

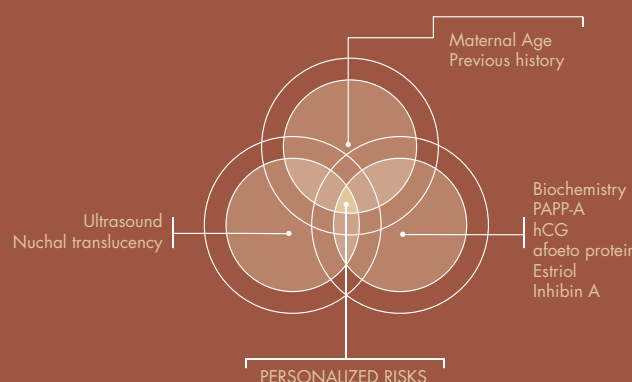
## Prenatal DIAGNOSIS

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Chromosomal abnormalities constitute one of the most important causes of perinatal mortality and neonatal morbidity. With an incidence of approximately 1/700, trisomy 21 (Down syndrome) is by far the most common chromosomal anomaly. These children have an average IQ of 40 and a very high risk of dementia (40%).

Approximately 40% will have a major cardiac malformation at birth but improvements in surgical techniques have increased their life expectancy to 50 years. The psychosocial and financial costs to care for these children are therefore enormous.

The advent of early and reliable prenatal screening tests will help to decrease the incidence of children born with chromosomal anomalies. This is a review of the currently available methods of prenatal screening.



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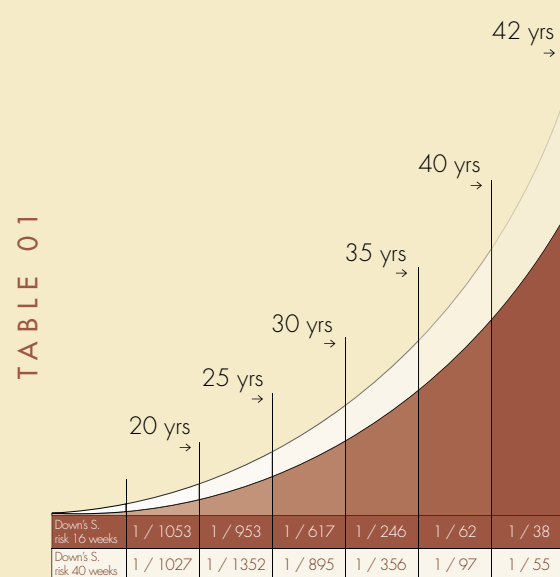
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## Individualized risk SEQUENTIAL SCREENING

Incidence of Down syndrome, Maternal/gestational age



Snijders, 1999

Prenatal screening tests help identify individuals at risk of having a fetus with a trisomy. In order to determine this individual risk we have to assess the base risk of the mother which is dependant on her age and multiply it by a series of risks ratios which will be determined by the prenatal test performed.

### A-BASIC RISK

The base risk depends on the maternal age (Table 01) and the presence of a previous history of trisomy. The risk of trisomy increases with maternal age and due to the high intra-uterine mortality rate, decreases with gestational age. Approximately 90% of trisomies are the result of new non-dysjunction events. A previous history of trisomy increases the risk related to maternal age by 0.75%. For example a 25 year old woman at 12 weeks of gestation will see her risk of trisomy go from 0.106% (1/946) to 0.856% (1/117) with a previous history of trisomy.

### B- RISK RATIOS

The presence of trisomy 21 will be associated with a number of ultrasound signs which can be observed early (nuchal translucency) or late (nuchal fold). The fetoplacental unit of the trisomic fetus will also secrete different amounts of certain biochemical markers (ex: hCG). The risk ratios (RR) for trisomy will be the result of the ratio of the percentage of trisomic fetuses with a positive marker/percentage of normal fetuses with a positive marker. The base risk of the mother is then multiplied by each risk ratio in order to obtain the individualized risk.

RR. = % Trisomic fetusus with a + marker  
% normal fetusus with a + marker

### BASE RISK X RISK RATIOS

#### BASE RISK

X RR. (NT ± nasal bone)

X RR. (1st trimester biochemical markers)

X RR. (2nd trimester biochemical markers)

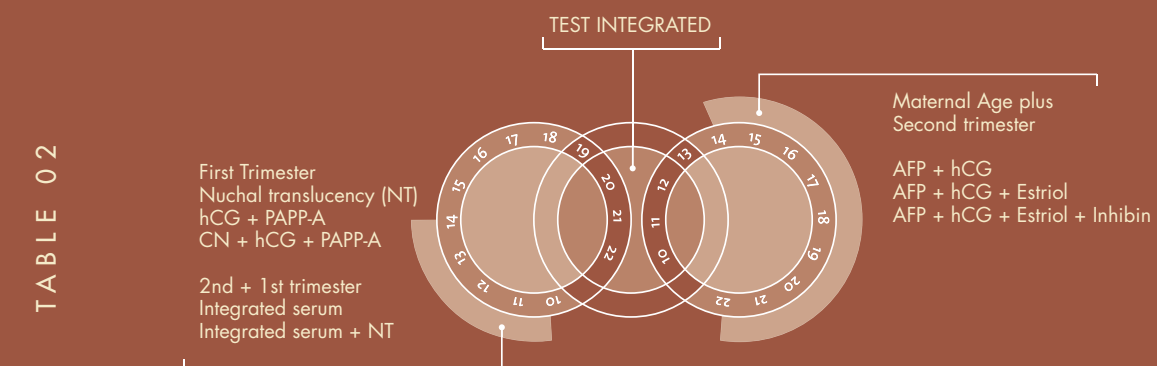
X RR. (2nd trimester ultrasound markers)

## Performance of the prenatal diagnosis test AND CUT-OFF LEVEL FOR POSITIVE SCREENING

When the individualized risk of a trisomy reaches a certain cut-off level, the screening is considered positive and a diagnostic test (amniocentesis/chorionic villus sampling) is suggested to the parents. The best prenatal tests will have the greater detection rate (sensitivity) as well as the greater the specificity (positive predictive value).

## Second trimester SCREENING (15-21 WEEKS) FOR TRISOMY 21

Starting at 15 weeks a number of other biochemical markers can be used to screen for Down syndrome. These include inhibin- A (1.7 MoM), estriol (.75 MoM) and Alpha-fetoprotein (.75 MoM). hCG can be used either in the first or second trimester. The integration of first trimester screening NT plus second trimester biochemical markers allows for a decreased false positive rate as seen in tables 02 and 03.



Benn, P. Lancet, 2003

Test	Nbr false + for 85% detection	Chance of trisomy if test +
Nuchal translucency	20	1/104
Second trimester markers	6.2	1/32
Combined	6.1	1/32
Integrated serum	2.7	1/14
Integrated	1.2	1/6

Wald N. +ass. Étude S.U.R.U.S.S. - Health technol. Assess., 2003

During the 18-20 week ultrasound, a number of soft markers have been associated with the risk of trisomy 21 which can modulate this final risk. For example, as shown in table 04, a woman with a risk evaluated at 1/250 with the integrated test will have her risk reduced to 1/833 with a negative 18-20 week scan.

	(RISK RATIOS)		
	Positive	Negative	If isolated
Pli nuchal	53	0.67	9.8
Short humerus	22	0.68	4.1
Short femur	7.9	0.62	1.6
Foci	6.4	0.75	1.1
Hyperechogenic bowel	21	0.87	3
Major malformation	32	0.79	5.2

Normal ultrasound RR : 0.3

Nyberg, 2001, Bromley, 2002

### DETECTION OF OTHER ANOMALIES

Alpha-fetoprotein determination of the second trimester will detect approximately 80% of neural tube defects. 90% of trisomies 18 and 13 can be detected by biochemical markers of the first or second trimester. If the NT is > 95 percentile for gestational age, there is a significant risk of cardiac anomaly and therefore a fetal echocardiogram should be done at 22 weeks of gestation.

### CONCLUSION

In view of these results, it appears that maternal age and NT should not be the only screening test available for detection of trisomies. The integrated test, including the first and second trimester markers, is the test which allows for the highest detection rate with the lowest rate of false positives. Therefore this test is associated with

the least number of unnecessary amniocenteses and loss of normal fetuses. However in order to achieve this level of detection, the result of the first trimester testing (PAPP-A +NT) cannot be communicated to the patient and the result can be given only after the addition of the second trimester markers after 15 weeks of gestation. For the patients who desire an early result the combined test (NT+ PAPP-A +hCG) in the first trimester offers the best alternative. When no NT determination is available, the integrated serum test constitutes the best alternative.

Finally, the 18-20 week ultrasound can offer a last modulation of the risk for those couples unsure about undergoing a diagnostic procedure (amniocentesis) following the risk obtained after initial testing.



### ULTRASOUND MARKERS

#### • Nuchal translucency (NT)

Nuchal translucency represents an accumulation of fluid in the soft tissue behind the neck during the first trimester. In trisomic fetuses the NT is increased 2 folds. If used alone this marker has a 70% detection rate for a false positive of 5%. The combination of first trimester biochemical markers and the NT measurement (combined test) gives a detection rate of 85% with a false positive rate of 5%.

#### • Nasal bone measurement

On ultrasound during the first trimester the nasal bone is absent in 70% of trisomy 21 and only 1% of normal fetuses. The incorporation of this marker could lead to a detection rate of 90%. However there appears to be important racial differences and more population studies are needed in order to use this marker on a routine basis.