

Screening

“the systematic application of a test procedure to identify individuals at sufficient risk to warrant diagnostic investigations”

- CVS 12wks
- Amniocentesis 16wks
- Morphology Ultrasound 18wks

Aim is to maximise detection of affected pregnancies and minimise false +ves

Screening for trisomy 21

Biochemical Markers;

2nd Trimester

AFP

free β hCG

uE3

Inhibin A

1st Trimester

free β hCG

Papp-A

Other Markers;

Nuchal Translucency

←———— Maternal age —————→

←———— Gestational age —————→

Marker Levels Change Significantly with Gestation

Measured levels are converted to Multiples Of the Population Median or **MoM** values.

Reference is therefore 1 MoM

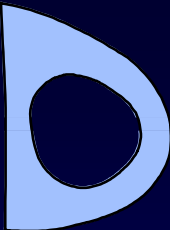
beta hCG at 10 wks GA

Patient $\frac{120 \text{ IU/L}}{60 \text{ IU/L}} = 2 \text{ multiples}$

Median 60 IU/L

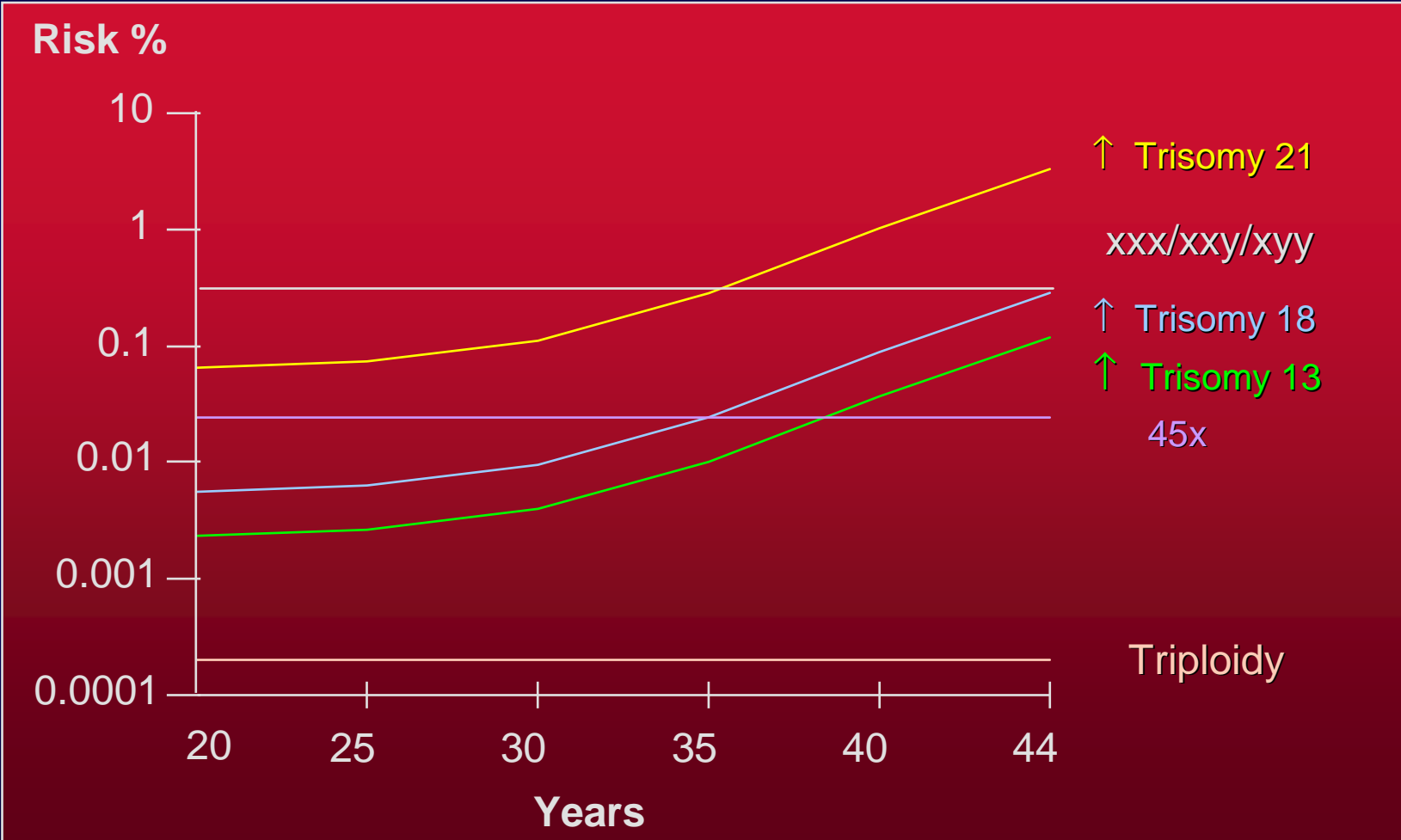
MoMs are independent of gestational age and concentration Units

LogMoM values are used in calculations as they exhibit a Gaussian distribution (Mean +/- SD)

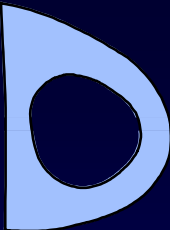


Background Risk

Maternal age

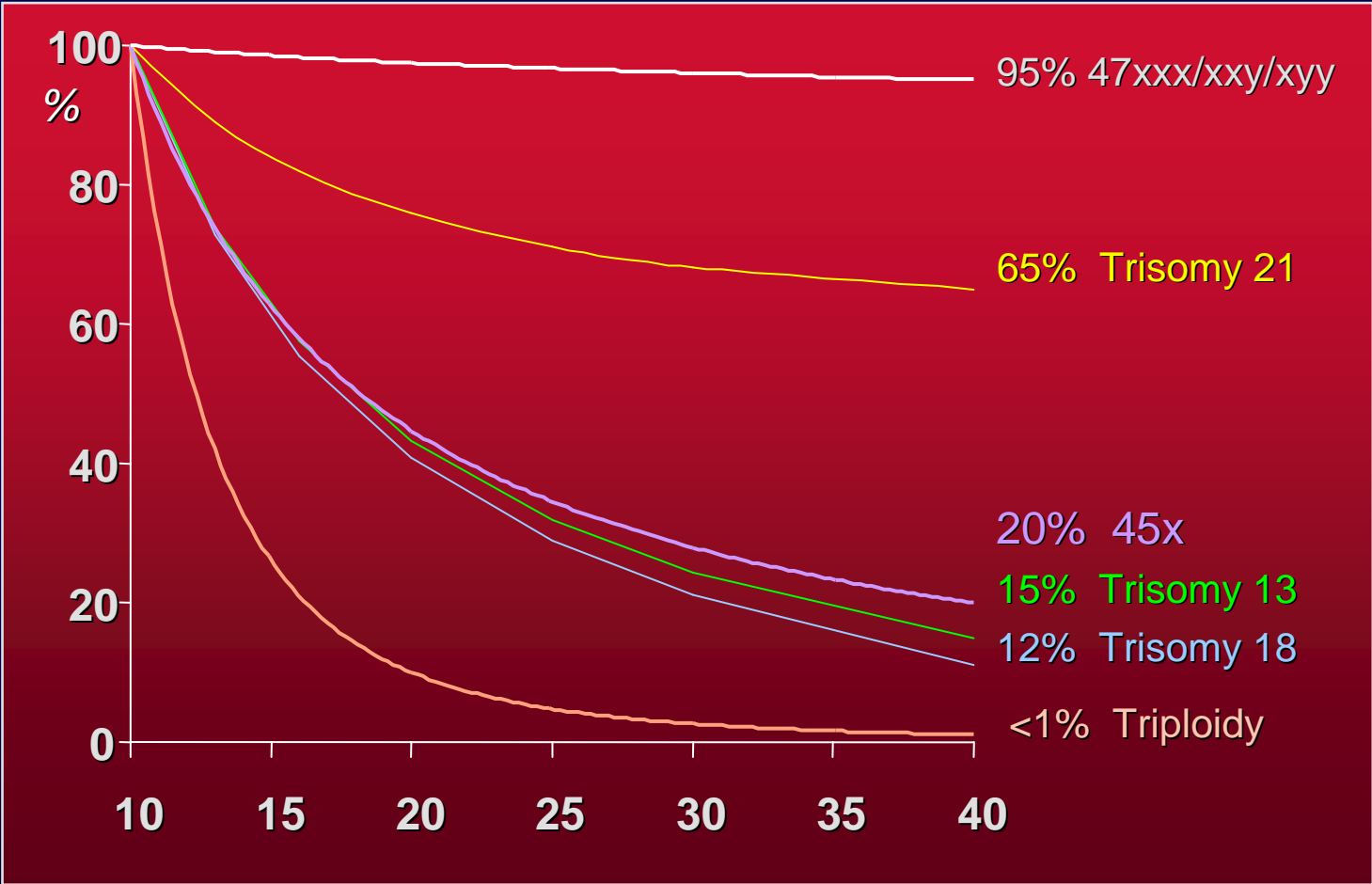


Snijders et al 1995 Nicolaidis et al., The 11-14-week scan, London 1999



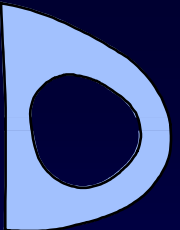
Background Risk

Gestational age



Snijders et al 1995

Nicolaides et al., The 11-14-week scan, London 1999



Assessment of Risk

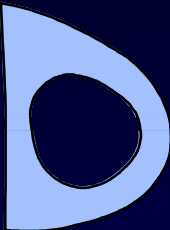
Previous Chromosomal Abnormality

Trisomy 21
Trisomy 18
Trisomy 13

} ↑ +
0.50 - 0.75%

45XO
47XXY/XXX
Triploidy

} ↔



Screening for trisomy 21

Effectiveness of different methods of screening

100,000 pregnancies

Screen positive 5%
N=5,000

Trisomy 21
N=200

| Method of screening | Detection rate | Number detected |
|---|----------------|-----------------|
| Maternal age | 30% | 60 |
| Serum biochemistry at 16 wks | 65% | 130 |
| Nuchal translucency (NT) at 12 wks | 75% | 150 |
| Fetal NT & β -hCG & PAPP- A at 12 wks | 90% | 180 |

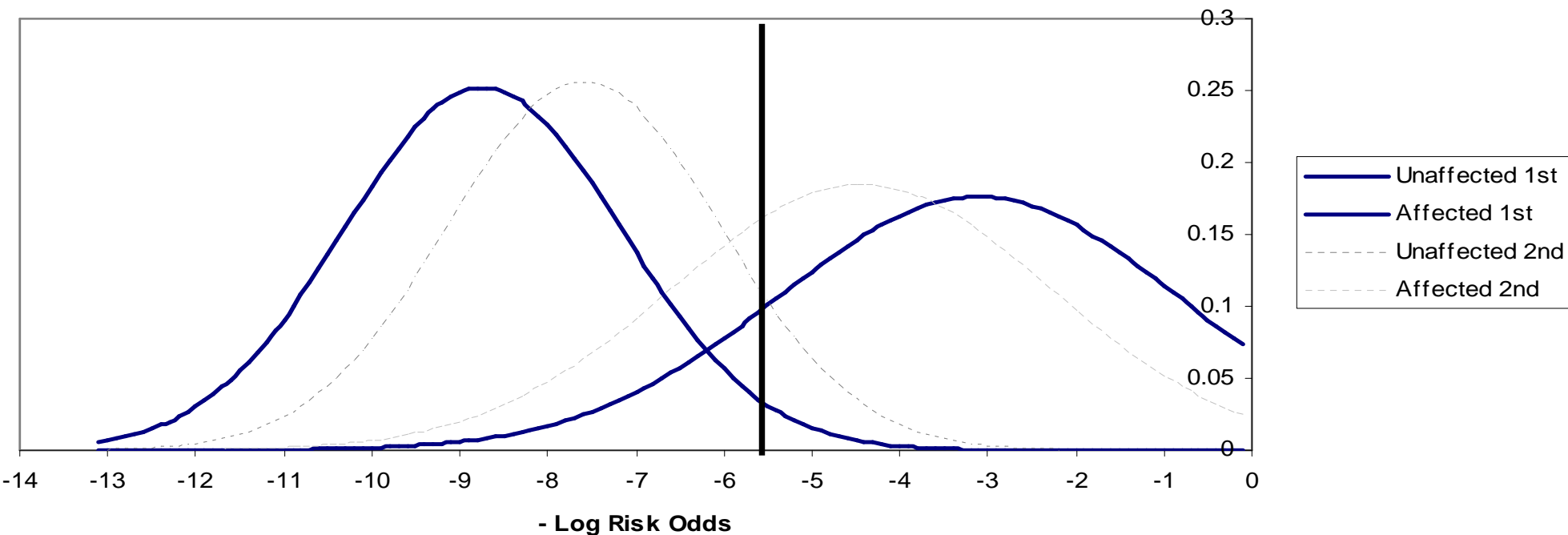
Nicolaides KH. Fetal nuchal translucency. Am J Obstet Gynecol 2004

| | Maternal Age Screening alone | Second trimester biochemical screening | First trimester combined screening |
|--|-------------------------------------|---|---|
| Amniocenteses performed per case detected | 250 | 40 | 20 |
| Fetal loss per case of Down syndrome detected | 1 : 1 | 1 : 5 | 1 : 10 |

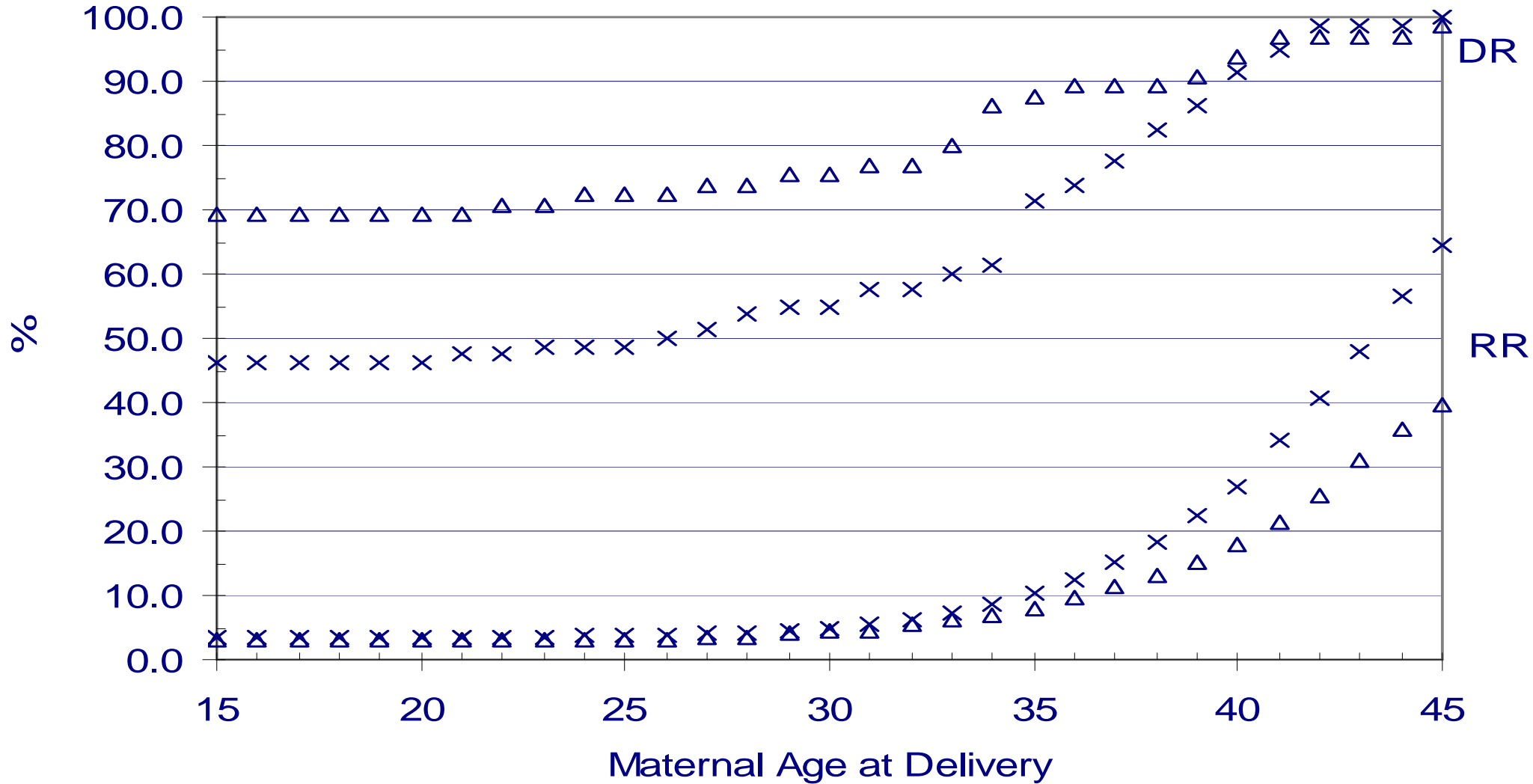
Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003; 7(11):1-77

1st trimester Risk Odds show better separation between Unaffected and Affected pregnancies when compared to 2nd trimester Risk Odds.

Risk Odds
1st Trimester vs 2nd Trimester

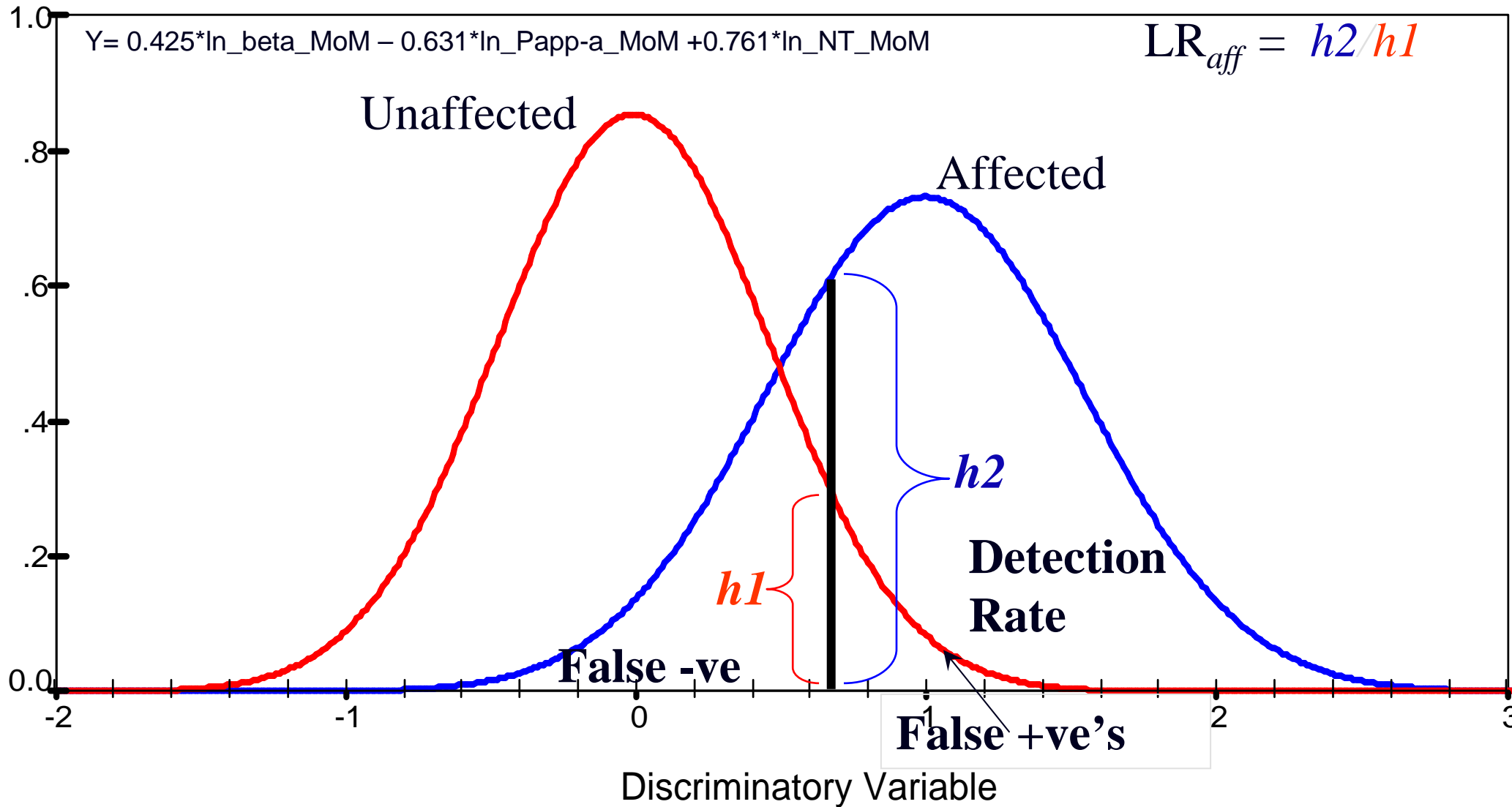


Age Specific Performance
 Comparison of 1st and 2nd Trimester Screening.
 Maternal Age vs Recall and Detection



× %RR 2nd × %DR 2nd △ %RR 1st △ %DR 1st

DS Risk = Mat. Age Risk x LR

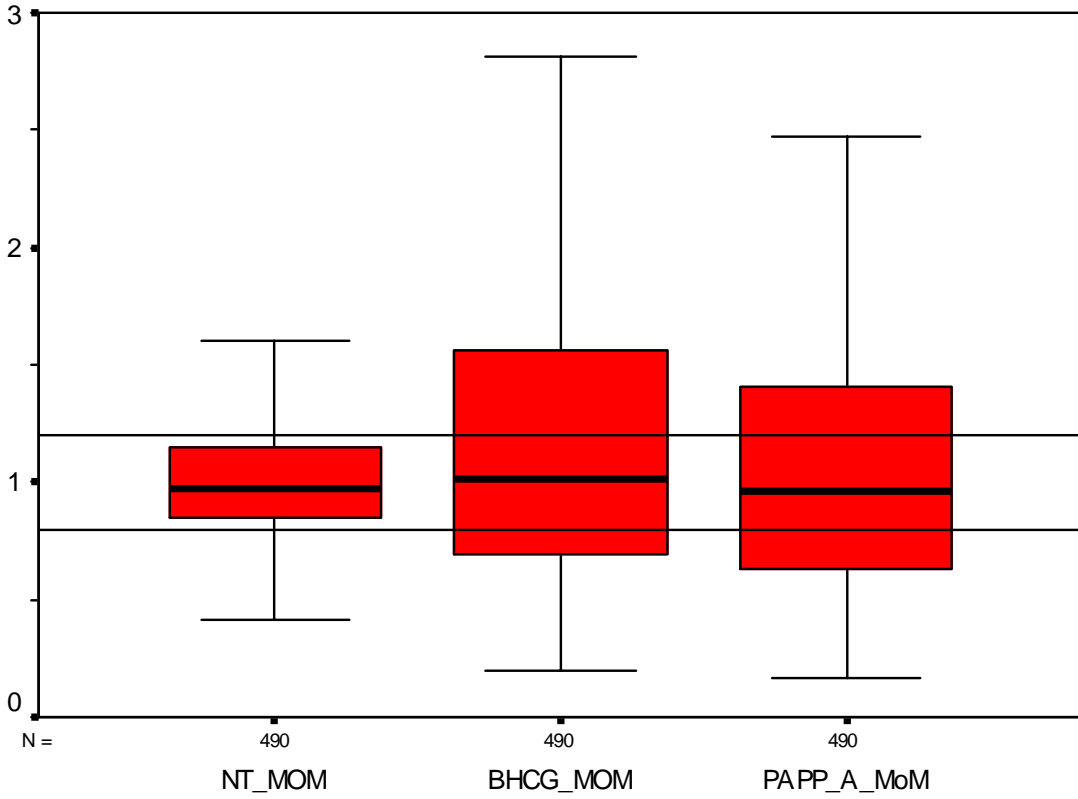


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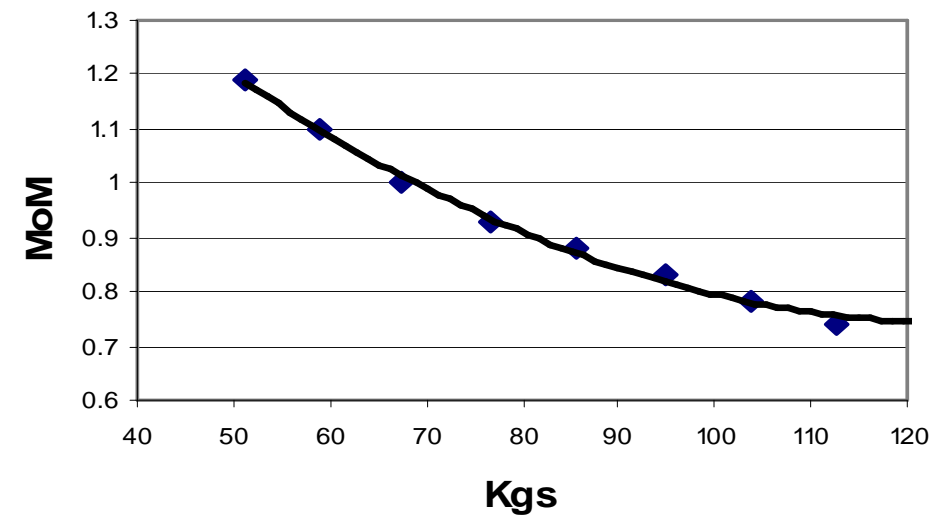
DS Risk = Mat. Age Risk \times LR

- 20 yrs = 1 in 1600 \times 2 = 1 in 800
- 30 yrs = 1 in 1100 \times 2 = 1 in 550
- 35 yrs = 1 in 500 \times 2 = 1 in 250
- 40 yrs = 1 in 156 \times 2 = 1 in 78
- 45 yrs = 1 in 40 \times 2 = 1 in 20

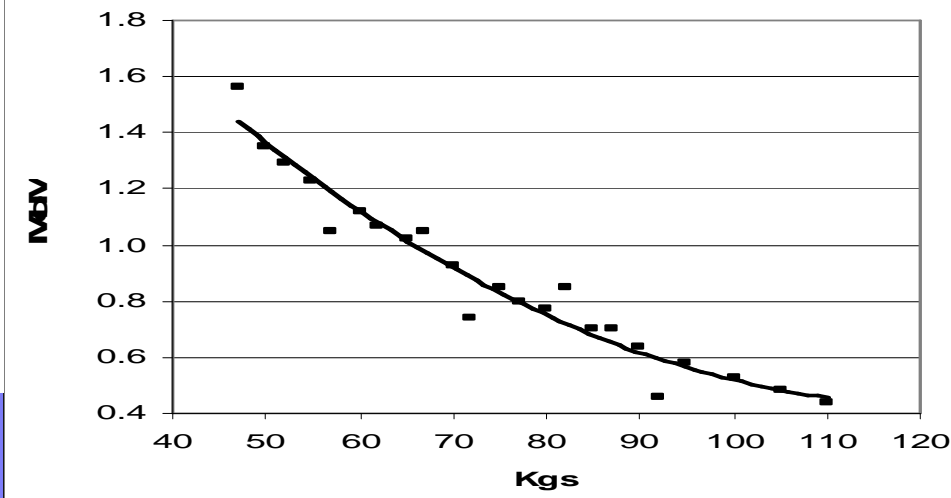
Unaffected 1st Trimester



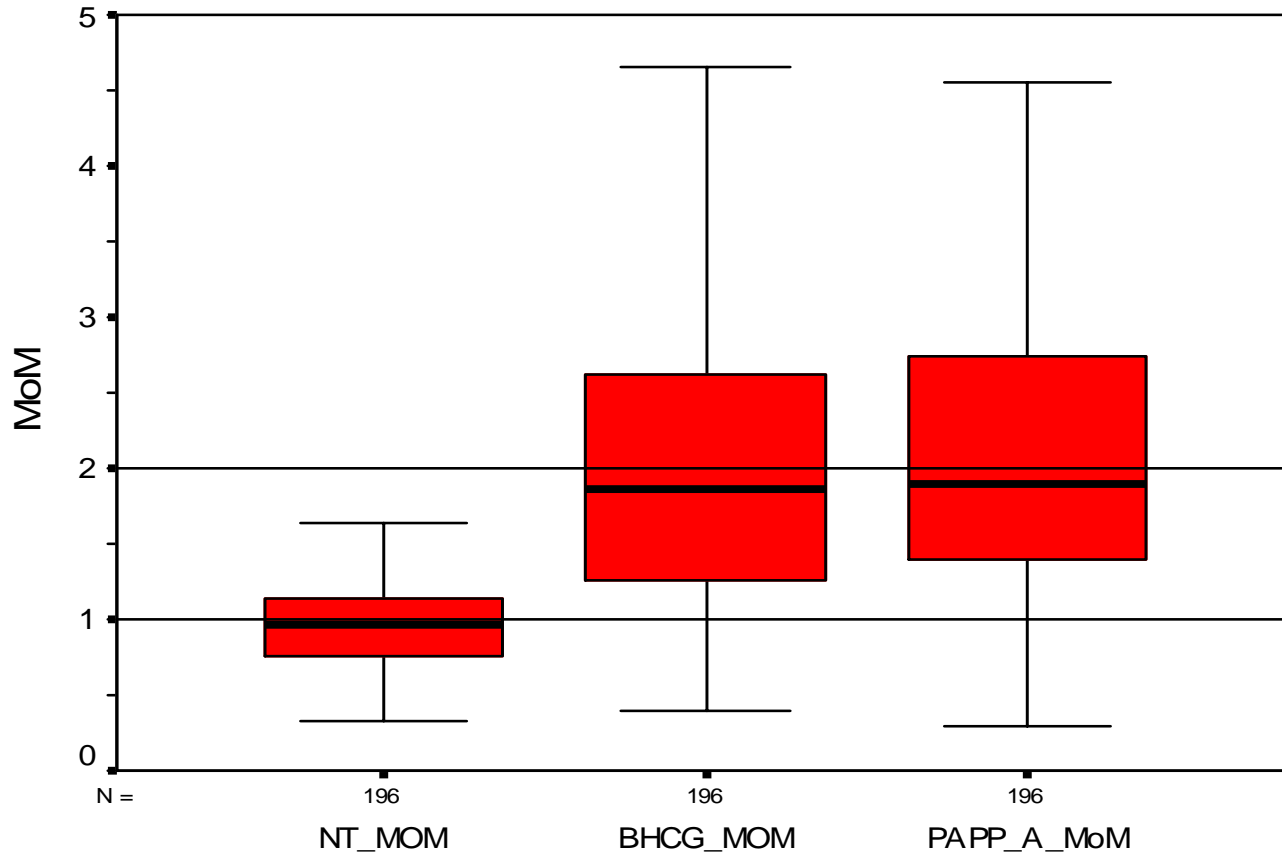
Beta MoM's vs Weight Kg



Pappa MoM's vs Weight Kg



Twins 1st Trimester



(1990–2003) 1:70 to 1:55

** Assisted reproduction*

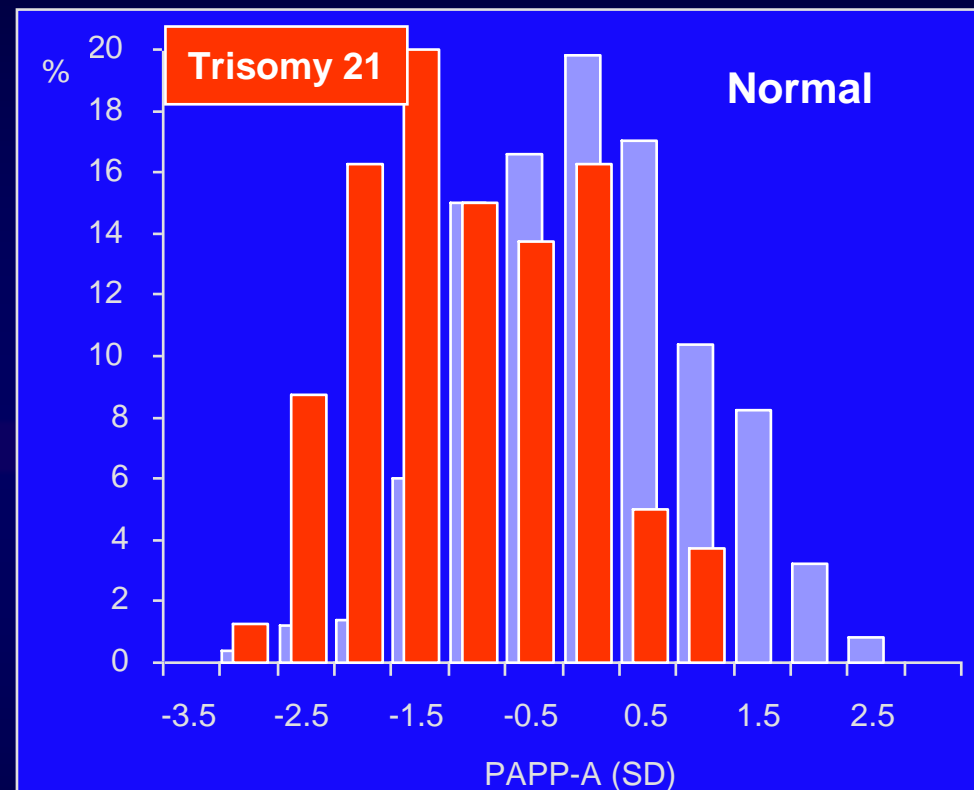
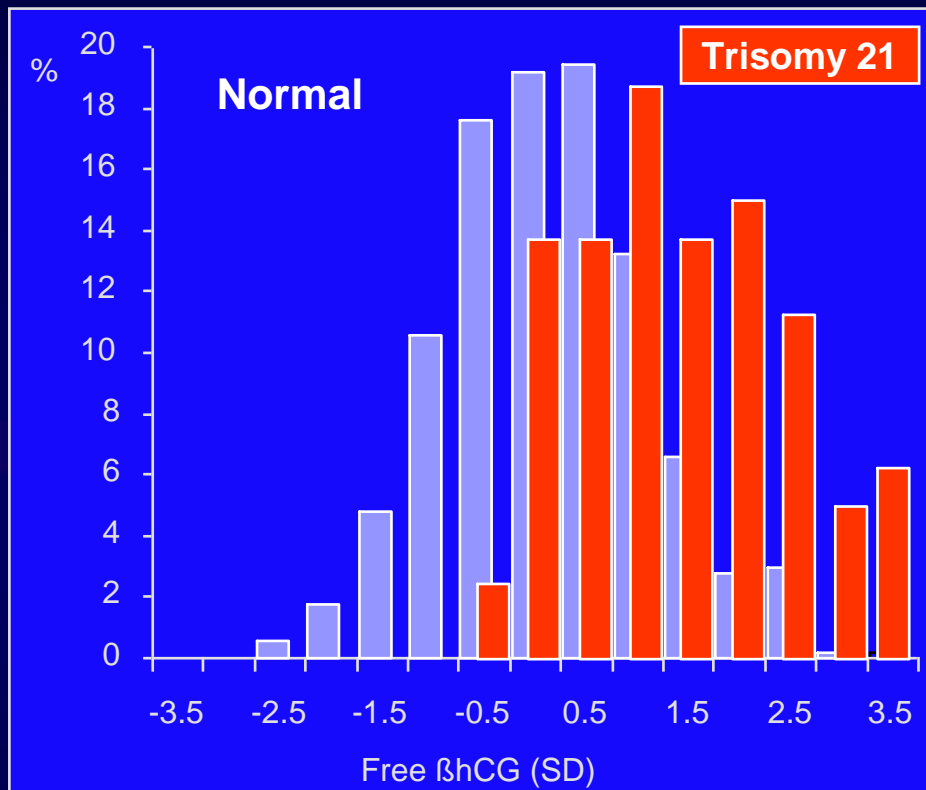
** Rate of twinning increases with age.*

>17% of pregnancies are now to women 35yrs or over, up from <9% in 1990.

FMF software uses data as published by Spencer, Br J Obstet Gynaecol March 2003, Vol. 110, pp. 276-280. Median MoMs free B-hCG = 2.15 and Papp-A = 1.93 weight corrected.

Biochemistry and Screening for trisomy 21

Maternal serum free β -hCG & PAPP-A at 11-13⁶ wks



- In trisomy 21 pregnancies at 11-14 weeks, maternal serum free β -hCG is increased and PAPP-A is decreased
- The alterations in maternal serum biochemistry are independent of fetal NT thickness
- Screening by fetal NT and serum free β -hCG and PAPP-A identifies 90% of cases for FPR of 5%

• **β -hCG**: higher in Africans & IVF pregnancy, lower in smokers; **PAPP-A**: higher in Africans, lower in IVF & smokers

Biochemistry and screening for trisomy 21

OSCAR: Fetal NT, maternal serum free β -hCG & PAPP-A at 11-13⁺⁶ wks

Singleton pregnancies $n=75,821$; Maternal age 31 (13-49) yrs



Normal

Trisomy 21

Trisomy 18/13

Other defects

Risk ≥ 1 in 300

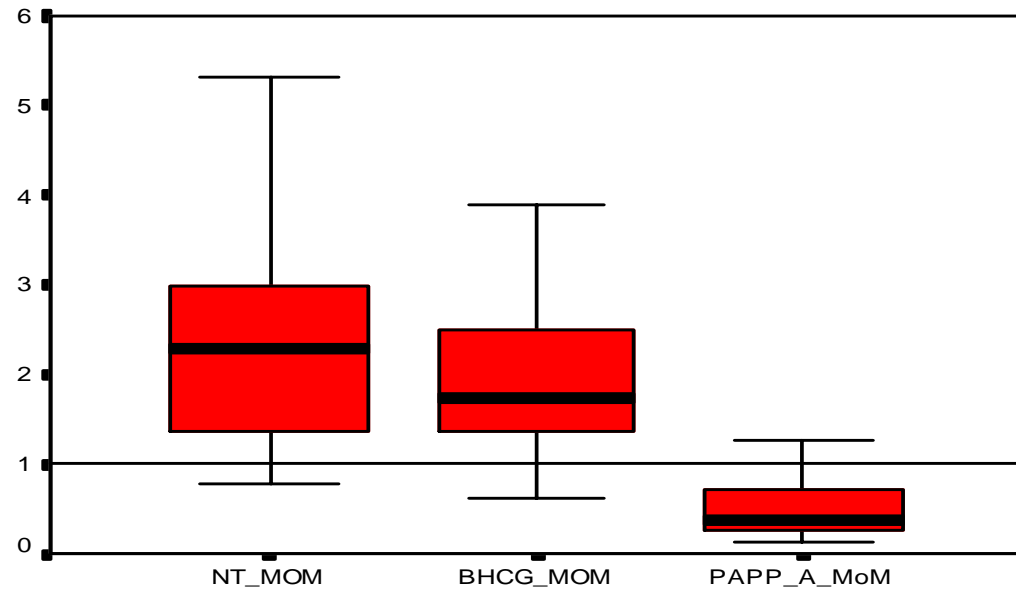
3,909/75,277 (5.2%)

301/325 (92.6%)

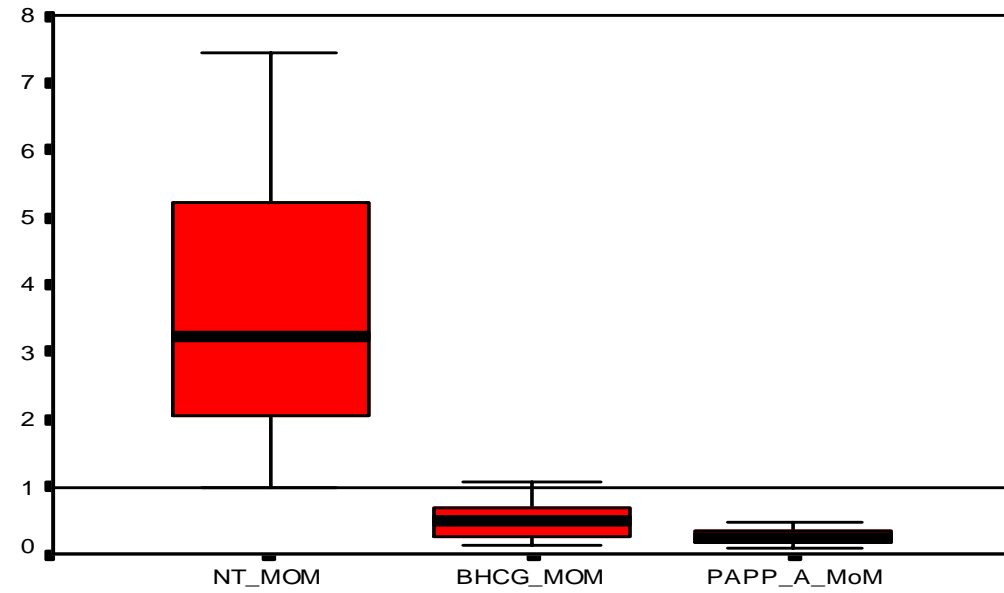
108/122 (88.5%)

83/97 (85.6%)

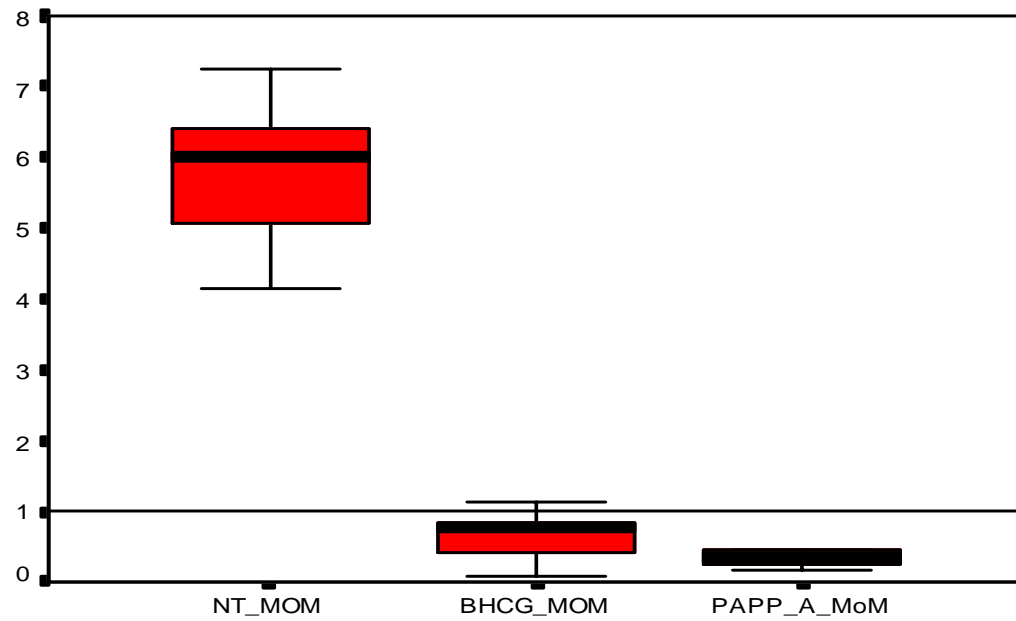
Down syndrome First Trimester



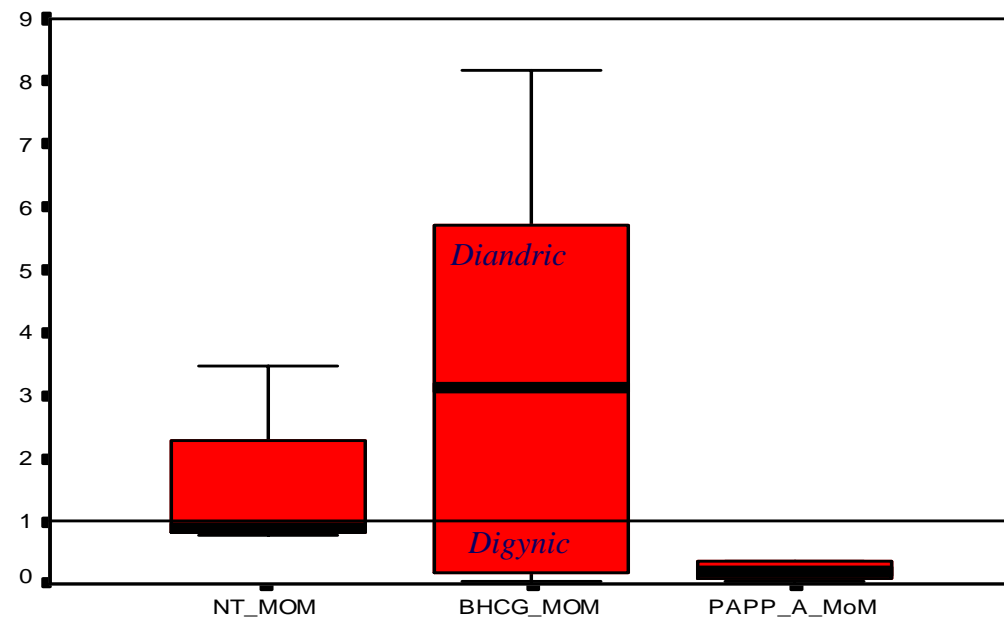
Trisomy 18 First Trimester

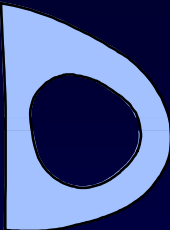


Turners syndrome First Trimester



Triploidy First Trimester





Biochemistry and Screening for Trisomy 21

Combined or Integrated Screening?

Combined

Integrated

11-13 weeks:

NT
PAPP-A
 β hCG

NT
PAPP-A

15-20 weeks:

hCG
AFP
UE3
Inhibin A

Biochemistry and Screening for Trisomy 21

Integrated Screening

DR
FPR 5%

Double test

71%

61%

Triple test

77%

66%

Quadruple test

83%

75%

Nuchal translucency

34%

77%

NT & β -hCG/PAPP-A

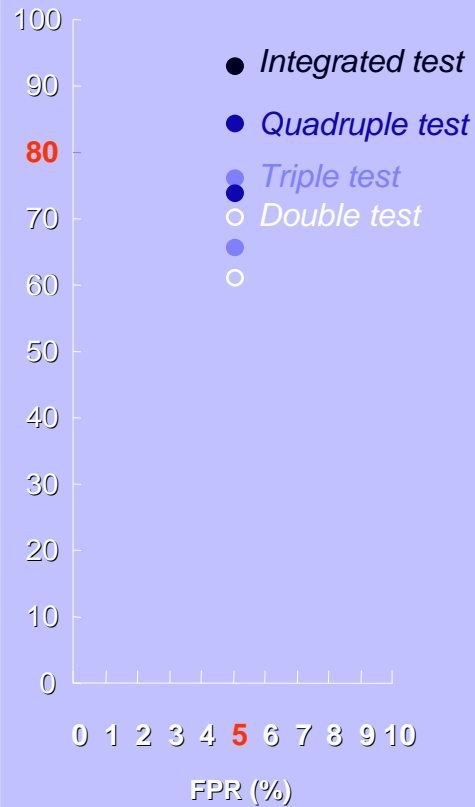
83%

90%

Integrated test

93%

DR (%)



FPR for DR 85%

Malone
Wald
2004

2.8%

Wald
1999

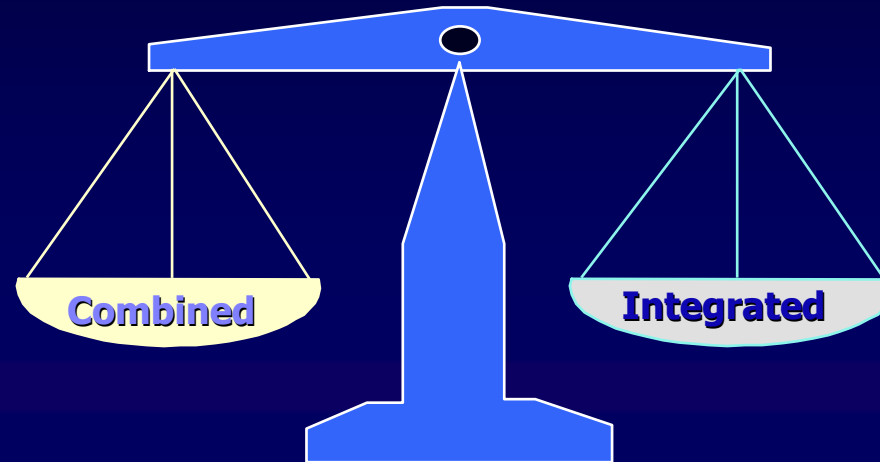
1.0%

Wald
2003

1.2%

Biochemistry and Screening for Trisomy 21

Combined or Integrated Screening?



High detection rate

Single visit

Earlier screening result

Early reassurance (for most)

Early Diagnosis / ToP

Multiphase anxiety

Increased default rate

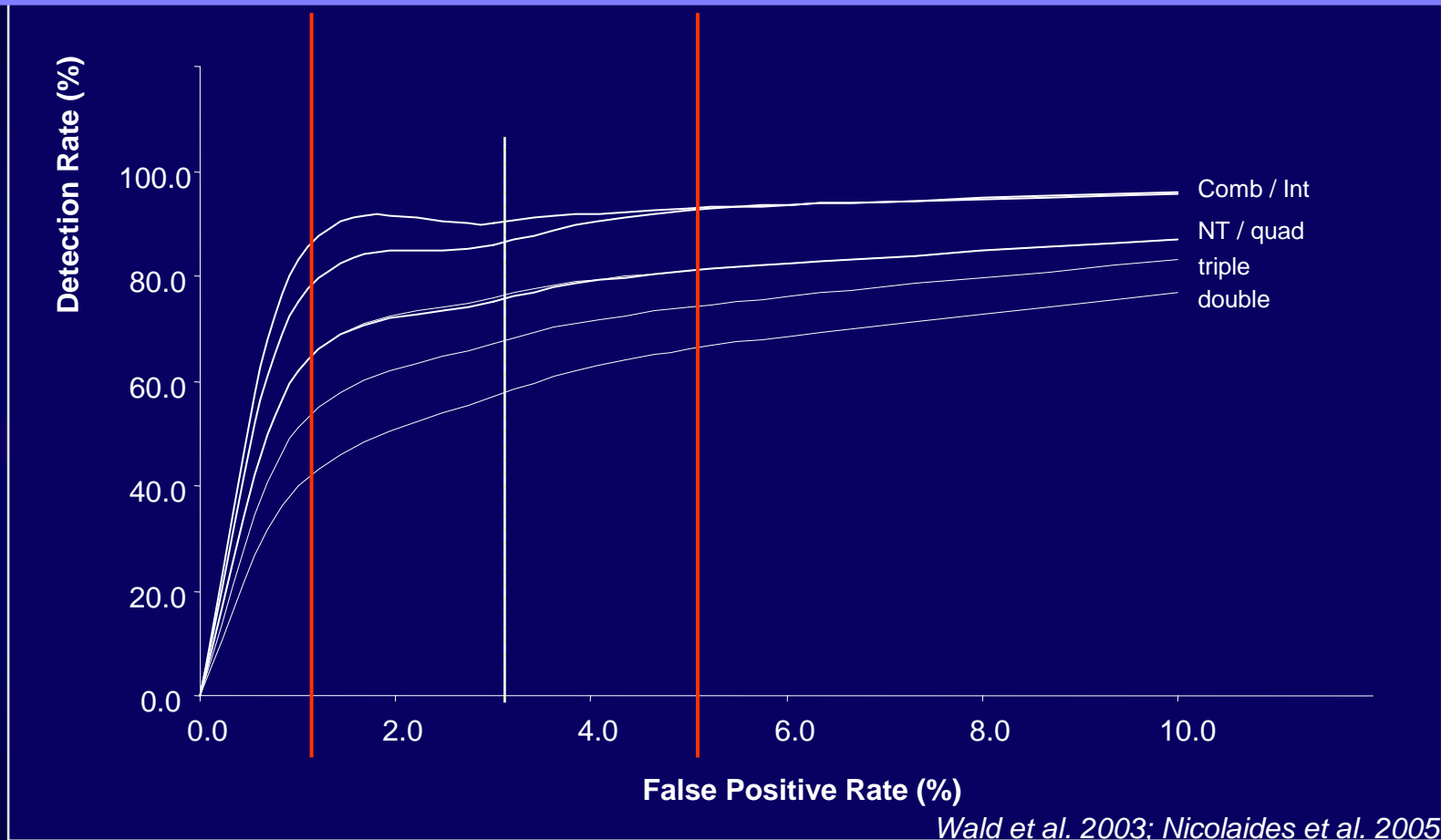
Delayed screening result

Delayed diagnosis

Late termination

Biochemistry and screening for trisomy 21

Receiver Operator Curves for Down Screening Tests



UKNSC ~ benchmark by April 2007 ~ 3% FPR 75% DR

http://www.nelh.nhs.uk/screening/dssp/model_bestpractice.pdf

http://www.phgu.org.uk/info_database/diseases/downs_syndrome/downs.html#published

<http://www.nchta.org>



Biochemistry and screening for trisomy 21

Women's attitudes towards screening

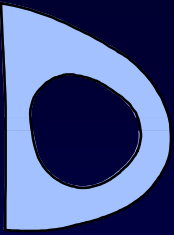
Monni: options of NT or triple test
information on CVS and Amnio
496 of 500 opted for NT

Lancet '98

Kornmann:

109 2nd trimester screen - 76% would prefer 1st trimester
49 declined 2nd trimester screening - 2 would consider earlier
79 had CVS - 32% would have had 1st trimester screening

Prenat Diagn '97



Biochemistry and screening for trisomy 21

Women's attitudes towards screening

Hypothesis: when informed about the rate of miscarriage of Downs pregnancies, most women would prefer to delay screening.

Results: the clear majority of women wanted the earliest possible test, even if this only identified pregnancies destined to miscarry

Rates of fetal death in Down syndrome pregnancies.

| Fetal loss rate study | Age Range Years | First Trimester Fetal Loss rate (cases) | Second Trimester Fetal Loss rate (cases) |
|--------------------------------------|--------------------|--|---|
| Hook <i>et al.</i> (1995) | 16-49 | 75% (8) | 50% (168) |
| Halliday <i>et al.</i> (1995) | 36-43 | 31% (39) | 18% (73) |
| Macintosh <i>et al.</i> (1995, 1996) | 35-48 | 48% (302) | 24% (610) |
| Bray and Wright (1998) | 35-50 | 31% (341) | 12% (1159) |
| Morris <i>et al.</i> (1999) | 16-49 | 31% (441) | 24% (2035) |
| Snijders <i>et al.</i> (1999) | 35-45 | 31% (221) | 21% (317) |

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Assume 10% will abort before 2nd TR
_____ (90% progress to 2TR).

OBS prevalence of T21 in 1st TR = 1:347

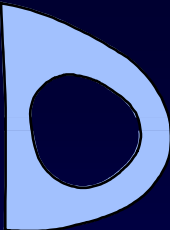
17,600 pregnancies x 1:347 = 50 cases

45 cases progress to 2nd TR

61.9% Detected in 2nd TR = **27** cases

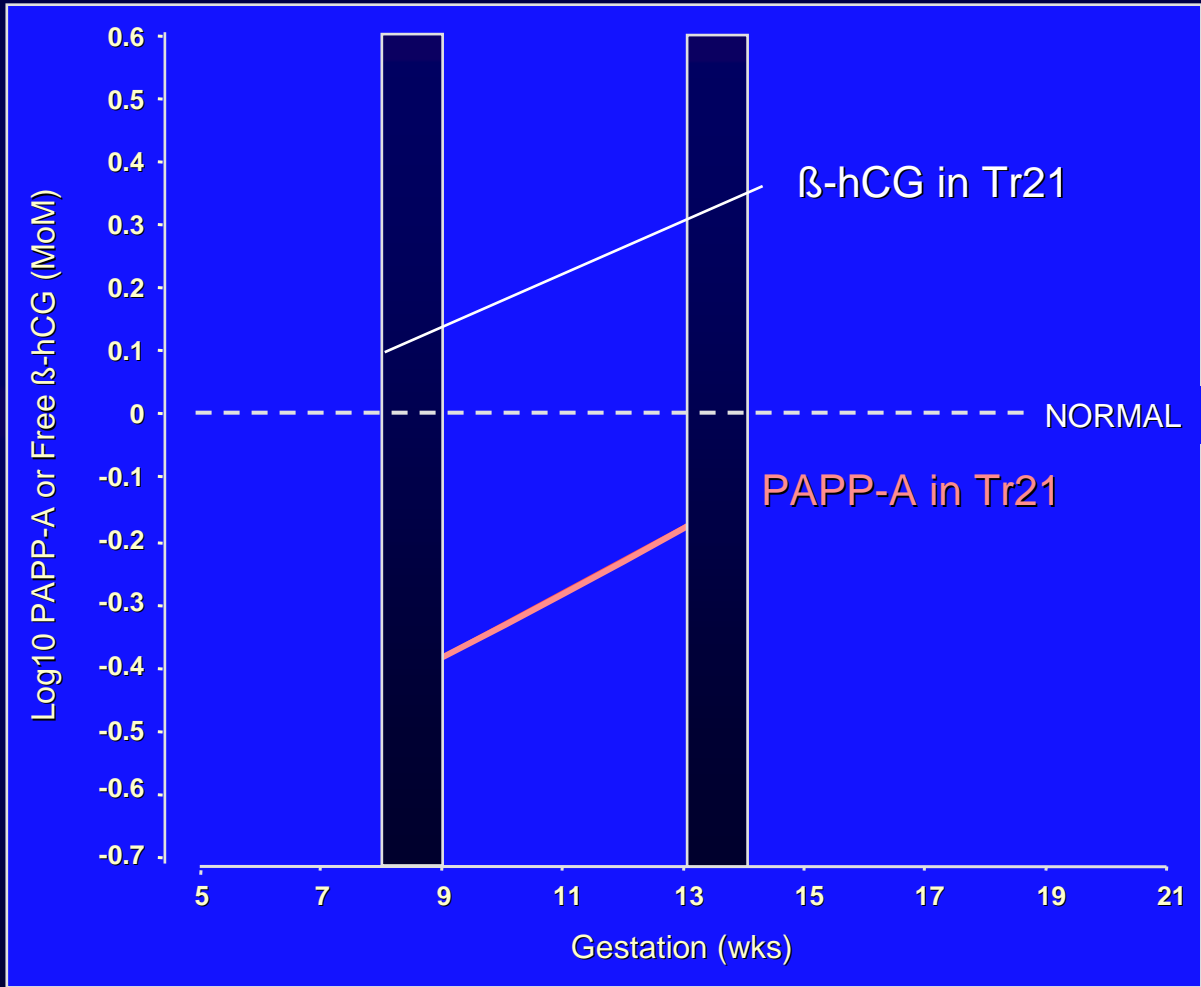
77.8% Detected in 1st TR = **35** cases

_____ or **8** more viable cases.



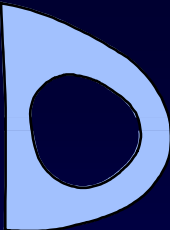
Analytical error in biochemical screening

Gestational Changes in BhCG and PAPP-A in T21



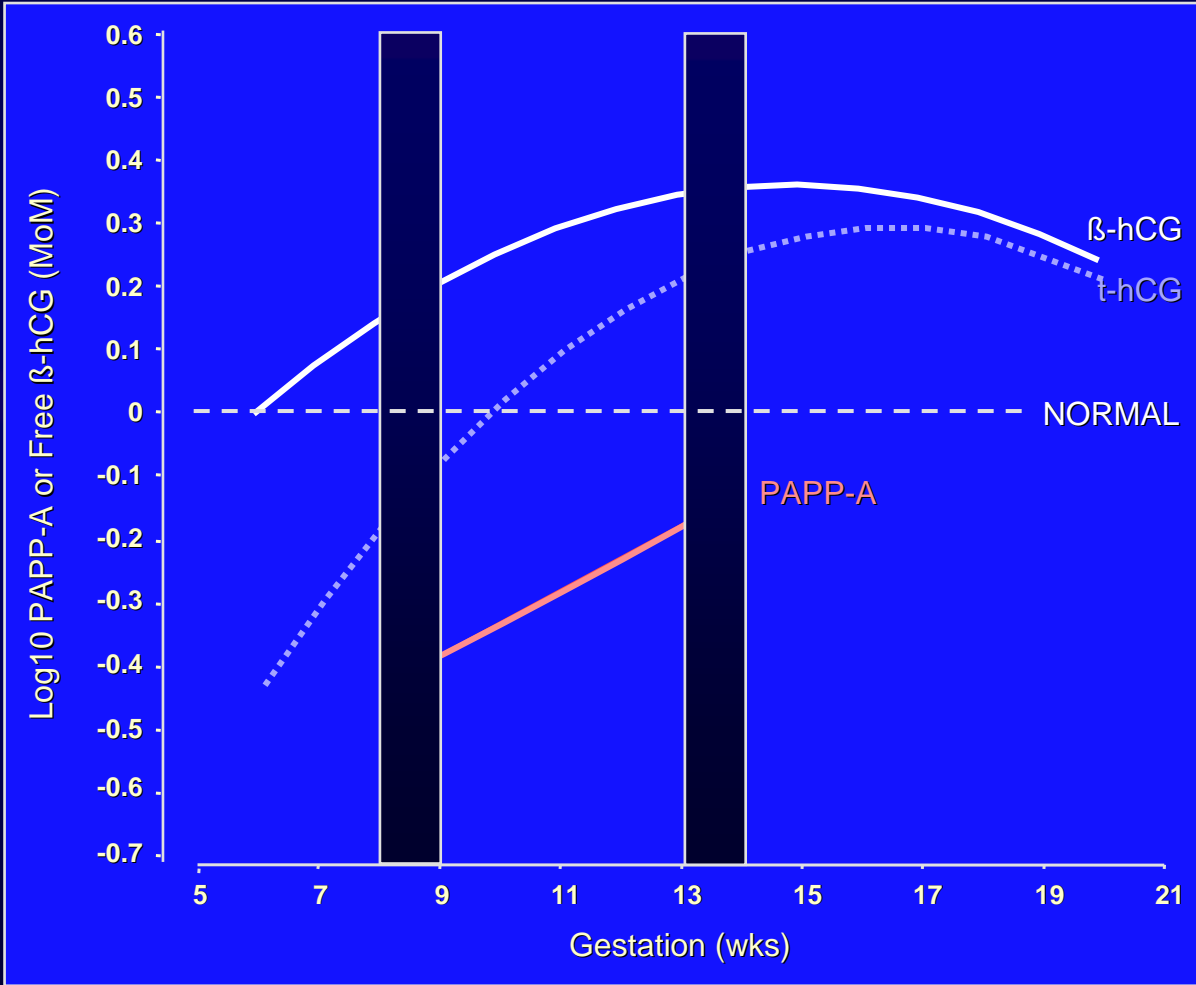
At 10 wks PAPP-A is better

At 14 wks β -hCG is better



Analytical error in biochemical screening

Screening performance with difference types hCG



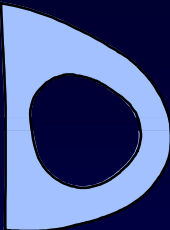
Spencer et al, Ann Clin Biochem 2002;39:567-76.

Screening by PAPP-A & hCG (free β vs total)

Detection Rates at 5% FPR (using correct variable separation model)

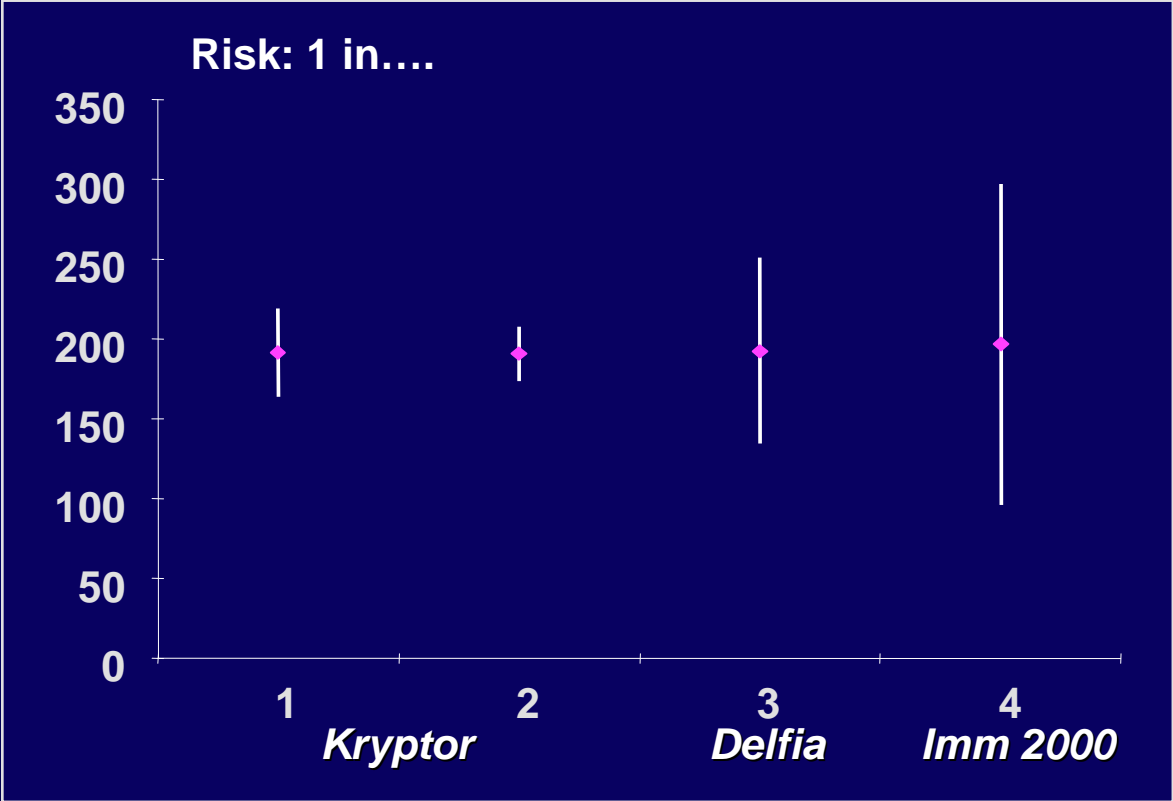
| GA (wks) | Free β | Total | |
|----------|--------------|-------|------|
| 8 | 72.5 | 67.9 | 4.6 |
| 9 | 70.6 | 62.1 | 8.5 |
| 10 | 68.8 | 58.4 | 10.4 |
| 11 | 66.9 | 56.5 | 10.4 |
| 12 | 64.9 | 55.8 | 9.1 |
| 13 | 62.6 | 55.7 | 6.9 |
| 14 | 60.1 | 55.6 | 4.5 |
| Overall | 65.1 | 56.3 | 8.8 |

Spencer et al, Ann Clin Biochem 2003 40;219-31.



Analytical error in biochemical screening

Impact of analytical error in risk assessment

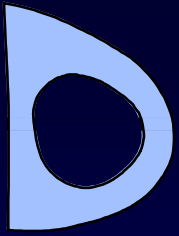


Age 24y
CRL 55mm NT 2.2mm
fB-hCG 2.50MoM
PAPP-A 0.55MoM

| | Marker CV | LR CV |
|---|-----------|-------|
| 1 | 2.5% | 7% |
| 2 | 1.5% | 4% |
| 3 | 4-5% | 15% |
| 4 | 6-7% | 25% |

Spencer 2003 DS News

FMF risk calculation software has specific medians and distributions for Kryptor and Delfia. These systems meet the analytical imprecision criteria.



- *Risk Calculation*
- *MoM values*
- *Maternal Age*
- *Gestational Age*
- *Recurrence Risk*
- *Singleton vs Twins*
- *Maternal Weight*
- *Ethnic Origin*
- *Smoking*
- *IVF*
- *Analytical Imprecision*
- *NT vs Biochemistry vs Combined vs Integrated*

