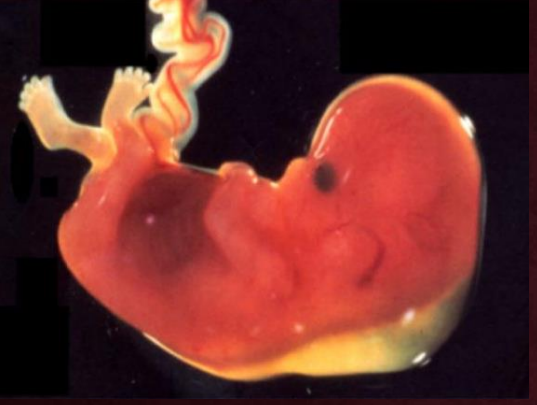
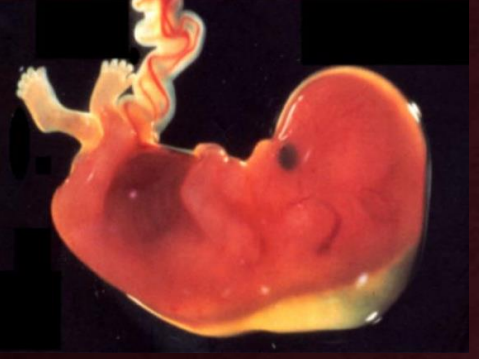


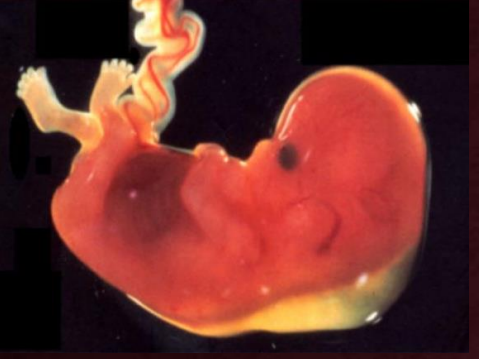
PRENATAL SCREENING FOR COMMON ANEUPLOIDIES

Dr.Maryam Maktabi
perinatologist



FIRST-TRIMESTER COMBINED TESTS

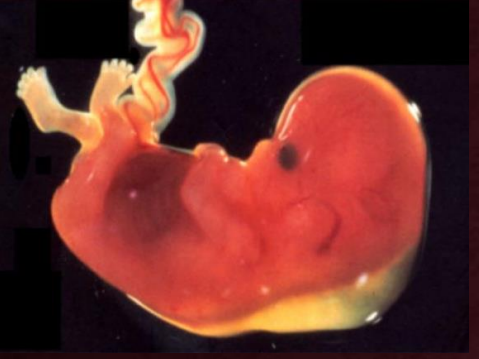
Early risks assessment and diagnosis of fetal abnormalities allow the couple maximum time for decision making; privacy since others may not be aware of the pregnancy termination; and, if chosen, safer methods of pregnancy termination.



The first-trimester screening test consist of three markers

- Maternal serum beta human chorionic gonadotropin (beta-hCG or free beta-hCG subunit)
- Maternal serum pregnancy-associated plasma protein A (PAPP-A)
- Ultrasound measurement of nuchal translucency (NT)

The combined test detects approximately 85% of Down syndrome.

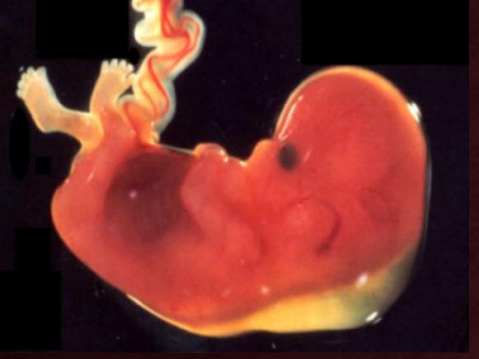


Every woman has a risk that her fetus/baby has a chromosomal defect.

The prior risk depends on maternal age and gestation.

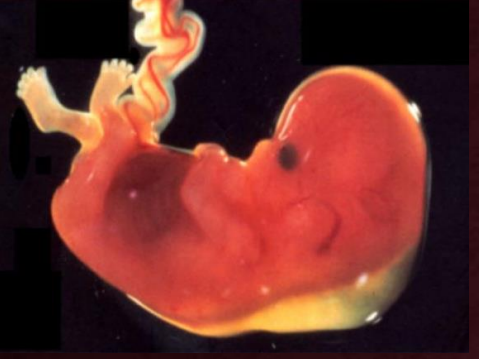
The patient specific risk is calculated by multiplying the prior risk with a series of likelihood ratios which depends on the results of a series of screening tests.

The likelihood ratio for a given sonographic or biochemical measurement is calculated by dividing the percentage of chromosomally abnormal fetuses by the percentage of normal fetuses with that measurement.



TIMING OF BLOOD SAMPLE AND ULTRASOUND

Between 11+0 and 13+6 weeks of gestation.
CRL 45 to 84 mm

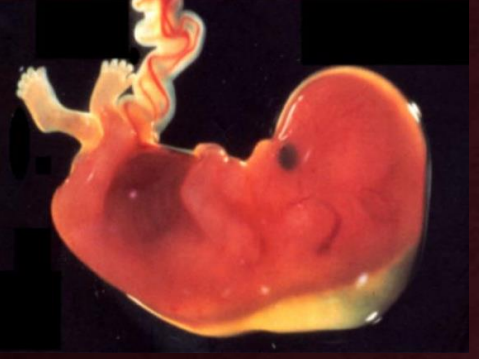


Beta-hCG

Screening performance improves as gestational age advances within this interval.

PAPP-A

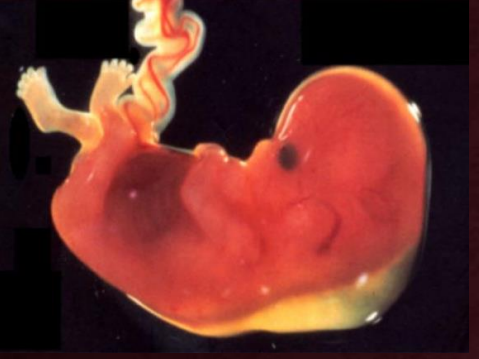
Performance as a screening marker for down syndrome decreases with increasing gestational age between 9+0 and 13+0 weeks.



In euploid pregnancies the average free beta-hcg is 1 MoM and PAPP-A is 1 MoM.

In aneuploid pregnancies the average MoM values of free beta-hcg and PAPP-A are:

- Trisomy 21 free beta-hcg 2.0 PAPP-A 0.5
- Trisomy 18 free beta-hcg 0.2 PAPP-A 0.2
- Trisomy 13 free beta-hcg 0.3 PAPP-A 0.3
- Turner free beta-hcg 1.2 PAPP-A 0.5
- Digynic Triploidy free beta-hcg 0.2 PAPP-A 0.1
- Diandric Triploidy free beta-hcg 9 PAPP-A 0.7



Nuchal translucency

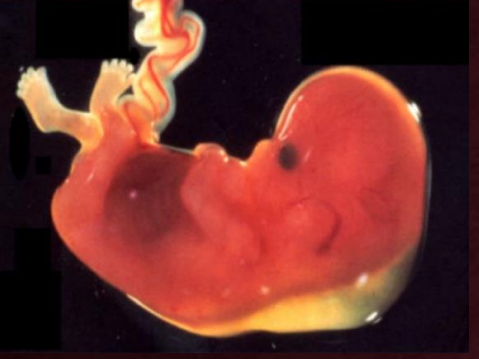
NT is the sonographic appearance of fluid under the skin behind the fetal neck in the first trimester of pregnancy.

Implications of high NT

Increased fetal NT thickness is associated with:

- Trisomy 21 and other major chromosomal abnormalities
- More than 50 fetal defects and genetic syndromes
- Fetal death

However in the majority of cases the NT resolves and the babies are born healthy

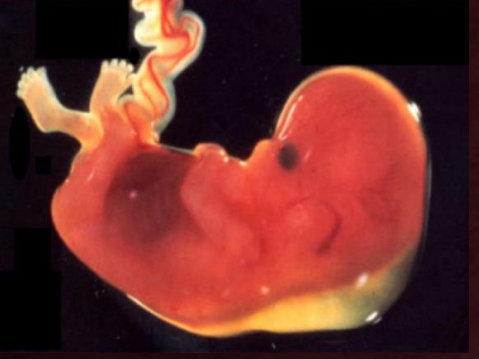


OTHER FIRST-TRIMESTER SERUM SCRENING TESTS

Placental growth factor (PIGF)

Alpha fetoprotein (AFP)

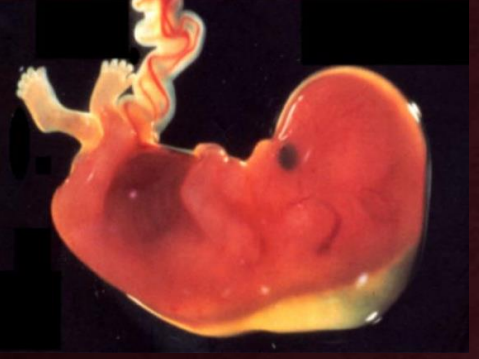
A combination of four serum markers (PIGF, AFP, beta human chorionic gonadotropin [hCG], and pregnancy-associated plasma protein A) between 11+0 and 13+0 weeks of gestation can detect up to 90% of Down syndrome pregnancies but with a false-positive rate of approximately 20%. Useful in areas where NT is unreliable, unavailable, or too costly for routine use.



Inhibin A. an effective Down syndrome maker between 11+0 and 13+6 gestational weeks. Its levels are, on average, elevated in pregnancies affected with Down syndrome.

First-trimester combined screening can also be improved by using two or three additional ultrasound markers, such as:

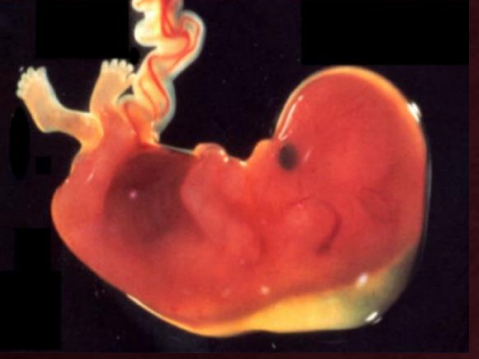
- nasal bone
- tricuspid regurgitation
- ductus venosus flow



INTEGRATED TESTS

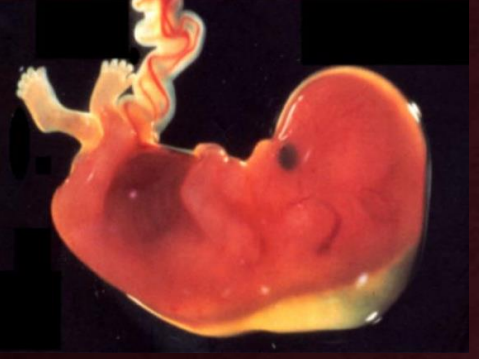
in the first trimester pregnancy-associated plasma protein A between 9+0 and 13+6) weeks, and an ultrasound measurement of NT.
The information is kept until a second-trimester serum sample is drawn (alpha-fetoprotein, unconjugated estriol, inhibin A, and beta human chorionic gonadotropin [hCG])

This integrated test achieves an 85% detection rate (DR) at a 1% false-positive rate (FPR)
The disadvantage of the integrated test is that final test results are not available until the second-trimester.



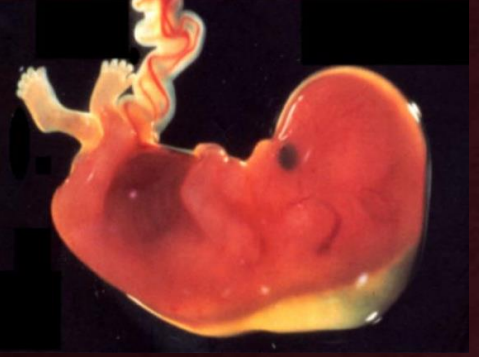
SERUM INTEGRATED TEST

The same as the full integrated test but with out ultrasound measurement of NT.



SEQUENTIAL SCREENING

Performing the first-trimester portion of the integrated screen and then offering counseling and chorionic villus sampling to women whose results place them at the very high risk (eg, ≥1 in 50, or approximately the highest 0.5%) of an affected fetus.

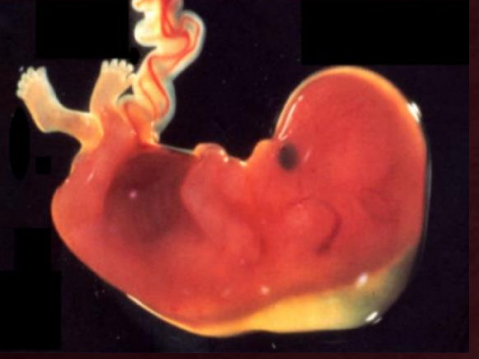


MANAGEMENT

Screen-positive first-trimester combined test results

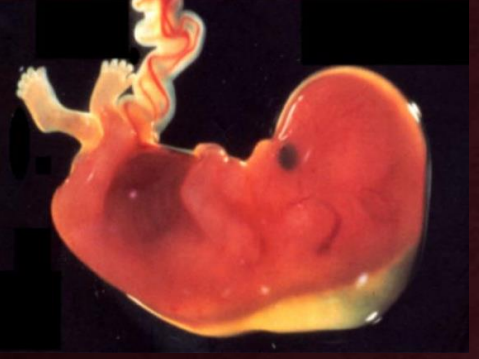
After a positive screening test, it is helpful to have a genetic counselor meet with the parents to discuss the results along with diagnostic and management options.
Women with positive screening results are offered definitive fetal chromosomal analysis (karyotype, microarray) by CVS if they present prior to 14 weeks of gestation.
They may choose to undergo secondary screening using a maternal plasma-based test for cell-free DNA (cfDNA)

A positive of cfDNA test, the risk of Down syndrome is increased but still requires confirmation by an invasive diagnostic test (CVS, amniocentesis).



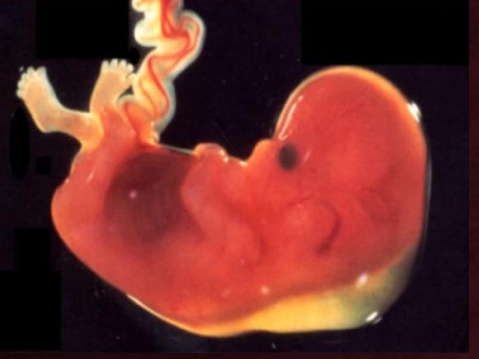
Screen-positive integrated test results

The same counseling issues that apply to women with first-trimester screen-positive results are applicable to those with a screen-positive integrated test result, except that amniocentesis is the diagnostic test offered instead of CVS since the screening result is provided in the early second trimester.

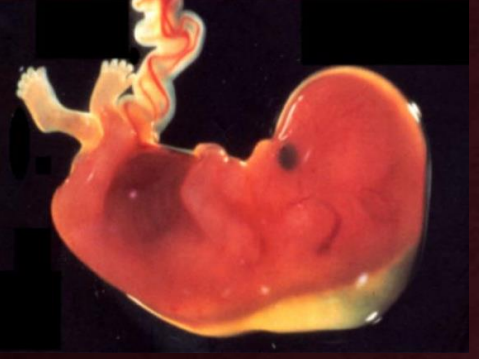


Screen-negative first-trimester or integrated test results

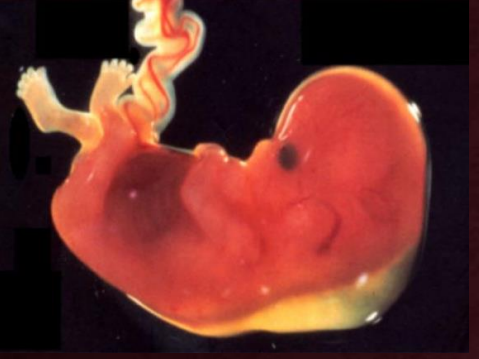
Negative test result means that patient's risk of having a baby with Down syndrome is less than a specified cut-off level; it does not exclude the possibility of Down syndrome.



Term	Description
NT measurement	The maximum width (in mm) of the translucent space at the back of the fetal neck is determined by ultrasound between 11 and 14 complete weeks of gestation.
Quadruple test	An early second-trimester test based on maternal serum measurements: AFP, uE3, free beta-hCG or intact/total hCG, and inhibin A together with maternal age.
Combined test	A late first-trimester test based on sonographic and maternal serum measurements: NT, free beta-hCG or intact/total hCG, and PAPP-A together with maternal age.

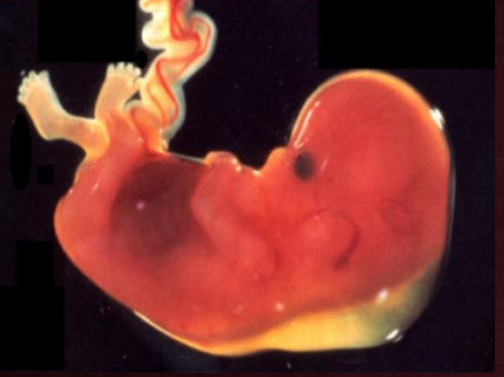


Integrated test (full)	**The integration of measurements performed during the first- and second-trimester into a single screening test result. Typically includes first-trimester NT and PAPP-A with the quadruple test in the second trimester together with maternal age. Usually the risk is only provided once all tests have been completed in the second trimester.**
Serum integrated test	**A variation of the integrated test (full) that does not include the ultrasound component of NT. For this test, the risk is only provided once all tests have been completed in the second trimester.**
Sequential (integrated) test	**A variation of the integrated test (full) in which a small proportion (0.5) of the highest risk women (>1:50) are identified as screen-positive in the first trimester. The remaining women are provided a risk after all tests have been completed in the second trimester. In some programs, the first-trimester risk is reported to all women, but only those >1:50 are considered screen-positive.**



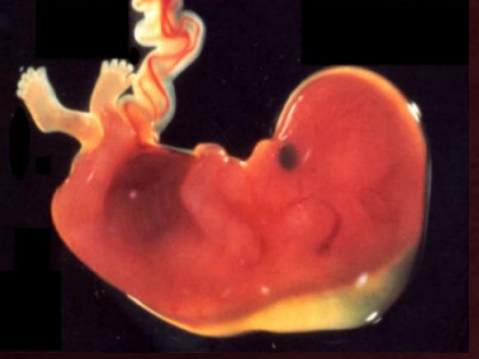
Detection of structural anomalies

Sonographic evaluation for detection of fetal structural anomalies is commonly performed at 18 to 20 weeks for optimal visualization.



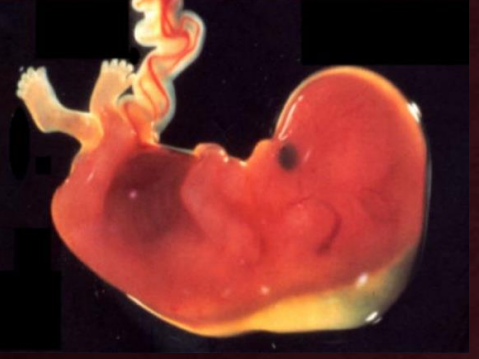
SOFT MARKERS

- Increased NT
- Increased nuchal fold- LR 11 to 18.6
- Cystic hygroma
- Absent nasal bone
- Echogenic bowel- LR 5.5 to 6.7
- Pyelectasis- LR 1.5 tp 1.6
- Ventriculomegaly- LR 25
- Shortened long bones- LR 1.2 to 2.2
- Echogenic intracardiac focus- LR 1.4 to 1.8
- Choroid plexus cysts
- Single umbilical artery



CELL-FREE DNA

- Circulating cfDNA is derived from both the mother and the placenta
- The source of cfDNA is apoptosis of placental cells and fetal erythroblasts
- After delivery maternal clearance of fetal cfDNA occurs rapidly. all fetal cfDNA eliminated within 2 days of delivery.

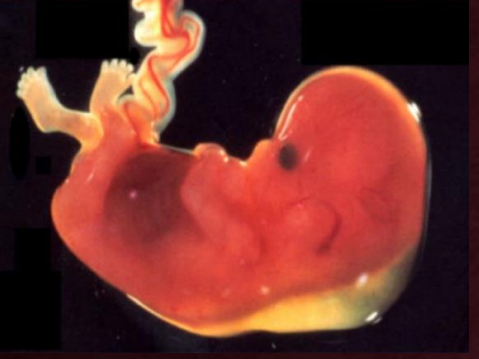


FETAL FRACTION

- an adequate amount of fetal-placental cfDNA must be present to obtain a reliable test result

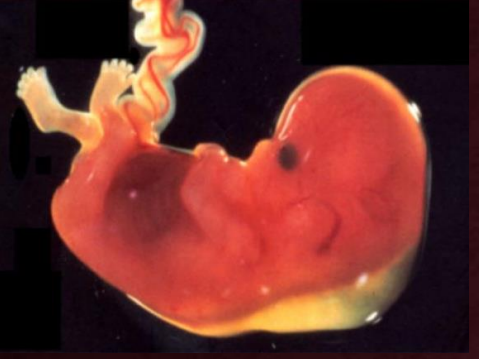
- A low fetal fraction may be due to:

✓ Early gestational age
✓ Suboptimal sample collection
✓ Obesity
✓ Fetal karyotype
✓ Maternal use of LMWH
✓ IVF
✓ Twin gestations



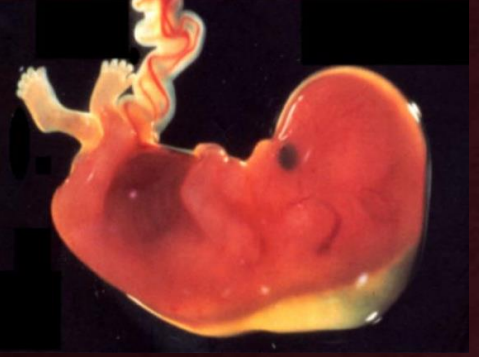
SCREENING PERFORMANCE

- Trisomy 21- DR 99.5%, FPR 0.05%
- Trisomy 18- DR 97.7%, FPR 0.04%
- Trisomy 13- DR 96.1%, FPR 0.06%
- Monosomy X- DR 90.3%, FPR 0.23%
- Trisomies 47XXX; 47XXY; 47XYY - DR 93%, FPR 0.14%



FALSE-POSITIVE cfDNA TEST RESULTS

- Confined placental mosaicism
- Demised twin
- Maternal mosaicism
- Maternal cancer
- Maternal copy number variants
- Technical issues
- Transplant recipient
- Recent blood transfusion

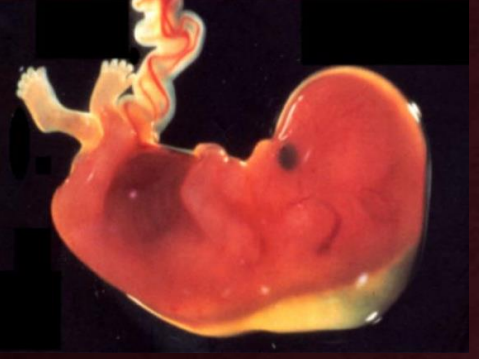


CLINICAL USE

- Secondary screening
- Contingent model

Intermediate-risk group (1:151 to 1:1000) represent 10 to 15% of the screened population. These women are informed of their intermediate risk and offered cfDNA screening after counseling.

- Primary screening
- Obese women

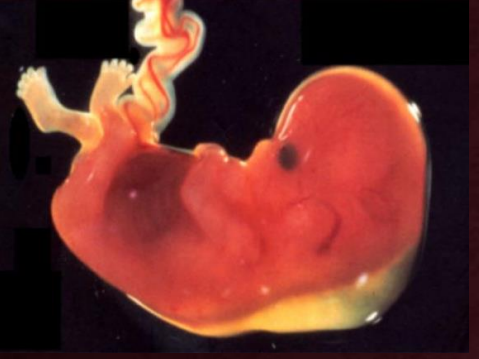


- Twins

The ACOG allows for or recommend cfDNA screening for common trisomies for twin pregnancies.

- Triplets

The data are even more limited.



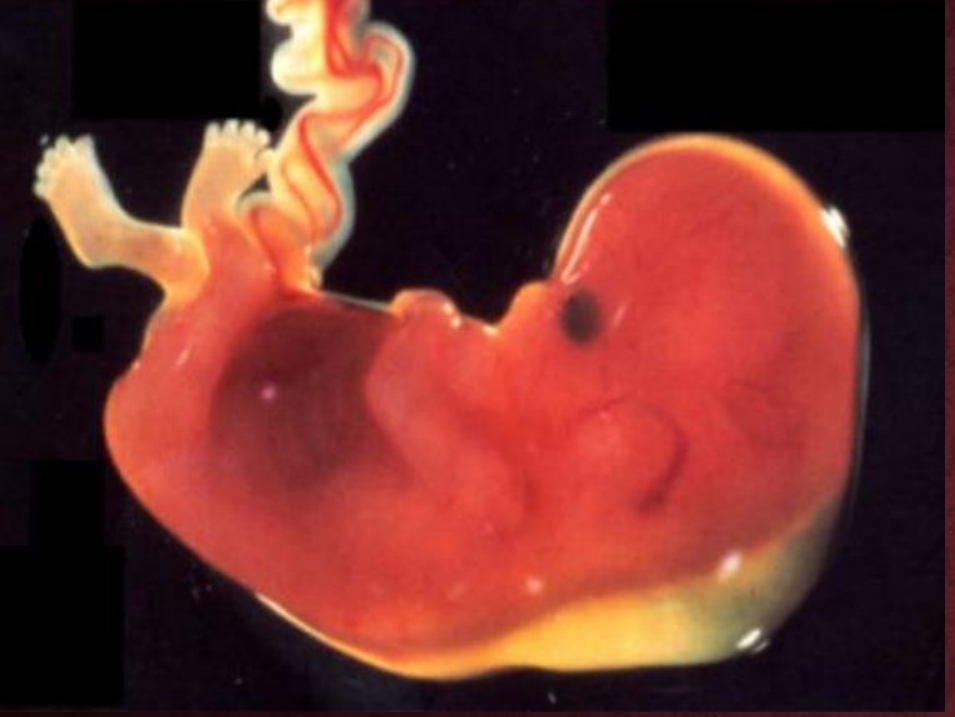
POST-TEST FOLLOW-UP

- Screen positive

Even with the high performance of cfDNA screening, invasive diagnostic testing must be offered to women in order to confirm the fetal karyotype.

- Screen negative

- No call



Thank you.