

History & Principles of Biochemical Screening for Down's Syndrome

Element C

Scope of Presentation

- What do we mean by 'screening'?
- Historical milestones
- Terminology
- Multiples of the median
- Serum markers
- Screening strategies

Aims and Objectives

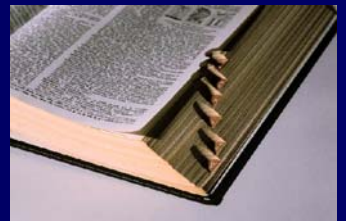
- To provide a clear explanation of the principles of screening for Down's syndrome for healthcare professionals involved in antenatal care
- Explain what we mean by the term 'screening'
- Explain terms commonly used in screening
- Briefly describe the screening markers and their efficacy in screening
- To ensure that women and their partners receive clear accurate information about the maternal serum screening test so that they can make informed decisions at each stage of the screening process

What is screening?

Screening is a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications.

UK National Screening Committee

Terminology



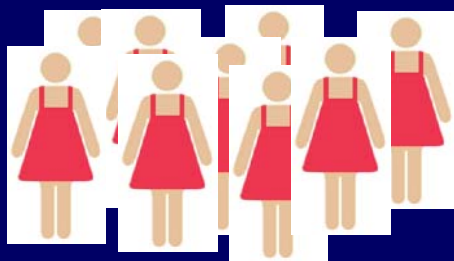
Diagnostic Tests

Diagnostic tests for Down's Syndrome give definitive information on fetal chromosomes by confirming the presence of a third copy of chromosome 21

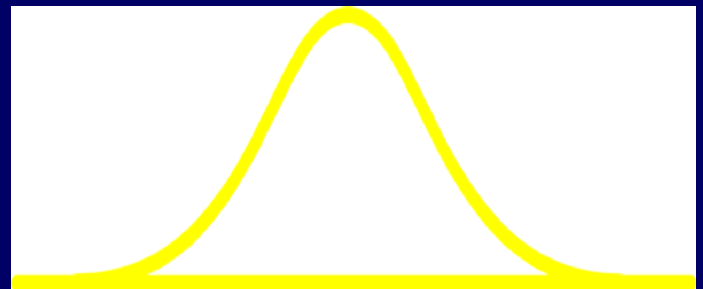
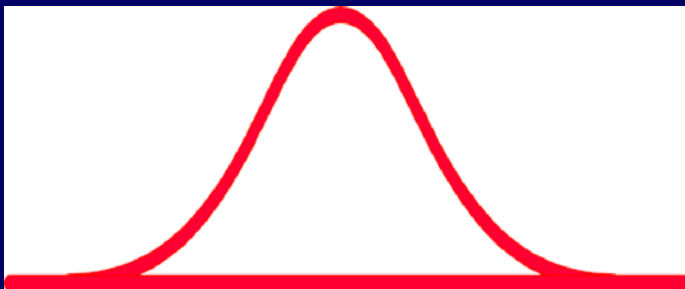
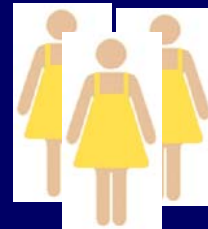
Screening Tests

Screening tests identify individuals as broadly 'high' or 'low' risk. Low risk results do not indicate 'no' risk. High risk results do not indicate that the baby definitely has Down's Syndrome, but should prompt the health care professional to offer further screening or diagnostic tests

Unaffected



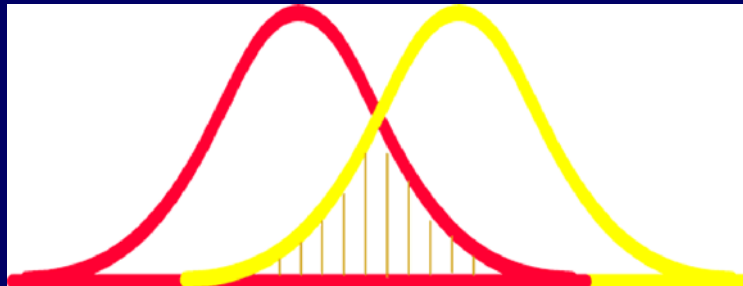
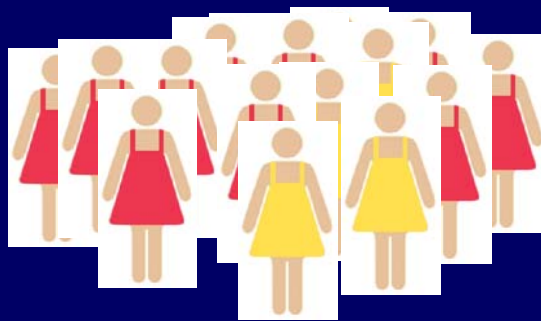
Affected



Diagnostic Testing

Unaffected

Affected



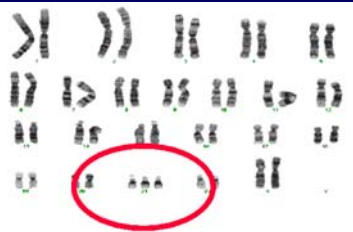
Screening Test

Historical Milestones

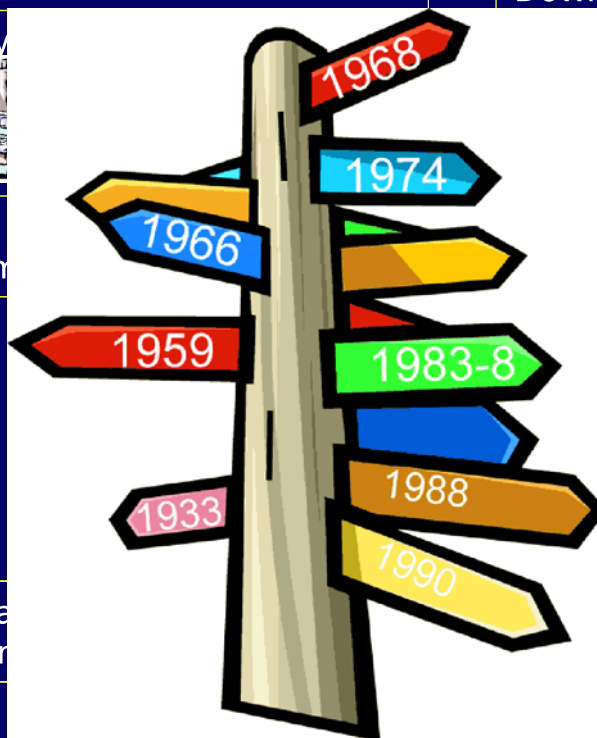
First chromosomal analysis from amniotic fluid



Trisomy 21 identified as cause of Down's Syndrome



Association between maternal age and Down's syndrome



Prenatal diagnosis of Down's syndrome



Raised AF-AFP associated with open Neural tube defects



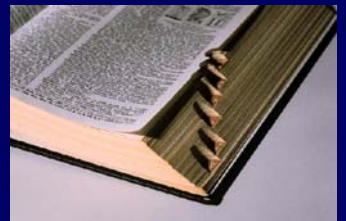
Maternal serum markers for Down's Syndrome

Triple test introduced

Nuchal translucency test introduced



Terminology



Uptake rate

The proportion of women from the pregnant population that choose to undergo screening

Affected population

Individuals who have the condition being screened for

Unaffected population

Individuals who do not have the condition being screened for

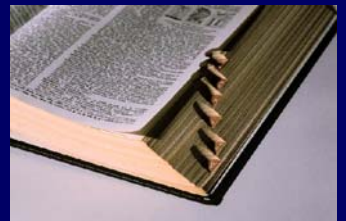
Terminology

Detection Rate (DR)

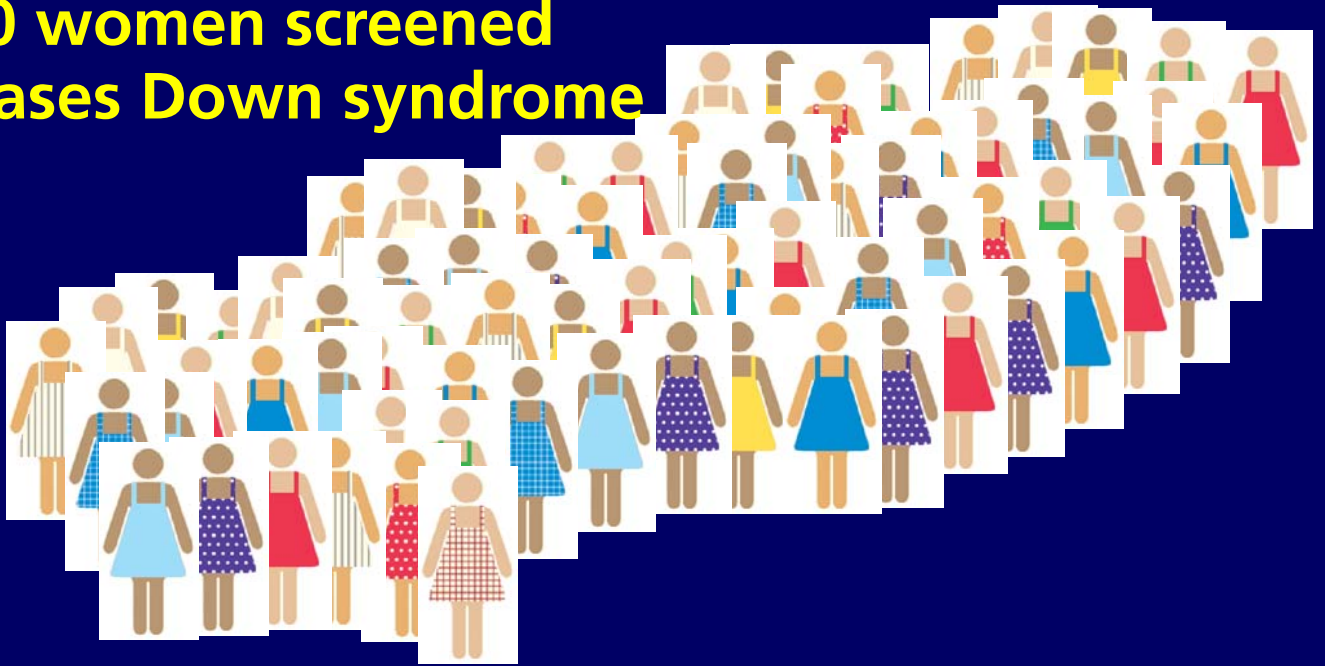
The proportion of affected individuals with positive screening results

False Positive Rate (FPR)

Proportion of unaffected individuals with positive test results



1000 women screened
10 cases Down syndrome

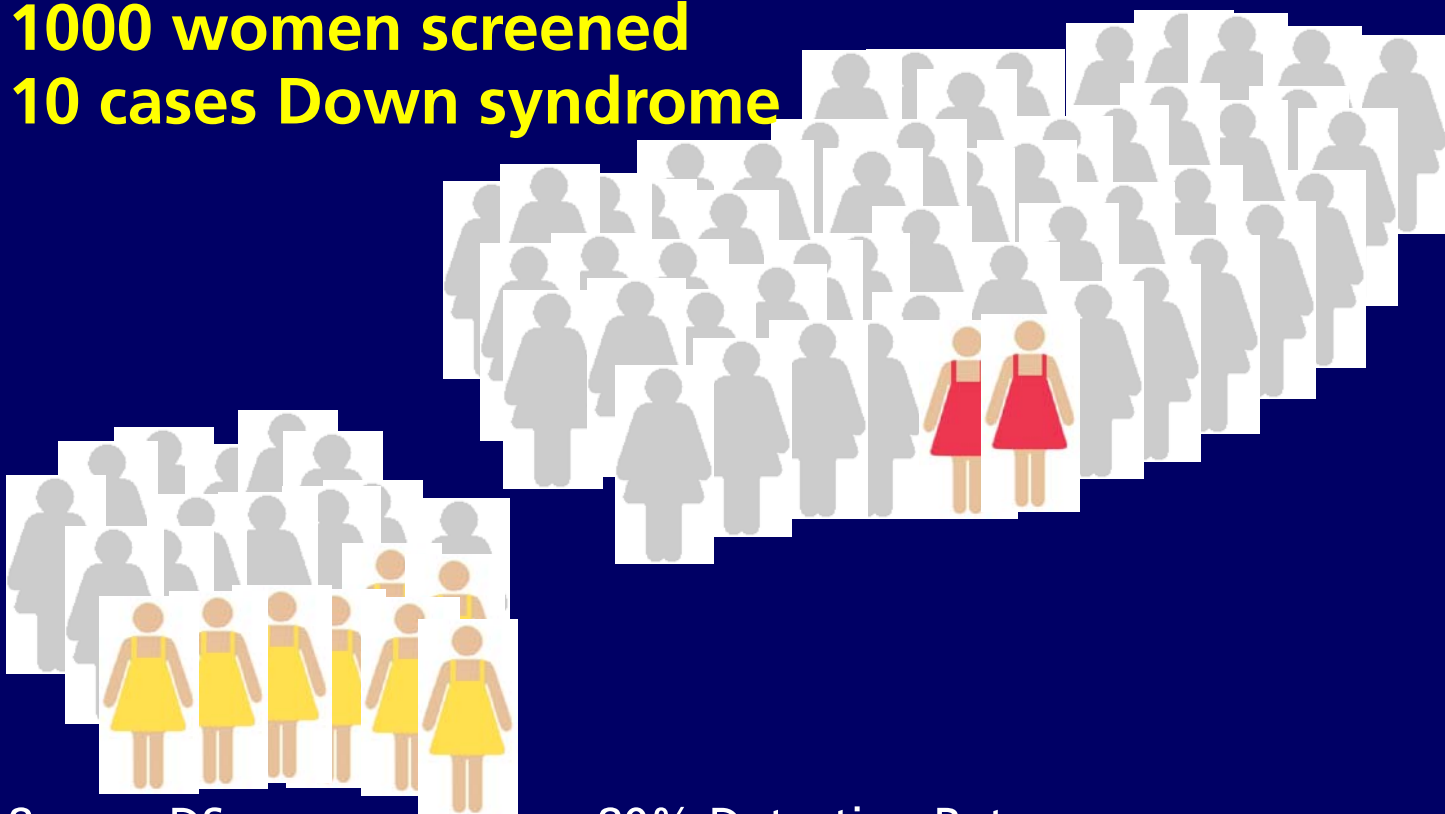


40 women
Risk DS > 1 in 250

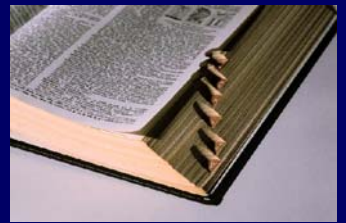


4% of women screened
are offered amniocentesis

1000 women screened
10 cases Down syndrome



Terminology



False Negative Rate (FNR)

The proportion of women who are given a lower risk result but have an affected pregnancy

Multiples of the Median - Defined

The serum marker concentration for a pregnant woman, divided by the median concentration value for unaffected pregnancies of the same gestational age

The Median and the Mean

The **median** value is the middle value if all values in a series are arranged in numerical order

1 4 4 5 9 24 30

median

The **mean** or **average** is the sum of the values in a series divided by the number of values

$$\frac{1 + 4 + 4 + 5 + 9 + 24 + 30}{7} = 11$$

mean

Why do we use Median?

1 4 4 5 9 24 30

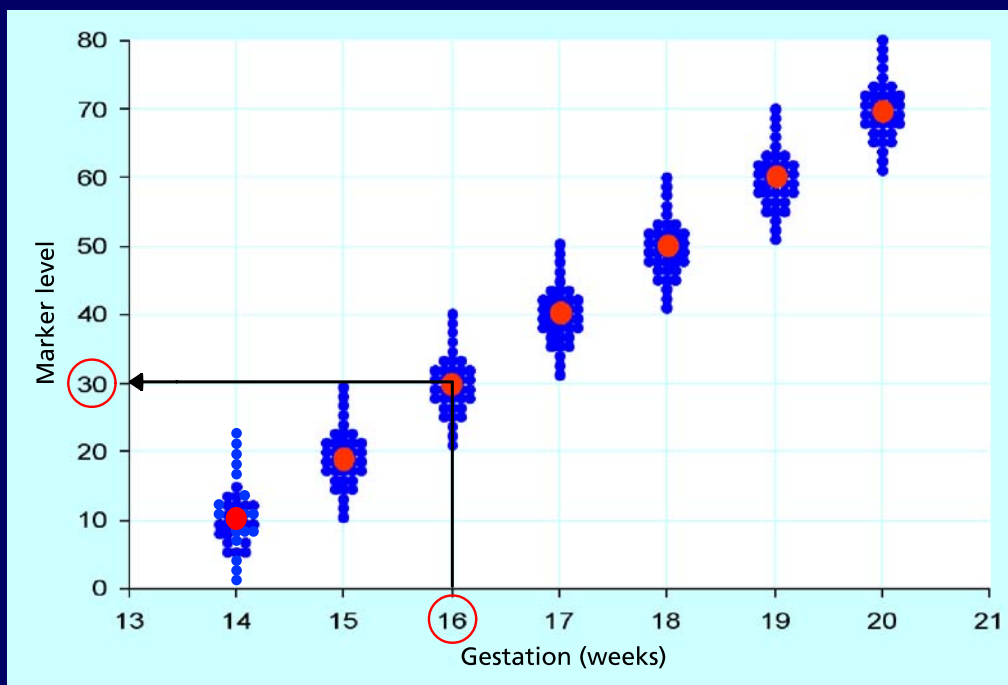
High values
skew Mean

Median = 5

Mean = 11

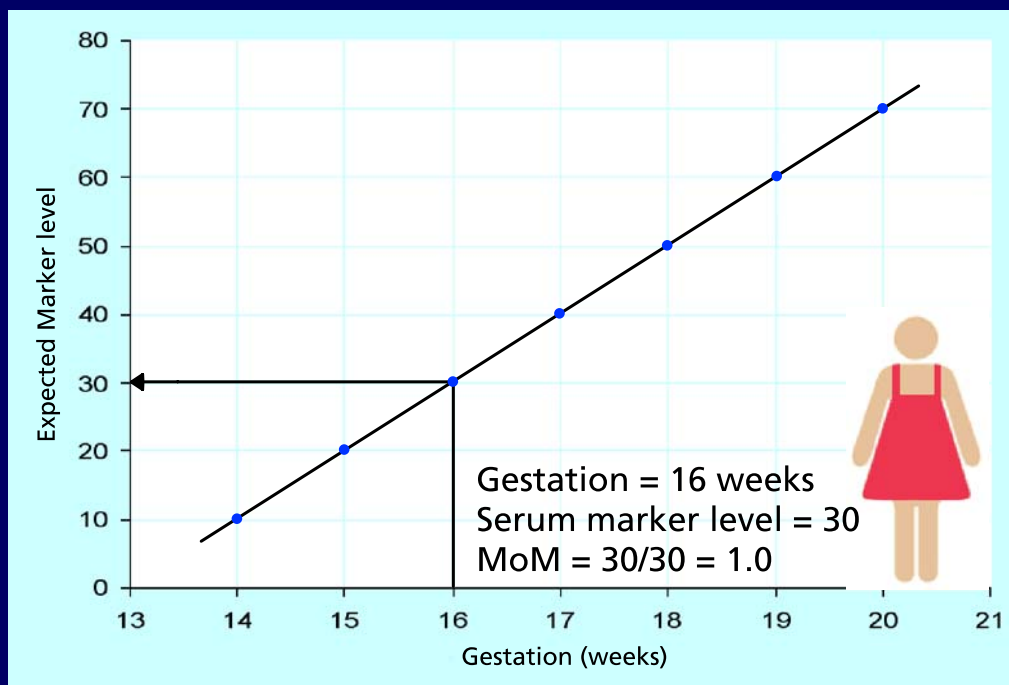
The median value is not influenced by very high or very low values

Multiples of Median (MoM)

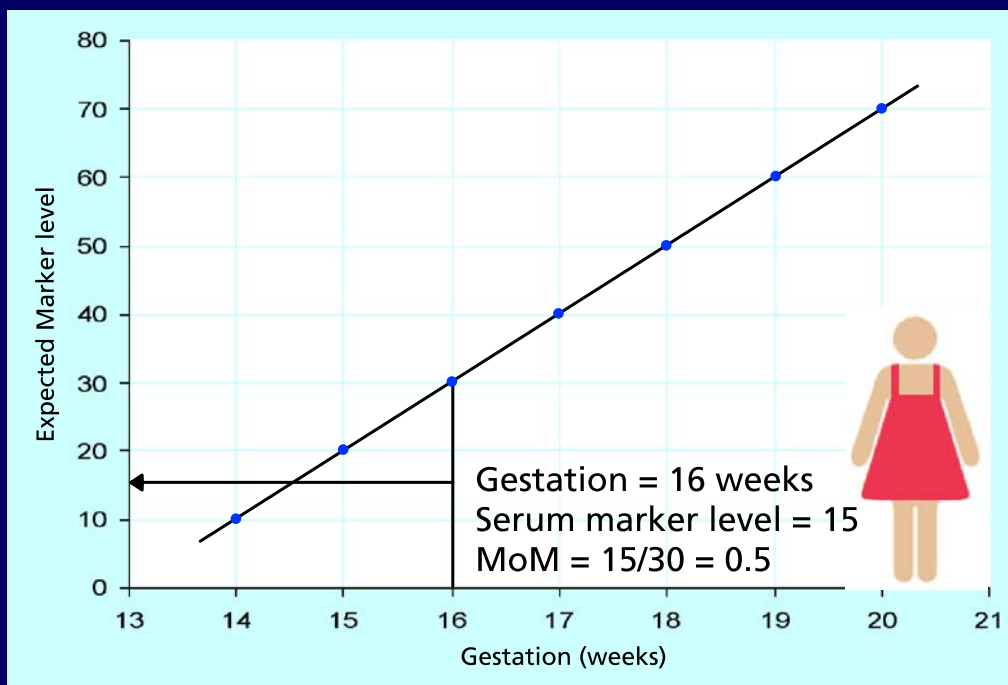


Median values for each marker are established by measuring a large number of samples at each week of gestation

Calculating a MoM Value



Calculating a MoM Value



Remember



Median values
change with
gestational age
(GA)

Wrong GA = Wrong MEDIAN

Wrong MEDIAN = Wrong MoM

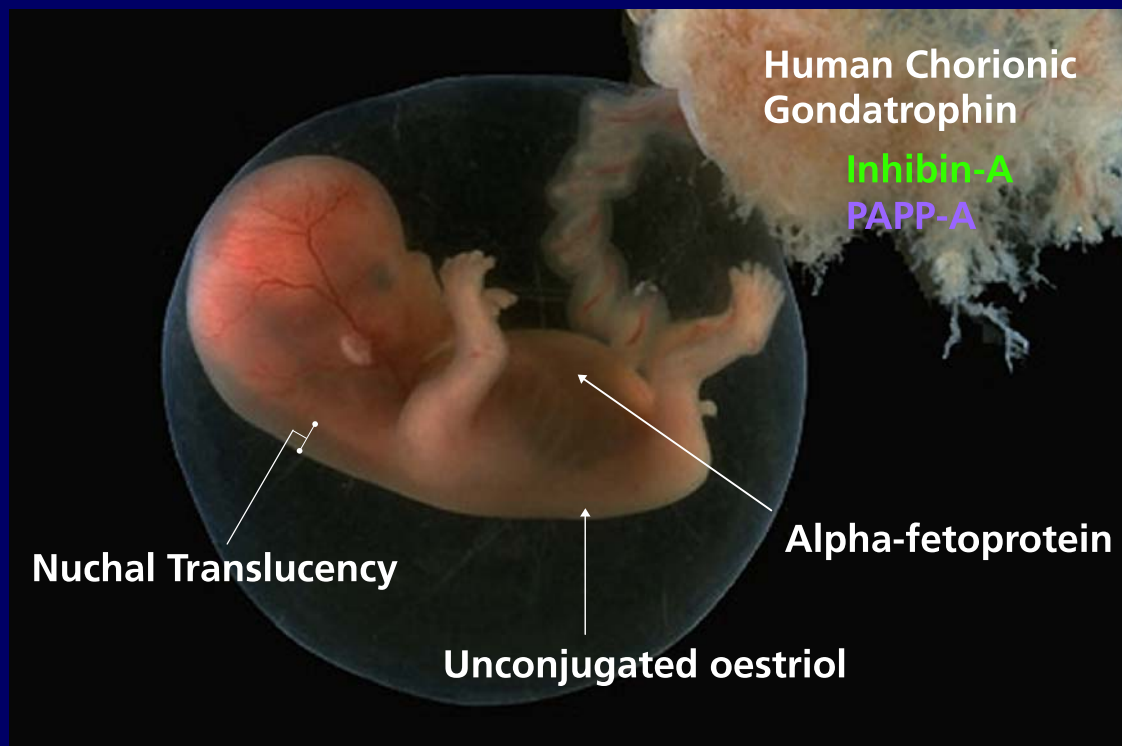
Wrong MoM = Wrong Risk



Maternal Serum 'Markers' used in Antenatal Screening for Down's Syndrome

- May be referred to as 'Analytes'
- Tend to have low sensitivity when used alone
- Serum markers levels may be affected by maternal weight

Screening Markers



First Trimester Serum Markers

PAPP-A

(Pregnancy Associated Plasma Protein-A)

- Originates mainly from placental syncytiotrophoblasts
- Concentration increase with gestation
- Screening sensitivity decreases with gestation
- Optimal sensitivity at 10 - 11 weeks gestation
- Levels reduced (0.34 - 0.58 MoM) in pregnancies affected by Down's Syndrome

B-hCG - A First and Second Trimester Screening Marker

Human Chorionic Gondotrophin

- Beta subunit of Hcg/intact hCG
- Produced by the syncytiotrophoblast cells
- Decreases with gestational age
- Sensitivity maintained in second trimester
- Raised levels in pregnancies affected by Down's Syndrome (i.e. 2.20 MoM)

Second Trimester Screening Markers

Alpha-fetoprotein (AFP)

- Produced by fetal yolk sac and liver
- Increases with gestation age
- Levels reduced in pregnancies affected by Down's Syndrome values in region of 0.75 MoM
- Levels increased in pregnancies affected by open spina bifida or abdominal wall defects e.g. gastroschisis

Second Trimester Screening Markers

Unconjugated oestriol (uE₃)

- Produced by placenta and fetal adrenals
- Increases with gestation
- Levels reduced in pregnancies affected with Down's Syndrome i.e. 0.64 - 0.72 MoM

Second Trimester Screening Markers

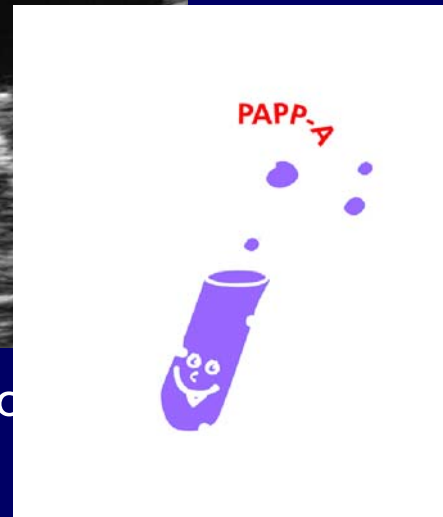
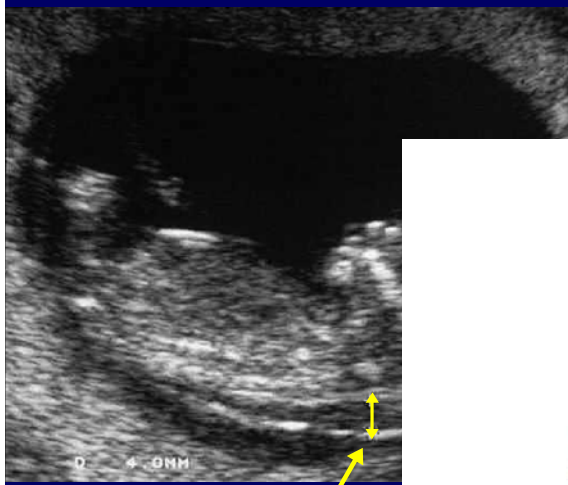
Inhibin-A (Inhibin)

- Produced by placenta
- Decreases with gestational age between 14 and 17 weeks whereupon it begins to increase again
- Levels increased in pregnancies affected with Down's Syndrome i.e. values in region of 1.80 MoM

Combined Test

Timing: 10 - 14 weeks

Optimally: 10 weeks



Integrated Test



10 - 20 weeks



+



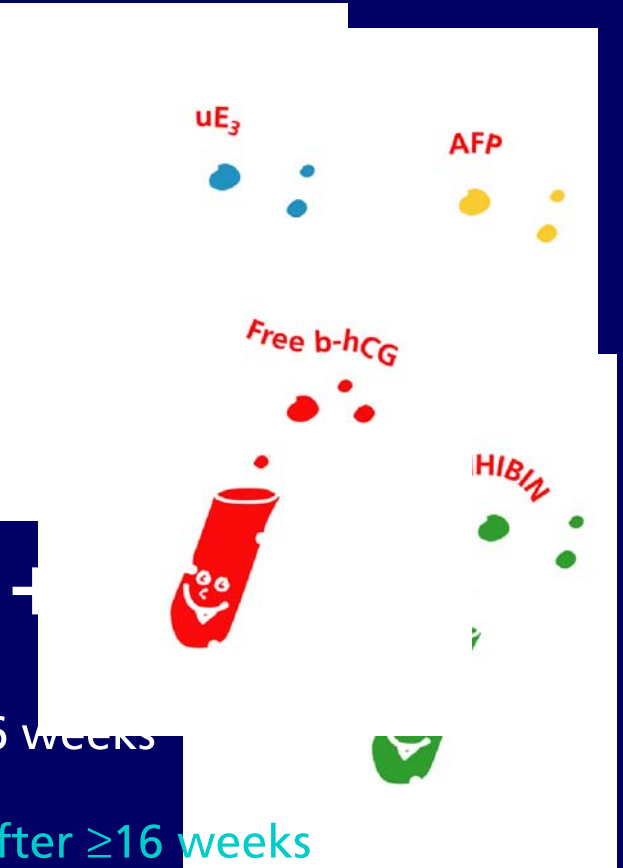
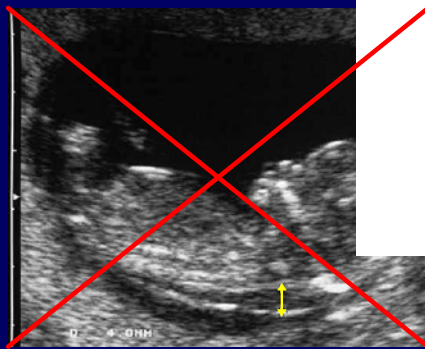
Quadruple or Triple test at 16 weeks

Integrated results reported after ≥16 weeks

Serum Integrated Test



10 - 20 weeks



Quadruple or Triple test at 16 weeks

Integrated results reported after ≥ 16 weeks

Double Test



Triple Test



Quadruple Test



Screening Strategies supported by the HTA SURUSS Report (2003)

