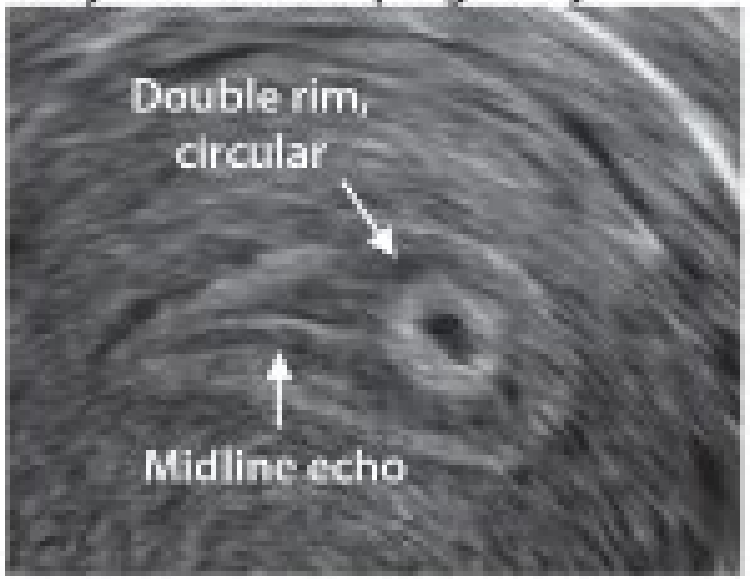
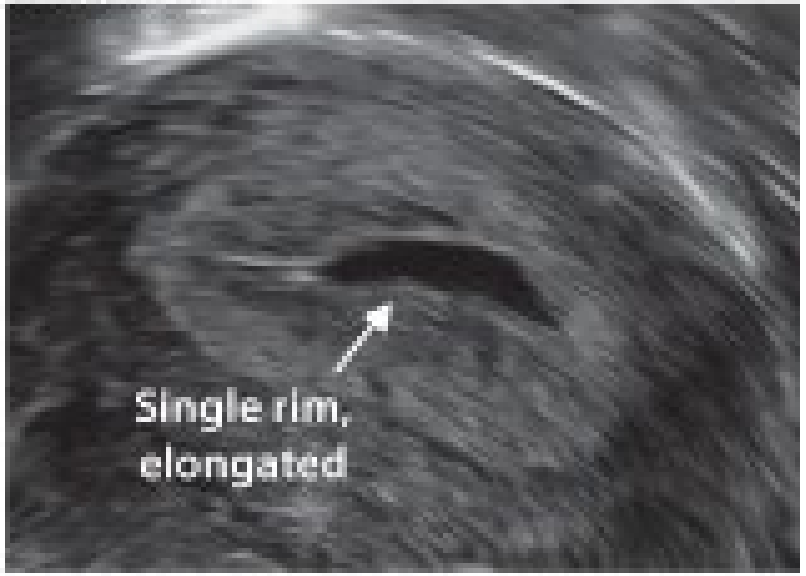
Ultrasound and diagnostic testing

Dr Penelope Fotheringham

Dating ultrasound

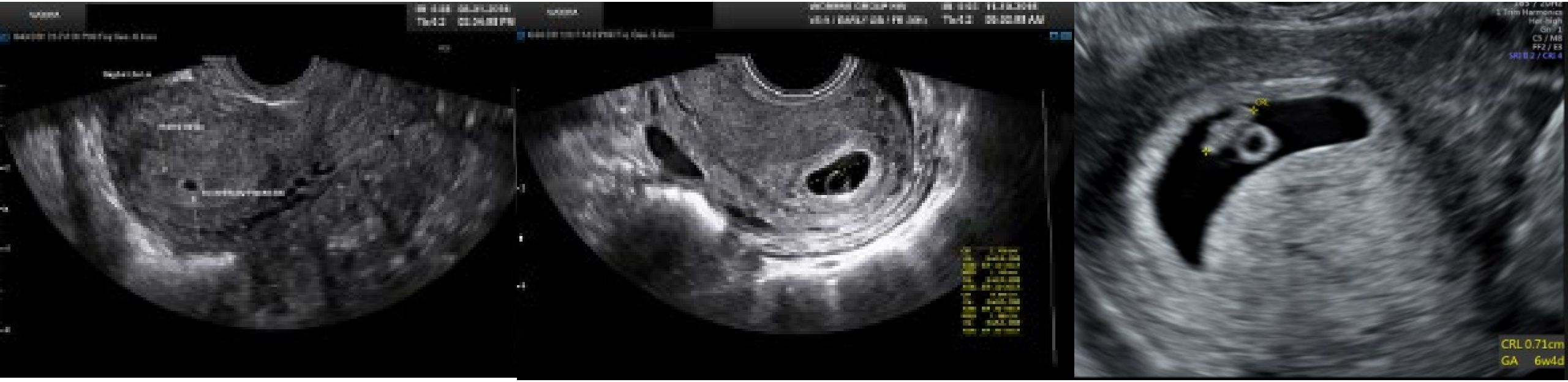
- Assessment of viability
  - Performed ≥ 6 weeks
  - Confirm the presence of an embryo with cardiac activity at the time of examination
  - Embryo first detectable at 1-2mm and ↑ 1mm/day
  - Cardiac activity may be seen when fetal pole ≥ 2mm
  - 5-10% of viable embryos will not have FHR 2-4mm

- Defining an intrauterine pregnancy (TA/TV)
  - Gestational sac = intrauterine pregnancy
    - Confounders – pseudo sac
  - Mean sac diameter (MSD)
    - More variable for gestation than FP/CRL
  - Yolk Sac
  - Fetal Pole
  - Crown Rump Length (CRL)

Ultrasound image / Characteristic	Early intrauterine pregnancy	Pseudosac
		
LOCATION	Below midline, buried into decidua	Midline, between endometrial layers
SHAPE	Circular and steady	Elongated, varies during scan
BORDER	Echogenic rim (double)	Single decidual layer
COLOR FLOW	High peripheral flow	Avascular

Day, A., & Jurkovic, D. (2012). The role of ultrasound in early pregnancy after assisted conception. In E. Jauniaux & B. Rizk (Eds.), *Pregnancy After Assisted Reproductive Technology* (pp. 14-35). Cambridge: Cambridge University Press. doi:10.1017/CBO9780511902604.003

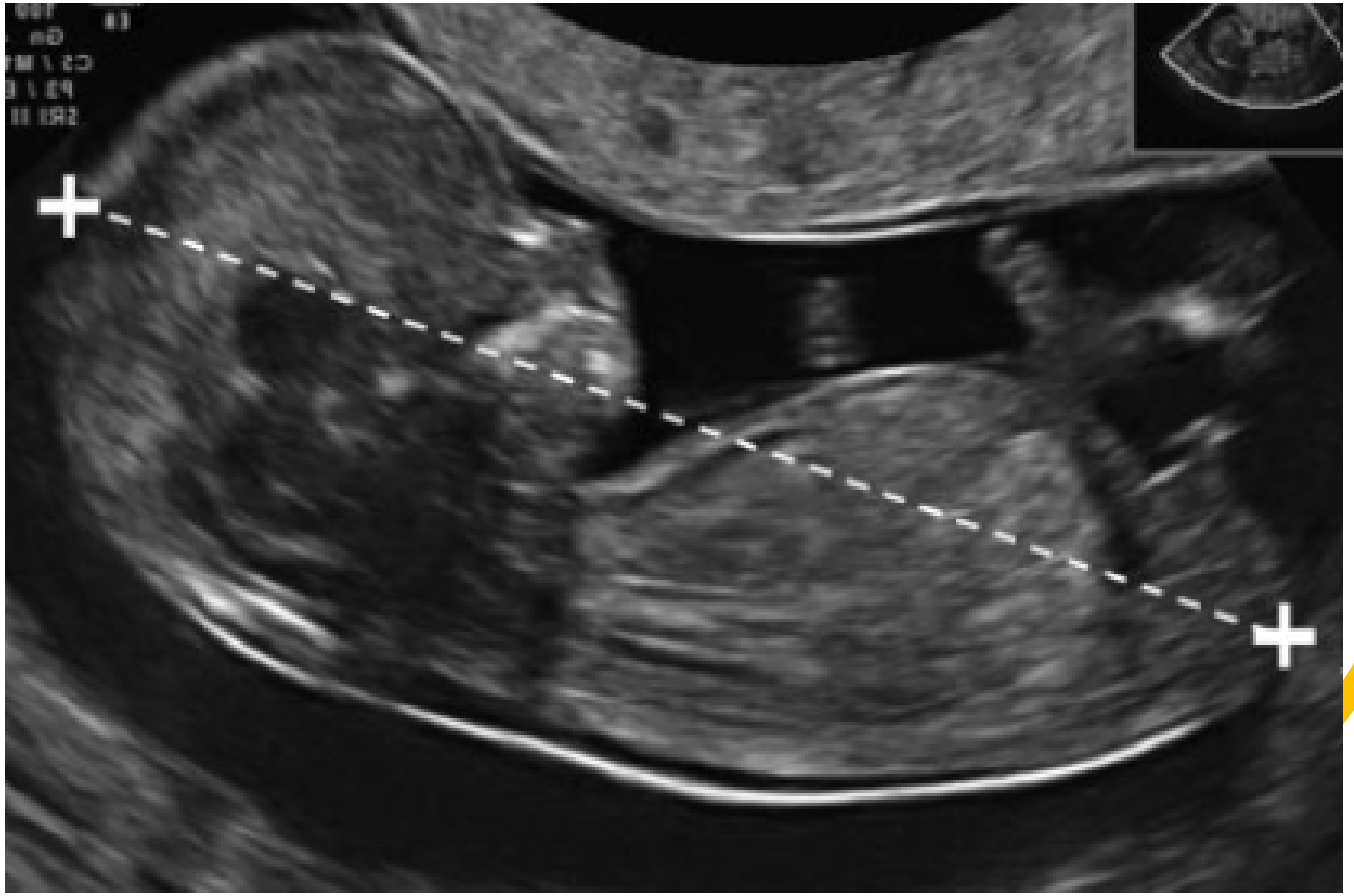
Days from LMP	28–35	35–42	42–49	49–56
Gestational sac	100%			
Yolk sac	0%	91%	100%	
Embryo with + FHTs	0%	0%	86%	100%



GLOW-M https://www.glowm.com/section-view/heading/Diagnostic%20Ultrasound%20in%20the%20First%20Trimester%20of%20Pregnancy/item/94#.YyphinZBy-Y

Structural Scan

- Offered between 11-13+6 weeks (45-84mm CRL)
  - Fetal size allows diagnosis of major fetal abnormalities
  - NT performs optimally
- Thus if NIPT done a structural scan still should be done in this timeframe!



CRL=60mm

ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan

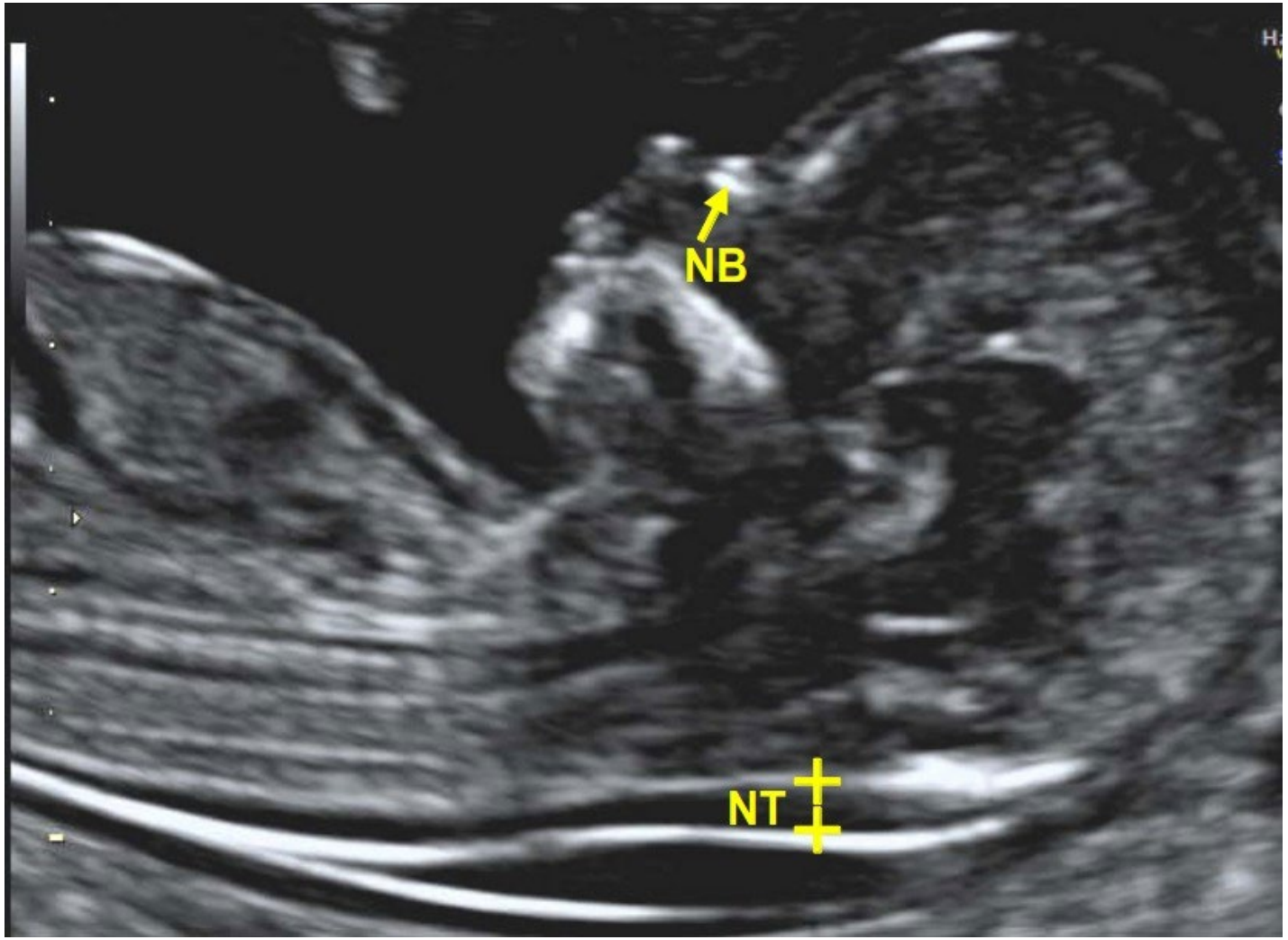
cFTS
(11^{+0} – 13^{+6} weeks)

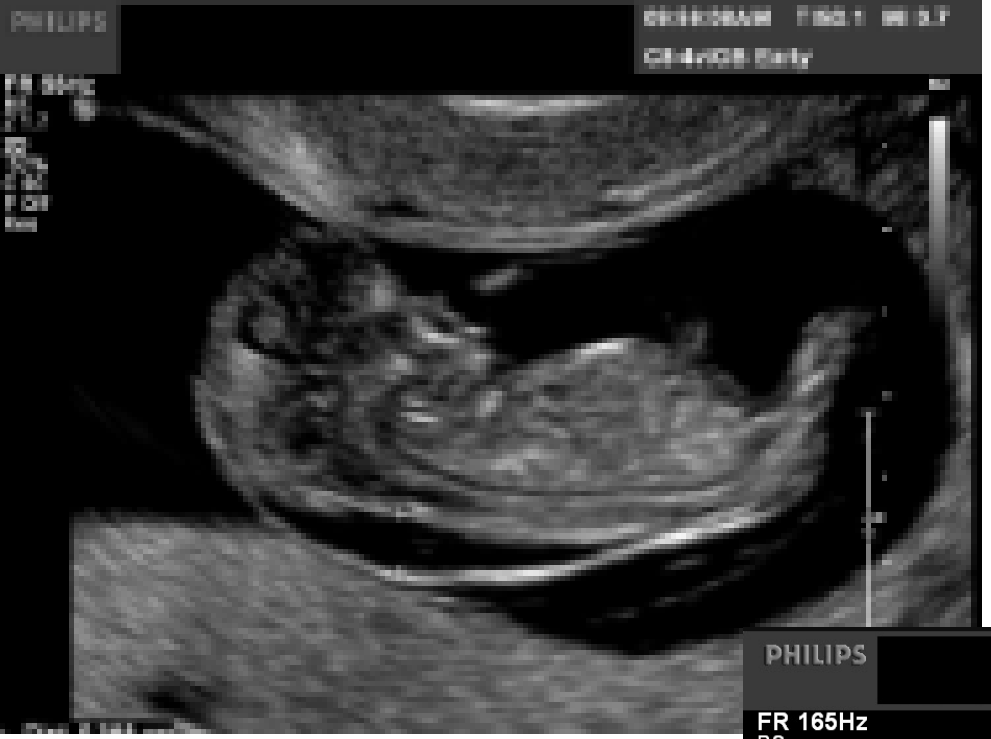
- The test incorporates maternal age, ultrasound measurement of the fetal size, the nuchal translucency (NT) and the fetal nasal bone, and maternal serum marker levels to generate an overall risk for trisomy 21, 13 and 18
- The maternal blood test measures the presence of two proteins: PAPP-A (pregnancy associated plasma protein) and free ß-subunit of human chorionic gonadotrophin (free ß-hCG).
- Low levels of PAPP-A may also predict issues with the placenta, resulting in adverse complications such as intrauterine growth restriction, preeclampsia, placental abruption, premature birth, or fetal death.
- For further understanding of the complexities of this CFTS test, you may choose to undertake some modules of the Nuchal Translucency Online Learning Program (NTOLP) accessed at http://www.nuchaltrans.edu.au/courses/ntolp

cFTS

- CFTS has a sensitivity of 85% and specificity of 95%[3]
- Algorithm which includes the ultrasound and serum markers along with maternal age, weight, ethnic origin, diabetic status and whether conception was spontaneous or via IVF
- Approximately 2-3% of tests give an increased risk result.
- The cut-off risk used to determine an ‘increased risk’ in NSW is 1 in 300

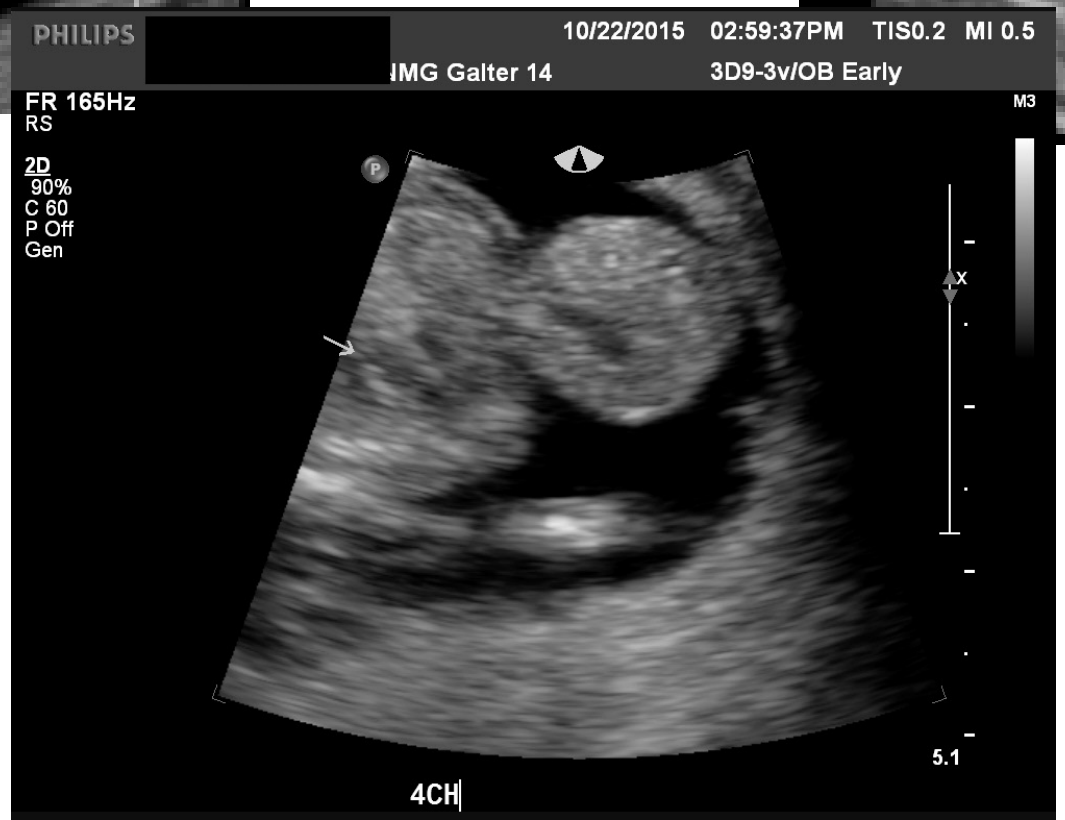
The Fetal Medicine Foundation

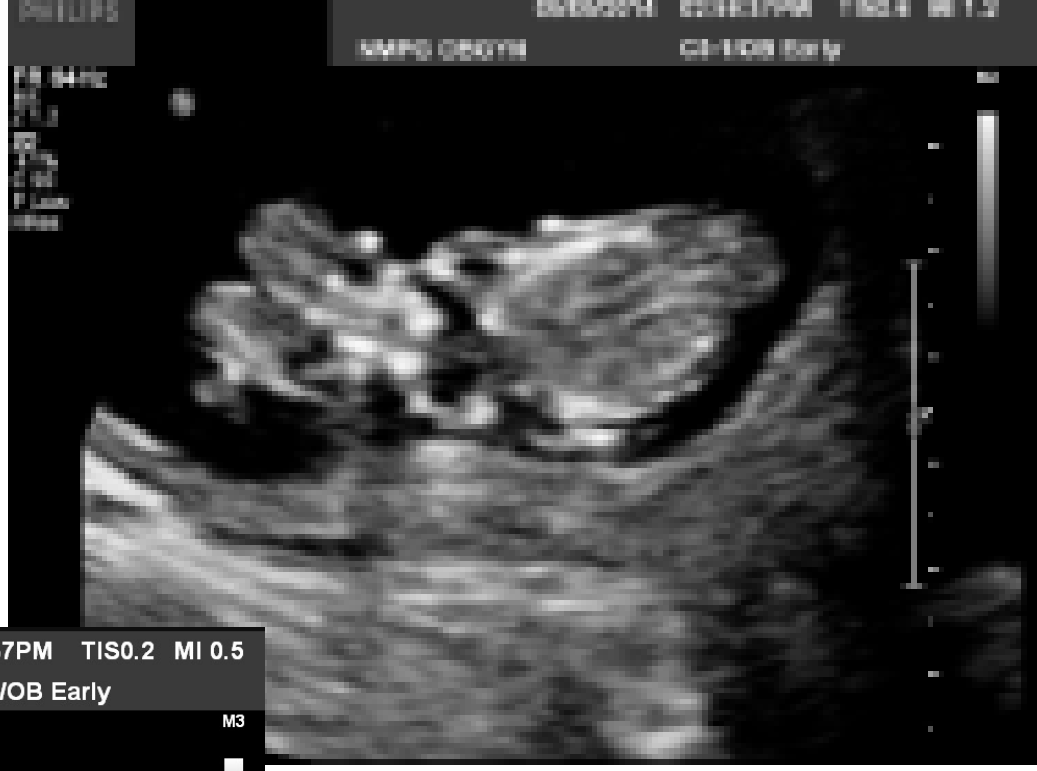




Cystic hygroma

Omphalocoele

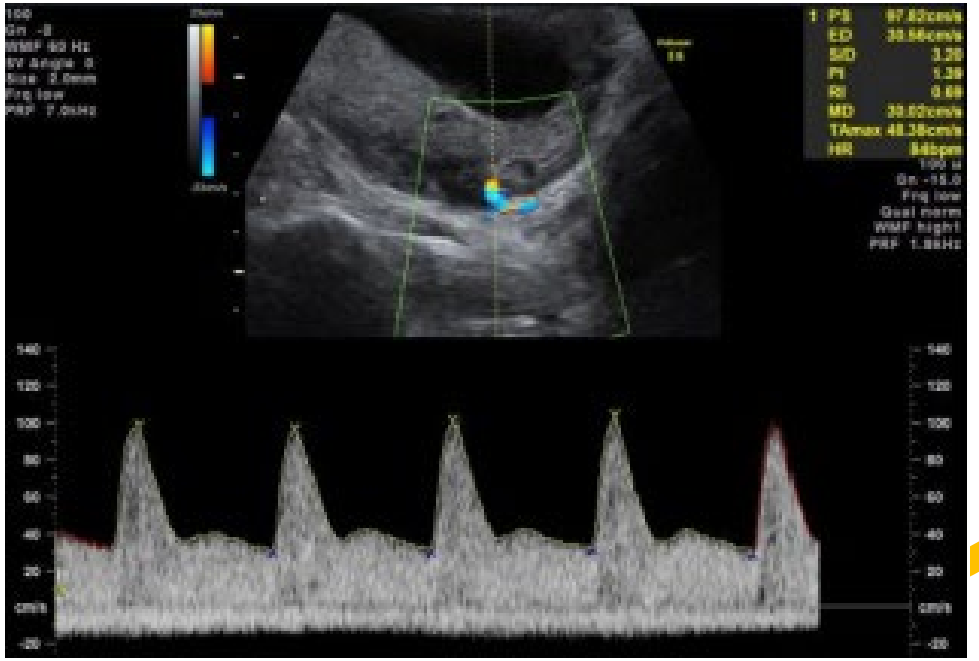




Acrania

Pre-eclampsia screening

- Doppler examination of the uterine arteries 11+0-13+6 weeks (TA/TV)
- Bilateral notching is associated with ↑ risk of PE but has a low sensitivity
- Pulsatility Index (PI) is more reliable
- Mean PI > 95th centile had a sensitivity of 27% for PE and a sensitivity of 60% for PE requiring delivery before 32 weeks[1]



https://www.isuog.org/resource/screening-for-pre-eclampsia.html
https://fetalmedicine.org/research/assess/preeclampsia/first-trimester

1. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11–14 weeks of gestation. Ultrasound Obstet Gynecol 2001; 18: 583–586.

NIPT (10+0 onwards)

- Cell free DNA (cfDNA) screening using maternal plasma can be performed reliably from 10 weeks.
- The test has the highest sensitivity (99%) and specificity (99.9%) of all screening tests for trisomy 21, 13 and 18. The test can also be used to identify sex and detect monosomy X (Turner syndrome).
- Results are usually available in one to two weeks.
- Test failures occur in 1-9% of samples most commonly due to low fetal fraction.
- The fetal fraction is the percentage of cell-free fetal DNA as a proportion of total cell-free DNA (maternal and fetal).
- Fetal fraction appears to be inversely proportional to maternal weight, thus the test may be less accurate as BMI increases.
- A false positive result may also occur due to placental mosaicism, maternal chromosome abnormalities, or rarely, maternal malignancy.

Australian Clinical labs Harmony Test

Down Syndrome (Trisomy 21)	✓
Edwards Syndrome (Trisomy 18)	✓
Patau Syndrome (Trisomy 13)	✓
Klinefelter Syndrome (47,XXY)	✓ OPTIONAL
Turner Syndrome (Monosomy X)	✓ OPTIONAL
Jacob Syndrome (47,XYY)	✓ OPTIONAL
Triple X Syndrome (47,XXX)	✓ OPTIONAL
DiGeorge syndrome (22q11.2 Deletion)	✓ OPTIONAL

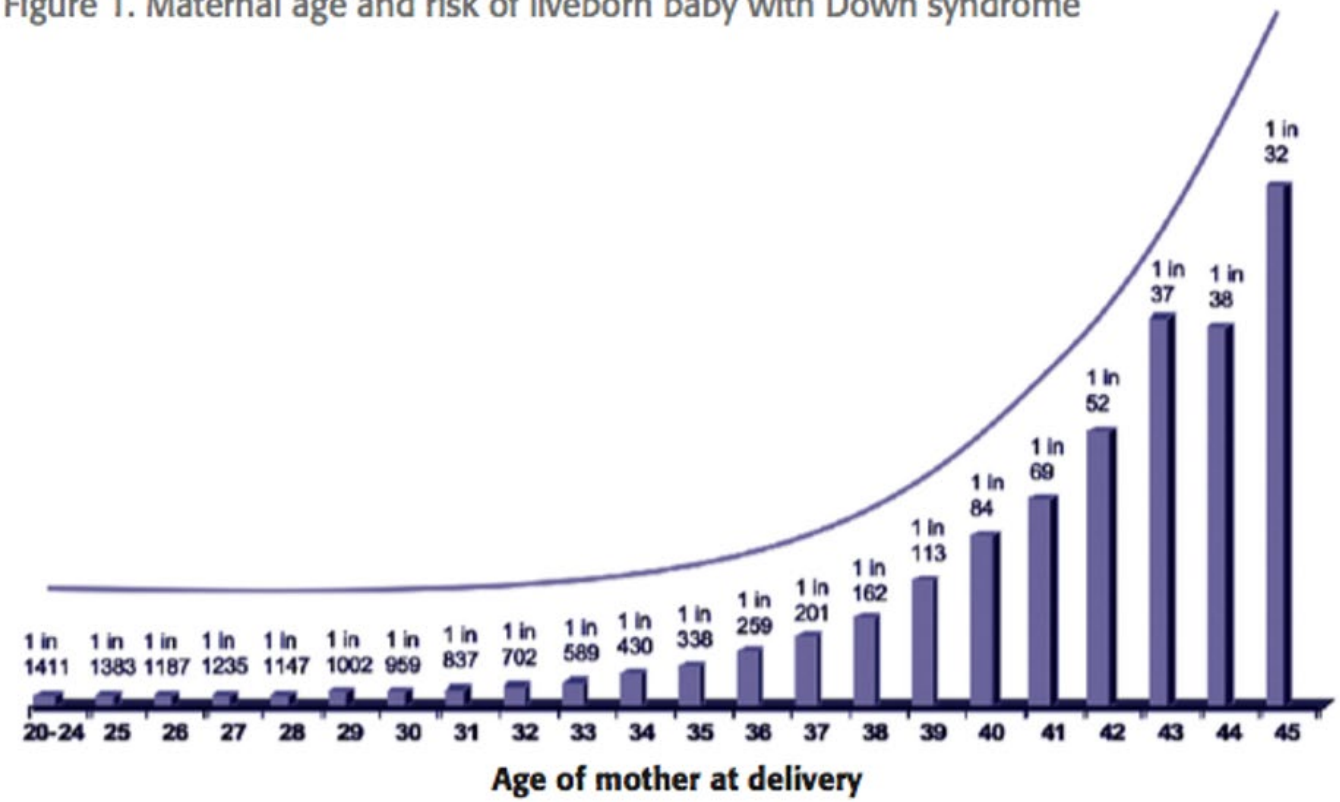
Harmony Prenatal Test Performance

Harmony Microarray-based performance

HARMONY	SENSITIVITY	SPECIFICITY	FALSE POSITIVE RATE
Trisomy 21	99.1% (95% CI: 94.9%-99.95%)	100% (95% CI: 94.4%-100%)	0% (95% CI: 0.0-0.6%)
Trisomy 18	100% (95% CI: 88.7%-100%)	100% (95% CI: 99.4%-100%)	0% (95% CI: 0.0-0.6%)
Trisomy 13	100% (95% CI: 75.8%-100%)	100% (95% CI: 99.4%-100%)	0% (95% CI: 0.0-0.6%)
Sex Chromosome Aneuploidies	100% (95% CI: 79.6%-100%)	99.7% (95% CI: 99.0%-99.9%)	0.3% (95% CI: 0.1-1.0%)
Monosomy X	100% (95% CI: 77.2%-100%)	99.9% (95% CI: 99.2%-99.9%)	0.1% (95% CI: 0.1-0.8%)
22q11.2	75.4% (95% CI: 67.1% - 82.2%)	99.5% (95% CI: 99.0% - 99.7%)	0.5% (95% CI: 0.3%-1.0%)
Fetal Sex	99.8% Accuracy (95% CI: 99.1 – 99.9%)		

Age related risks T21

Figure 1. Maternal age and risk of liveborn baby with Down syndrome



Devised from Table 2, Morris, JK, Mutton DE, Alberman E, 2005. Corrections to maternal age-specific live birth prevalence of Down's syndrome, Journal of Medical Screening, 12:202.

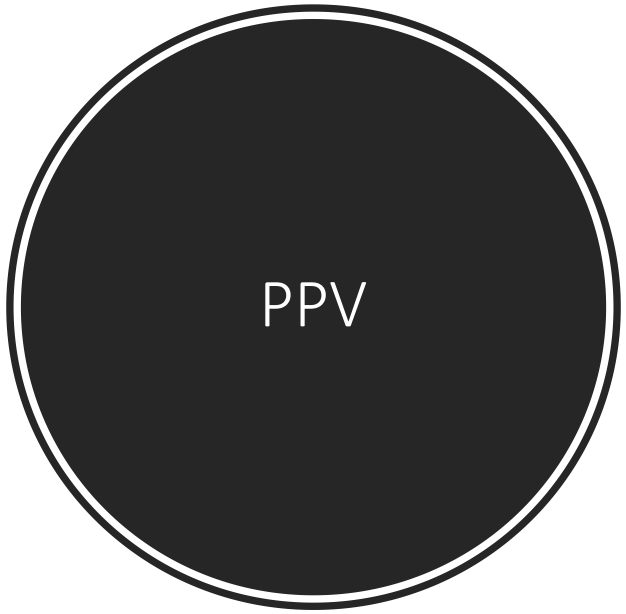


Table 1. Theoretical PPV as a function of estimated pre-test risk based on sensitivity and specificity data

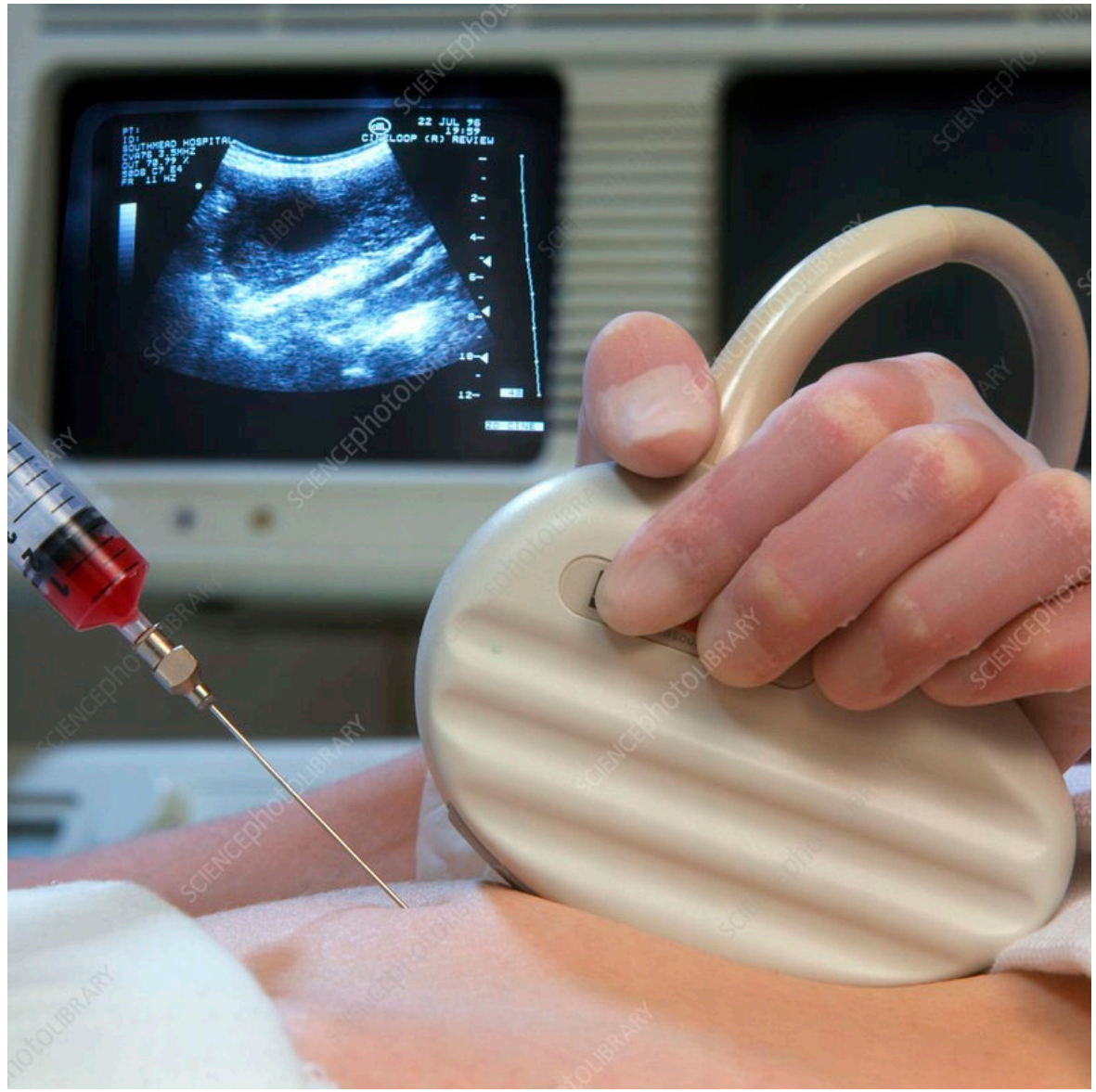
Estimated pre-test risk	Trisomy 21 (Sensitivity 0.993 Specificity 0.9996)[25]	Trisomy 18 (Sensitivity 0.974 Specificity 0.9998)[25]	Trisomy 13 (Sensitivity 0.938 Specificity 0.9998)[25]
1:10	99.64%	99.82%	99.81%
1:50	98.06%	99.00%	98.97%
1:100	96.17%	98.01%	97.93%
1:250	90.88%	95.14%	94.96%
1:400	86.15%	92.43%	92.16%
1:800	75.65%	85.91%	85.44%
1:2,000	55.39%	70.90%	70.12%
1:6,000		44.81%	43.88%
1:10,000		32.75%	31.93%
1:15,000		24.51%	23.82%
1:20,000			19.00%

Second trimester screening (15+0-20 weeks)

- Women in their second trimester may be offered maternal serum screening in conjunction with maternal age, gestational age and maternal weight to calculate a risk for trisomy 21.
- 15-20 weeks (best 16-18)
  - aFP, hCG, estriol, inhibin
- The 18–20 week morphology ultrasound is not recommended as a primary screening test for trisomy 21 due to its poor sensitivity and specificity.
- The combined second trimester test detects 75% of babies with trisomy 21 and approximately 5% of tests give an increased test result. For women age over 40 years, at least 50% will receive an increased risk result.
- It is strongly recommended **NOT** to have both first and second trimester screening tests as the false positive rate is greatly increased. A false positive result would mean that she is more likely to be offered an invasive diagnostic test and hence a greater risk of spontaneous loss of an unaffected fetus.

CVS 11+0 onwards

- A sample of chorionic villi (placental tissue) is removed by a fine needle under ultrasound guidance. The procedure is done either trans-abdominally or transvaginally dependent upon the position of the placenta.
- The tissue is used for chromosome analysis with results generally available in two weeks. A fast FISH (in-situ hybridisation) result can be obtained for chromosomes 21, 13, 18 X and Y within 24 hours.
- Some women experience cramping and occasionally vaginal bleeding after the procedure. The risk of miscarriage is approximately 1%. (NB. This risk is in addition to the ‘background risk’ of miscarriage that all women have in early pregnancy due to natural causes.)
- CVS has a 1% risk of equivocal results due to placental mosiacism i.e. the presence of a mixture of cells with normal and abnormal karyotype, or maternal cell contamination of the sample. In this case, amniocentesis may be necessary.
- CVS is used for fetal DNA analysis in situations of fetal genetic disorders like muscular dystrophy. This is because the CVS sample has a higher DNA content compared to an amniocentesis sample.
- CVS has 0.1% failure rate.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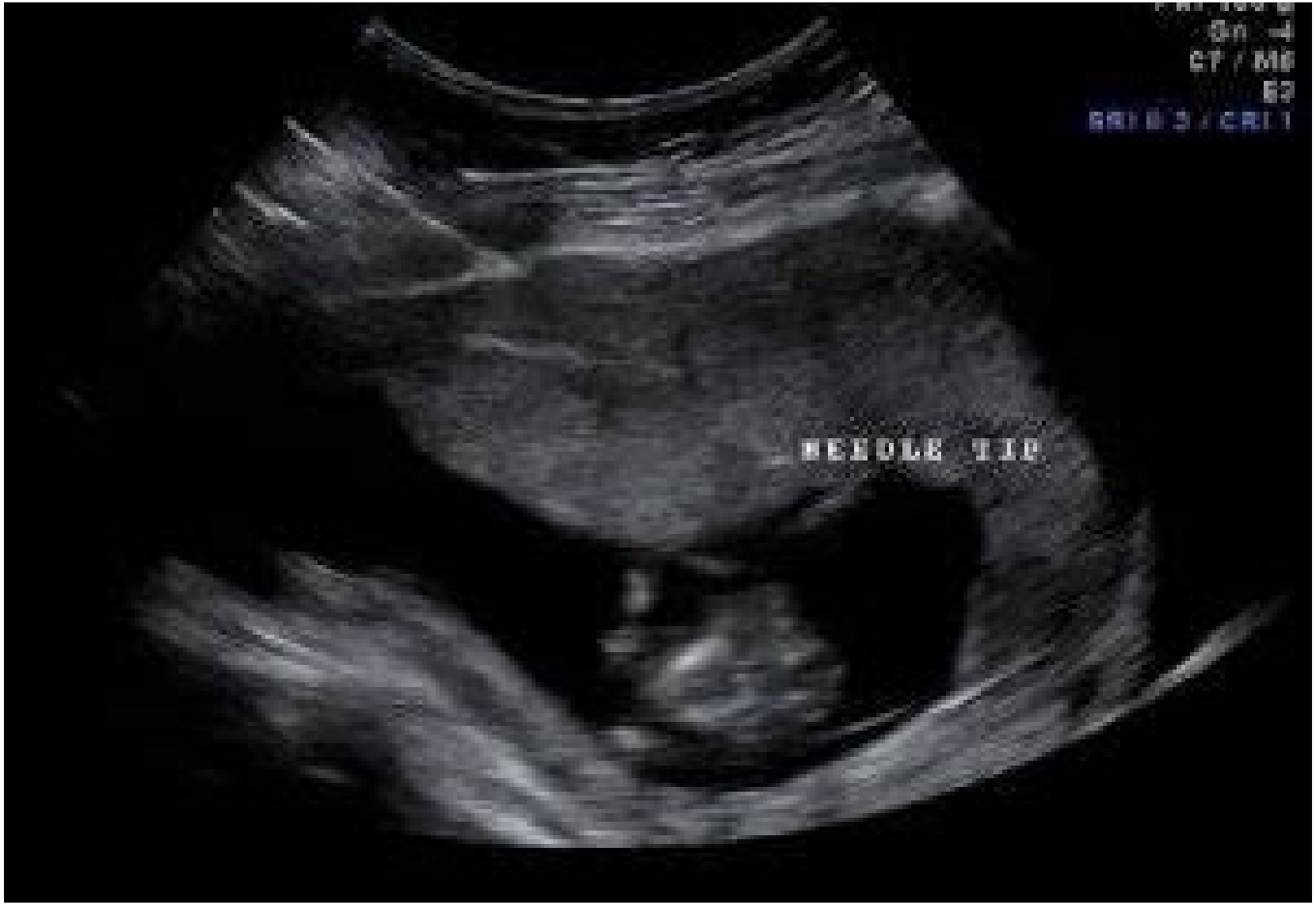
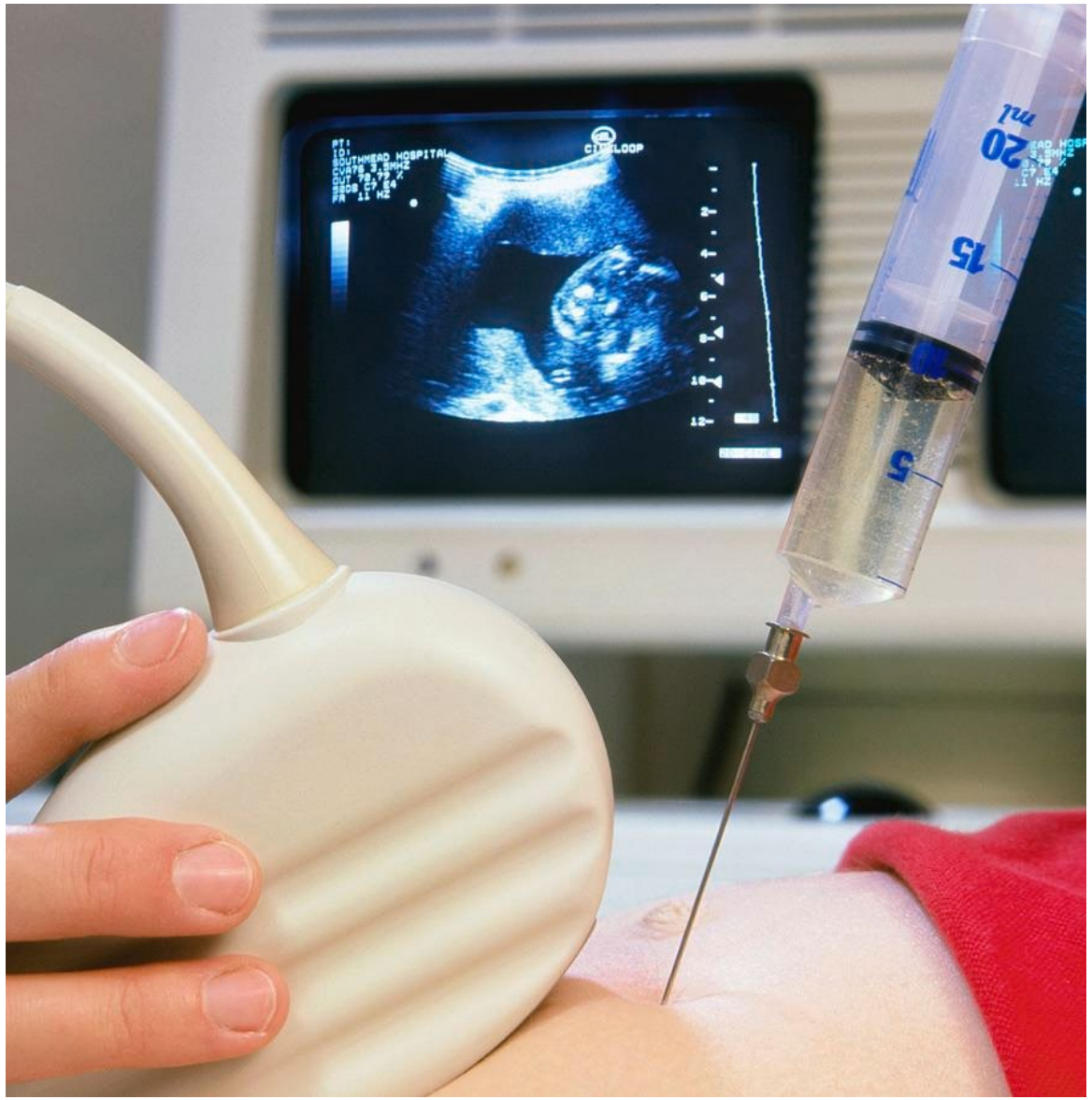
CINELOOP (R) REVIEW

Canberra Fetal Assessment Centre



Amniocentesis 15+0 onwards

- A sample of amniotic fluid is removed by a fine needle under ultrasound guidance. The procedure is done trans-abdominally.
- The fluid is used for chromosome analysis with results generally available in two to three weeks' although a fast FISH is available for trisomy 21, 13, 18 and sex chromosomal anomalies within 24 hours.
- Most women experience minimal discomfort, though some may experience pain as the needle is inserted through the uterine wall. The risk of miscarriage is lower than that for CVS and estimated to be approximately 0.5% (above the background risk).
- An amniocentesis will not detect placental mosiacism but rather reflects the chromosomal makeup of the fetal skin and lung cells. This makes amniocentesis the Gold Standard test for fetal chromosomal analysis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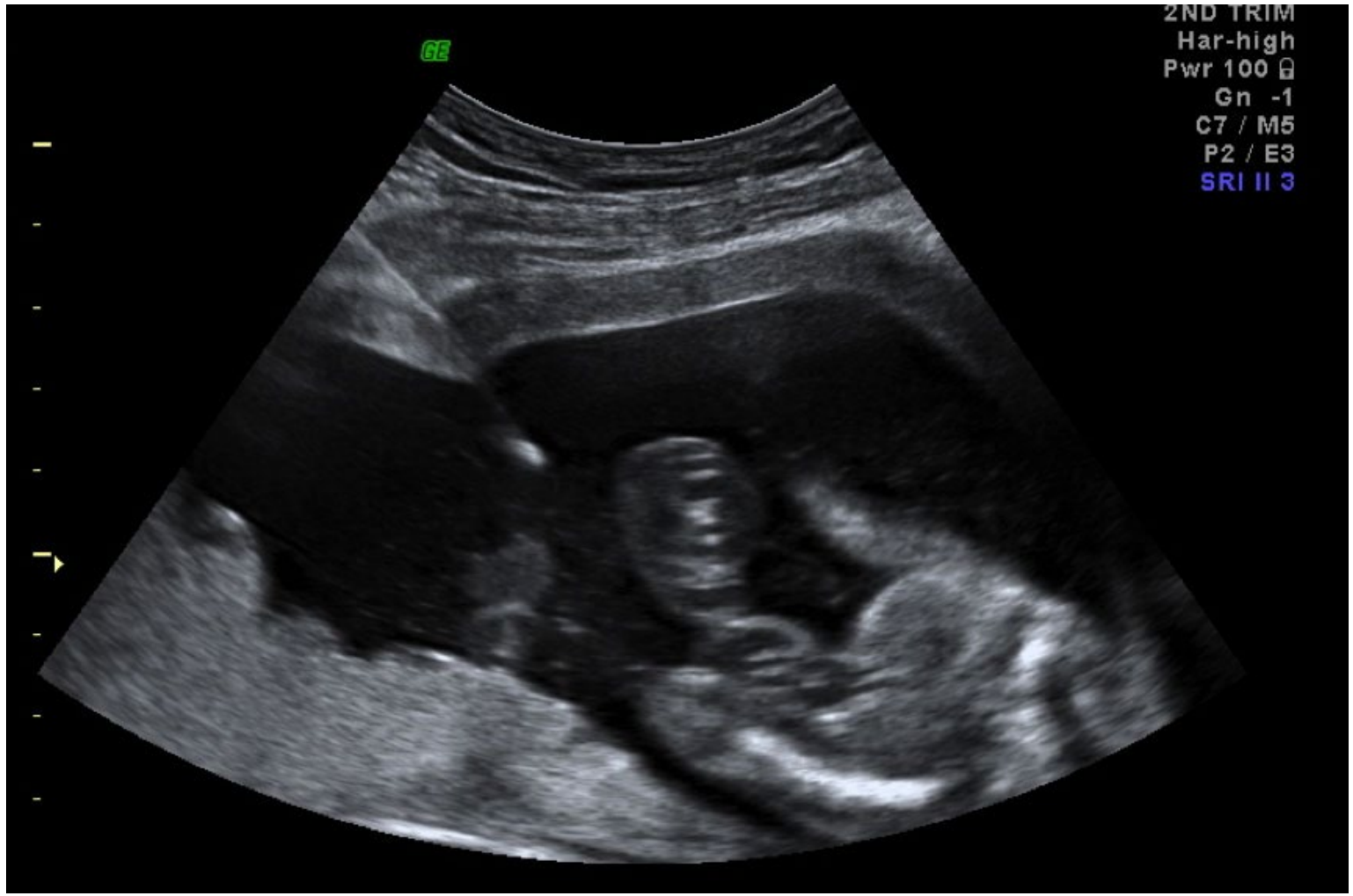
Canberra Fetal Assessment Centre



Ultrasound 18+0-20 weeks

- A second trimester ultrasound is commonly performed to check the baby's growth and development, detect neural tube defects (anencephaly, spina bifida), cardiac defects, gastrointestinal malformations, limb defects, urinary tract anomalies, and in some cases may identify markers associated with a chromosomal or other genetic condition like the nuchal fold (not translucency) or cardiac defect like a VSD.

Third trimester ultrasound

ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth

- BPD, HC, AC and FL should be measured on ultrasound scan from 14 weeks onwards
- Once the CRL exceeds 84 mm, HC should be used for pregnancy dating
- SGA fetuses typically have EFW or AC below the 10th percentile, although 5th centile, 3rd centile, –2SD and *Z*-score deviation have also been used as cut-offs in the literature.
- A LGA fetus is one whose size is above a predefined threshold for its gestational age. LGA fetuses typically have EFW or AC above the 90th percentile, although 95th centile, 97th centile, +2SD and *Z*-score deviation have also been used as cut-offs in the literature
- Macrosomia at term usually refers to a weight above a fixed cut-off (4000 or 4500 g)
- Computer modelling indicates that ultrasound scanning to measure AC at 2-week intervals is associated with false-positive rates for FGR in excess of 10%
- Ultrasound examination at 36weeks' gestation was found to be more effective than that at 32 weeks' gestation in detecting FGR and predicting related adverse perinatal and neonatal outcome47

Free education resources

- Fetal Medicine Foundation

The 11-13 weeks scan

Preeclampsia screening

Fetal abnormalities

Fetal echocardiography

Doppler ultrasound

Cervical assessment

Placenta Accreta Spectrum (PAS)

- Also have resources in other languages on 11-13 week scan that may be useful with patients.