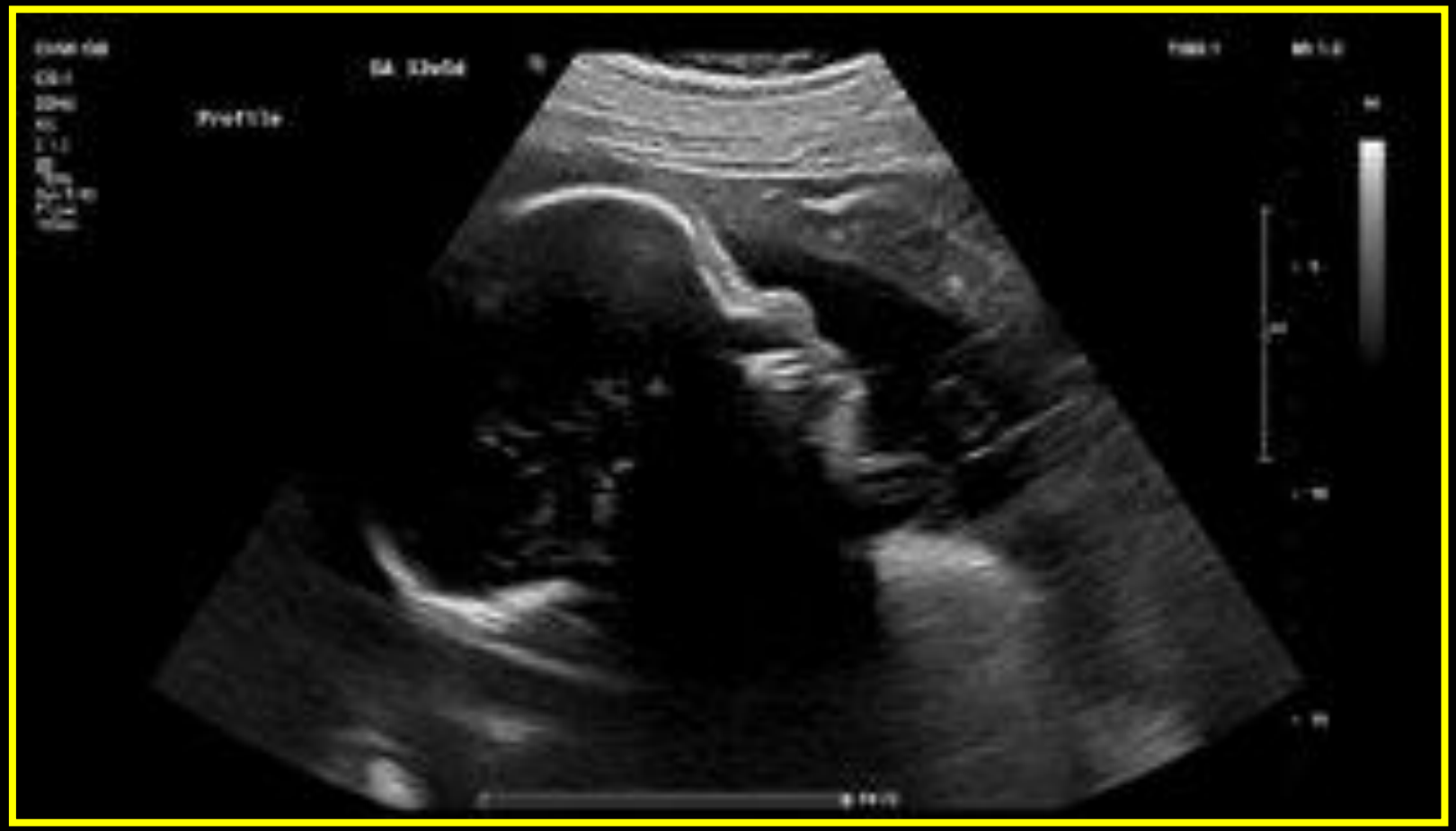

CHW OB
V9-2
25Hz
RS
2D
83%
Dyn R 59
P Low
HGen
GA 32w5d
TIB0.1
MI 0.6
M2
0
5
10
X3
BPD 8.37 cm
GA 33w5d 72 %
HC 30.43 cm
GA 33w6d 42 %
AUA 33w6d
F# 79

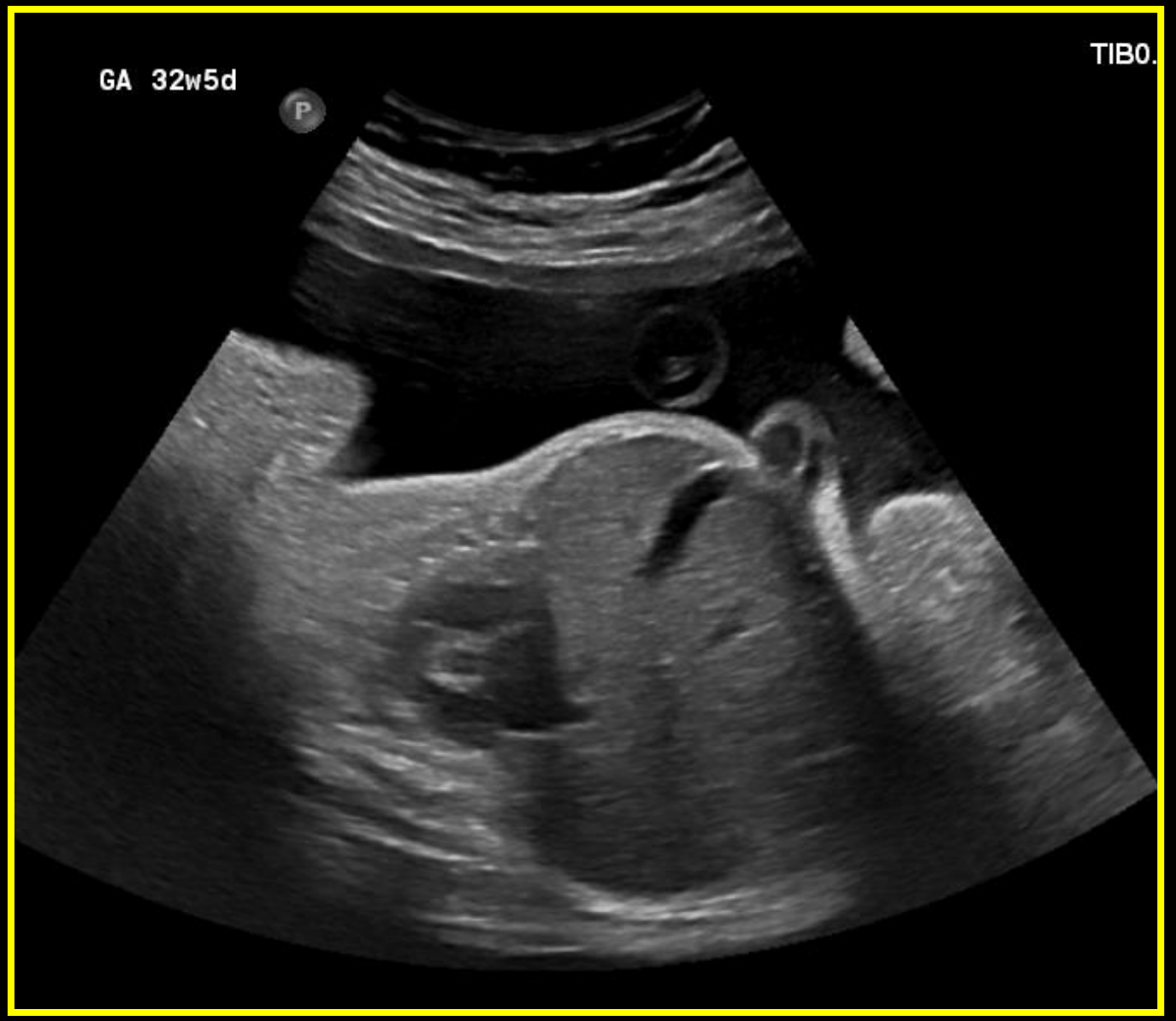

DELGADILLO, JOVITA
Sex F DOB 8/9/1990 30Y
CHW OB
V9-2
25Hz
RS
2D
83%
Dyn R 59
P Low
HGen
GA 32w5d
TIB0.1
CHW FETAL CONCERNS
IMG538
US OB/GYN FETAL MEDICINE ORDER
ORIGINAL/PRIMARY/OBSTETRICAL
M2
0
5
10
15
X3
AC 29.46 cm
GA 33w4d 72 %
AUA 33w5d
F#287


CHW OB
V9-2
36Hz
RS
2D
75%
Dyn R 59
P Low
HGen
GA 32w5d
Left Humerus
TIB0.1
MI 0.7
M2
0
5
Humerus 4.27 cm
GA 25w5d <5 %
F# 95


CHW OB
V9-2
36Hz
RS
2D
75%
Dyn R 59
P Low
HGen
GA 32w5d
Left Forearm
TIB0.1
MI 0.7
M2
0
5
10
X3
Ulna 4.22 cm
GA 27w2d <5 %
F#208


Left Femur
FL 4.40 cm
GA 28w2d +2 %
EFW(+) 1765 g
AUA 31w6d




GA 32w5d
P
TIB0.

Genetic Counseling

- Counseled regarding high likelihood of skeletal dysplasia
  - Significant overlap among skeletal dysplasias and specific diagnosis cannot be determined without genetic testing
- Amniocentesis with skeletal dysplasia panel recommended
- Reviewed need to complete amniocentesis ASAP so results will be available prior to delivery (2-3 week TAT)

Genetic Testing Results

- Likely pathogenic variant in the COL2A1 gene (c.2401G>C)
  - Ultimately diagnosed with spondyloepimetaphyseal dysplasia (SEMD), Strudwick type
- Delivery site determined based on genetic diagnosis

Key Points

- >50% of fetal anomalies are due to a genetic syndrome
  - Collaboration between MFM and genetic counselor is critical to provide the patient complete counseling
- Referral to our center should be made as soon as anomaly is noted so genetic work up can be initiated
- Genetic diagnosis can inform decision-making for the patient
  - Termination, delivery location, palliative care plan, etc