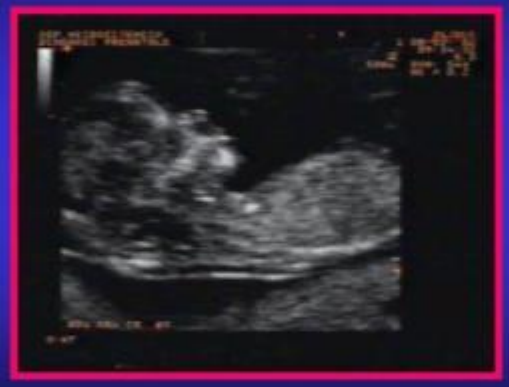
Fetal nuchal translucency: the Sardinia experience

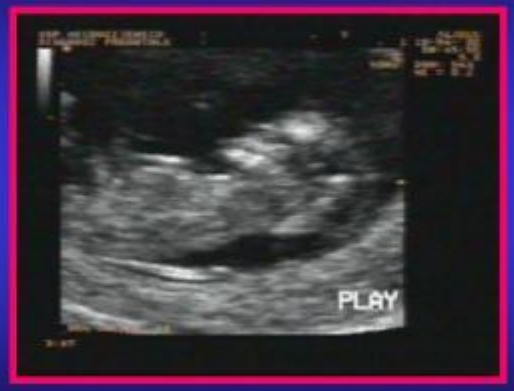
Giovanni Monni
Vietnam, March 2011

NUCHAL TRANSLUCENCY (11- 13.6 wks)



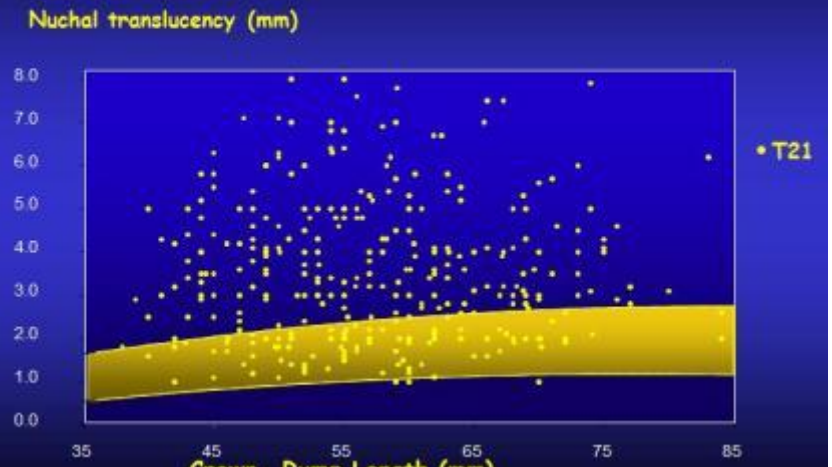
Transonic space behind the fetal neck

ENLARGED NUCHAL TRANSLUCENCY And TRISOMY 21



Szabo, Lancet 1991
Nicolaides, Br Med J 1992

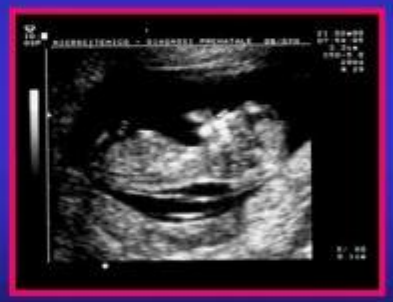
NUCHAL TRANSLUCENCY and TRISOMY 21



FETAL MEDICINE FOUNDATION

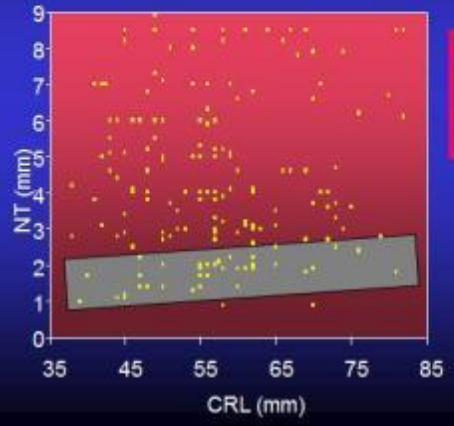
NUCHAL TRANSLUCENCY ENLARGED

- Chromosomopathies
- Trisomy 21
- Cardiopathies
- Structural anomalies
- Genetic syndromes



NUCHAL TRANSLUCENCY SCREENING

MULTICENTRE PROJECT (UK)
27 CENTRES; Trisomy 21 - 326 cases



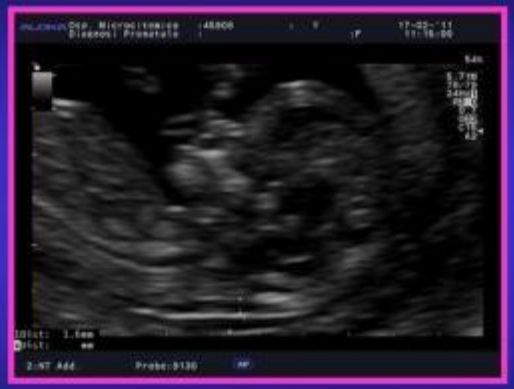
Cut-off	FP	DR
NT > 95th	5%	72%
1 in 300	8%	82%

Snijders, 1998

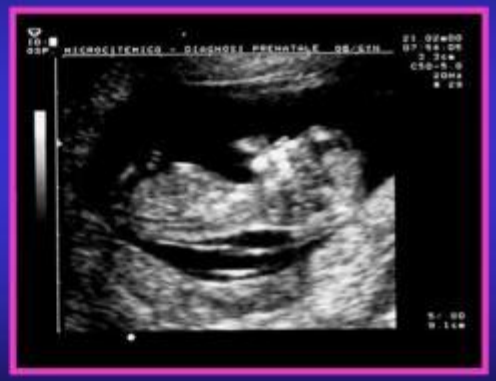
NUCHAL TRANSLUCENCY IN GENERAL POPULATION

Study	Cut-off	n. Fetuses	Tris 21 DR
Bewley	≥ 3mm	1368	33%
Kornman	≥ 3mm	923	29%
Taipale	≥ 3mm	10010	54%
Hafner	≥ 2,5mm 4233		43%
Orlandi	Delta value	744	57%
Pajkrt	≥ 3mm	1473	67%
Theodoropoulos	>95°	3550	91%
Snijders	>95°	96127	72%
Total	-	118428	70%

NT: THE TECHNIQUE



NUCHAL TRANSLUCENCY IN SARDINIA AT THE OSPEDALE MICROCITEMICO - CAGLIARI



RESULTS OF MEASUREMENT OF NT BEFORE AND AFTER TRAINING

	Before training 1995	After training 1996 -97
Number of operators	4	4
Number of patients	1176	1037
CRL (mm)	17-85	38-84
Techniques	Not Standard	Snijders
Cut off	≥3mm	(1) ≥1 in 300 (2) ≥1 in 100
Detection rate of chrom.abnorm.	30%	(1) 84% (85%*) (2) 76% (77%*)

Monni, Lancet 1997

SINCE 1996.....

Editorial

Second-trimester sonographic soft markers: what can we learn from the experience of first-trimester nuchal translucency screening?

T. K. LAU* and M. I. EVANS†

A sonographic marker as a screening tool requires the development of a precise protocol, proper operator training, certification, auditing of performance and re-certification

INDICATIONS FOR INVASIVE PRENATAL DIAGNOSIS FOR ANEUPLOIDIES IN ITALY

- Maternal age ≥35
- Previous affected fetus
- Abnormal karyotype in the parents
- Odds to be affected by Down syndrome greater than or equal to 1/250 calculated by biochemistry or ultrasound paraments

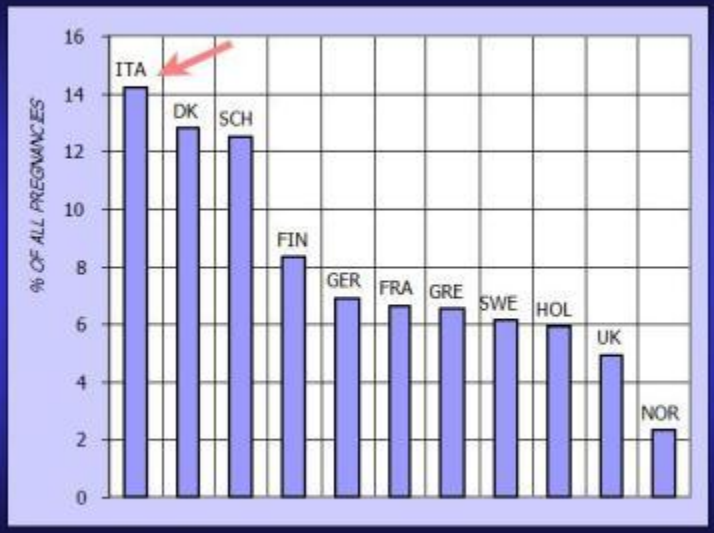
Decree of Health Minister 1998

MATERNAL AGE AT DELIVERY IN THE LAST 5 YEARS IN ITALY

	Up to 24 Years	25- 29 Years	30-34 Years	35-39 Years	40 and over	Total
North	7,8%	26%	44,1%	19,1%	3%	100%
North- East	8,1%	29,1	40,9%	18,7%	3,2%	100%
Center	6,7%	26,1	40,8%	20,5%	6%	100%
South	14,7%	33,9	34,2%	14,6%	2,6%	100%
Sicily and Sardinia	18,2%	33,1	30,7%	14,7%	3,3%	100%
Total	10,9%	29,7	38,5%	17,4%	3,5%	100%

Italian Institute of Statistics, 2002

INVASIVE TESTING RATE in EU

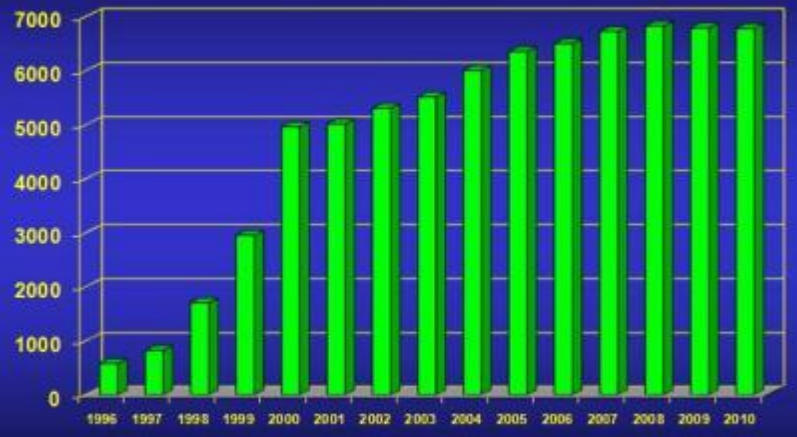


Tabor, Brahms Symposium ISUOG Paris 2003

SCREENING FOR DOWN SYNDROME BY NUCHAL TRANSLUCENCY

(66,000 cases)

Ospedale Microcitemico, Cagliari (May 1996- December 2009)



NUCHAL TRANSLUCENCY SCREENING OSPEDALE MICROCITEMICO (12,495 SINGLETON FETUSES)

Fetal Karyotype	Estimated risk		
	>1 in 300	*>1 in 200*	*>1 in 100*
Normal (n=10,001)	887 (9%)	607 (6%)	318 (3%)
Trisomy 21 (n=64)	58 (90%)	53 (83%)	49 (77%)

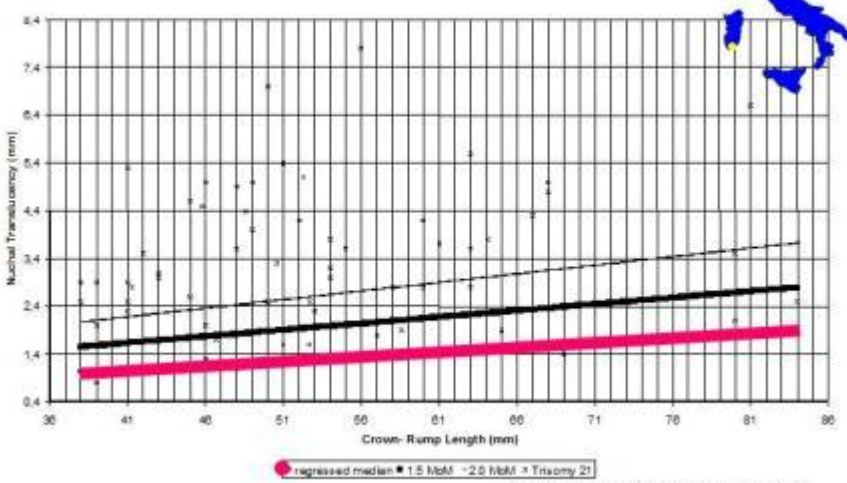
Zoppi, Ultrasound Obstet Gynecol 2001

NUCHAL TRANSLUCENCY AND TRISOMY 21 SCREENING (22 UK CENTRES)

Cut-off	*False positivie*	*Sensitivity*
NT > 95th	5%	72%
1 in 300	8%	82%

Snijders, Lancet 1998

FETAL NUCHAL TRANSLUCENCY SCREENING IN 12,495 PREGNANCIES IN CAGLIARI



Zoppi, Ultraound Obstet Gynecol, 2001

CHROMOSOMAL ABNORMALITIES IN β-THALASSAEMIA PATIENTS (maternal age < 35 yrs.)

Karyotype	*Maternal Age*	*Test*
Trisomy 21	34	pos
Turner	30	pos
Turner	31	pos

Monni, Prenat. Diagn. 1999

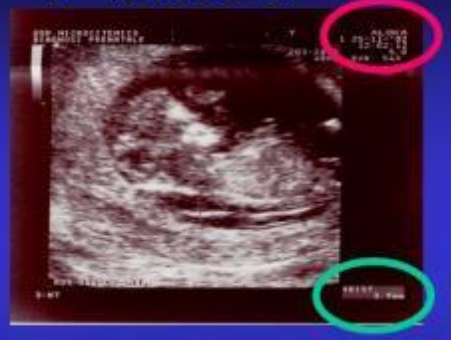
PATIENT'S ACCEPTABILITY BETWEEN 1st TRIM. NT SCREENING AND 2nd TRIM. BIOCHEMICAL SCREENING

Patients (No)	500
1st trimester NT choice	496
2nd trimester Triple test choice	-
Not answer	4

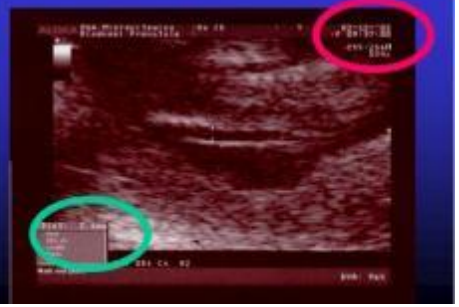
Monni, Lancet 1998

CHANGES OF ENLARGED NT AT 11- 14 WEEKS

1st measure



2nd measure in the same fetus



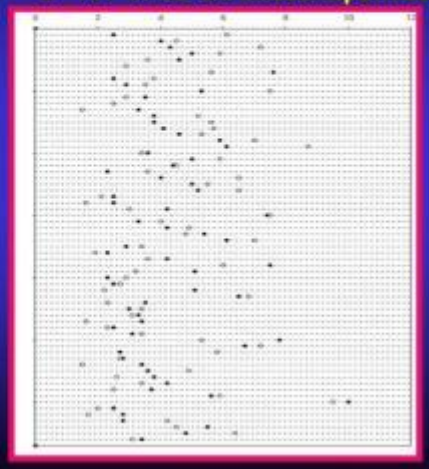
2 MEASUREMENTS IN THE SAME FETUS AT 11- 14 WITH ENLARGED NT

2° NT >/=

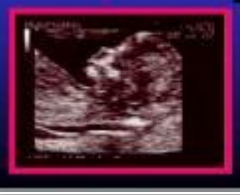
56% Chromosomopathies

25% Normal fetuses

1° NT 2° NT in 66 chromosomopathies



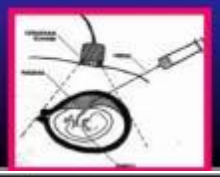
Zoppi Br J Obstet Gynaecol 2003



NUCHAL TRANSLUCENCY TEST IN WOMEN AGED 35 AND OLDER

- Could Decrease the Demand for Invasive Prenatal Diagnosis
- Could Lead to an Earlier Invasive Diagnosis of Chromosomopathies by CVS

Zoppi, Obstet Gynecol 2001



NT AND THE ACCEPTANCE OF INVASIVE PRENATAL DIAGNOSIS IN WOMEN AGED 35 AND OLDER

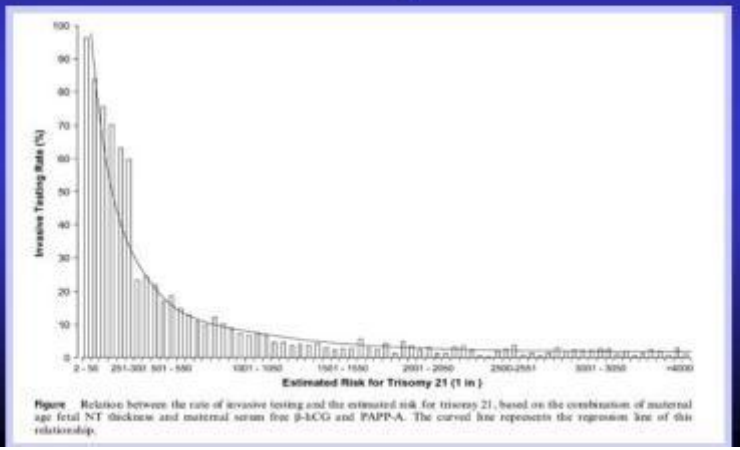
Group	1995	1999*
Patients	982	1386
Decision against prenatal diagnosis	221**(22%)	421**(30%)
Prenatal diagnoses	690	916
Median maternal age	38	37
Transabdominal- CVS	214 (31%)	266 (29%)
Amniocentesis	476 (69%)	650 (71%)
Chromosomal abnormalities	19	20
Chrom. abnorm. diagnosed by TA-CVS	6**(31.5%)	13**(65%)
Chrom. abnorm. diagnosed by AC	13 (68.5%)	7 (35%)

* After NT test

** Chi- squared test: p< 0.05

Zoppi, Obstet Gynecol 2001

Evidence-based obstetric ethics and informed decision-making by pregnant women about invasive diagnosis after first-trimester assessment of risk for trisomy 21



NT screening TEST

- Enhances patients autonomy and allow them to make appropriate decision, providing a more informed and rationale basis for deciding whether to resort to more definitive testing

Treadwell, Ultrasound Obstet Gynecol 2006

NUCHAL TRANSLUCENCY

- It should be performed only if requested by the woman
- It should be performed only by trained operators, with periodical audit control
- The accuracy of the nuchal translucency should be clearly explained to the woman
- The result of the test should indicate the estimated risk for trisomy 21, by considering ultrasound, maternal age and maternal history

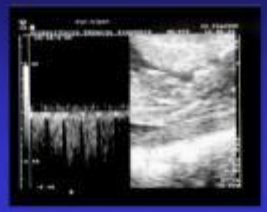
1ST TRIMESTER ULTRASOUND GUIDELINES
ITALIAN SOCIETY OF ULTRASOUND IN OB/GYN (SIEOG) 2002

BETTER ACCURACY OF NT TEST

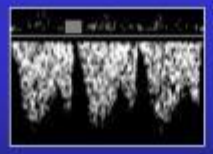
- Doppler velocimetry in the ductus venosus
- Nasal bone evaluation

ATRIAL CONTRACTION VELOCITY (ACV) IN THE DUCTUS VENOSUS

ACV present



ACV absent



ACV reverse

FIRST TRIMESTER DUCTUS VENOSUS VELOCIMETRY IN RELATION TO NUCHAL TRANSLUCENCY THICKNESS

NT Thickness	Fetuses	DV measured	ACV+	ACV-
≥95th centile	156	152	93 (61%)	59 (39%)
<95th centile	174	173	171 (98%)	2 (1%)
Total	330	325	264 (81%)	61 (19%)

DV= Ductus Venosus
ACV+ = Presence of forward velocity during atrial contraction
ACV- = Absence or inverted forward velocity during atrial contraction

Zoppi, Fetal Diagn Ther 2002

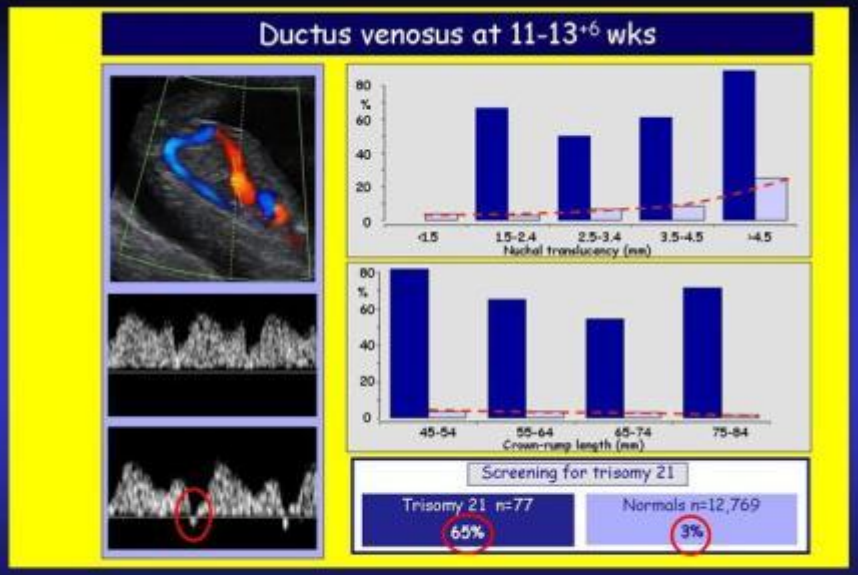
FIRST TRIMESTER DUCTUS VENOSUS VELOCIMETRY IN RELATION TO NUCHAL TRANSLUCENCY THICKNESS AND FETAL KARYOTYPE

Chromosomal abnormality	No.	ACV+	ACV-
Trisomy 21	20	6	14
Trisomy 18	8	1	6
Trisomy 13	1	-	1
45, X0	3	2	1
Triploidy	1	1	-
Other	1		1
Total	34	10 (30%)	23 (70%*)

All these chromosomal abnormalities had a NT ≥ 95th centile
In a case of tris. 18 with estrophia cordis, it was not possible to carry out the measurement of DV
*10% in normal karyotype fetuses

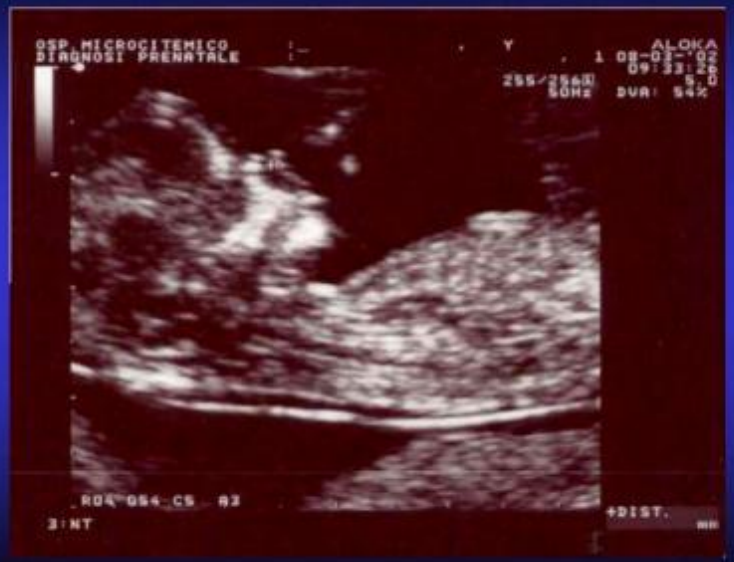
DV= Ductus Venosus
ACV+ = Presence of forward velocity during atrial contraction
ACV- = Absence or inverted forward velocity during atrial contraction

Zoppi, Fetal Diagn Ther 2002

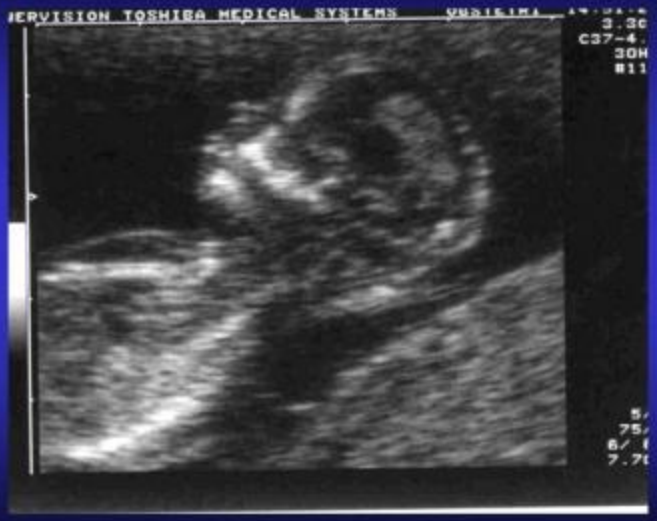


Nicolaides et al. 2008

NASAL BONE AT FIRST TRIMESTER BY ULTRASOUND



ABSENT NASAL BONE AND TRISOMY 21



NASAL BONE AT 11- 14 WEEKS GESTATION

	Normal Karyotype	TRISOMY 21
Present Nasal Bone	600 (99.5%)	16 (29.6%)
Absent Nasal Bone	3 (0.5%)	43 (72.8%)
Total	603	59

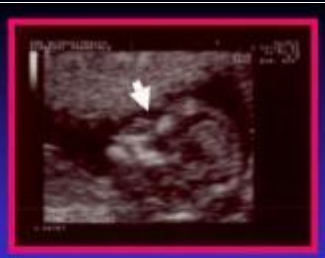
Absence of nasal bone was independent of NT thickness

Absent Nasal Bone Likelihood Ratio for Trisomy 21 was 146 and for present Nasal Bone 0.27

Cicero and Nicolaides, Lancet 2001

ABSENCE OF NASAL BONE AND DETECTION OF TRISOMY 21

Cagliari, September – November 2001



	Fetuses	TRISOMY 21	Other
Present Nasal Bone	875	1	1*
Absent Nasal Bone	5**	2***	-
Total Fetuses	880	3	1

* Trisomy 18
** Screen Positive Rate 0.5%
*** Sensitivity 66.6%

Monni, Lancet 2002

NASAL BONE AND TRISOMY 21 AT 1ST TRIMESTER IN 5,425 UNSELECTED PREGNANCIES

(5,532 fetuses)

September 2001 – September 2002

	Fetuses	TRISOMY 21
Present Nasal Bone	5,491 (99.4%)	8 (30%)
Absent Nasal Bone	34 (0.6%)	19** (70%)
Total Fetuses	5,525*	27

* 5,525 fetuses: visualization of the fetal profile (99,8%)
** 2 fetuses of Trisomy 21 with absent NB and normal NT

Fetal karyotype and pregnancy outcome available in 3,503 pregnancies
Median maternal age 32 years

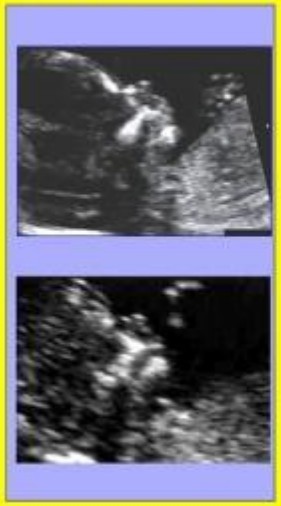
Zoppi, Prenat Diagn 2003

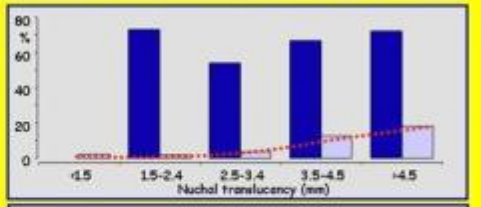
FETAL NASAL BONE AND OTHER CHROMOSOMOPATHIES AT 11- 14 WEEKS IN AN UNSELECTED POPULATION IN CAGLIARI

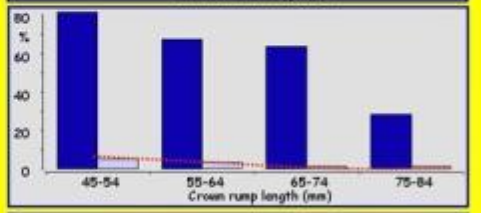
September 2001 – September 2002

N.	Maternal age	CRL	NT	Karyotype	Nasal bone
1	35	54.5	2.5	47, XXX	Present
2	31	52	1.7	47,xy,ish+der(13;18)(q14;q22)mat(wcp13+;wcp18+)	Present
3	42	53	2.5	47, XY+13	Present
4	30	45	4	47,XY+13	Present
5	36	50	11	45, X0	Present
6	37	52	6.8	[illegible]	Absent
7	32	61	10	[illegible]	Absent
8	33	46	4.1	[illegible]	Absent
9	41	63.5	6	[illegible]	Absent
10	38	51	8.1	[illegible]	Absent
11	43	58	6	[illegible]	Absent
12	39	45	7	47, XX +18	Present
13	30	54	3.5	[illegible]	Absent

ABSENT OR HYPOPLASTIC NASAL BONE







Screening for trisomy 21

Trisomy 21 n=621	Normals n=48,273
65%	1-3%

Nicolaides et al. 2008

ENALRGED NT AND TRICUSPIDAL REGURGIATIOM IN CASE WITH ABNORMAL KARYOTYPE

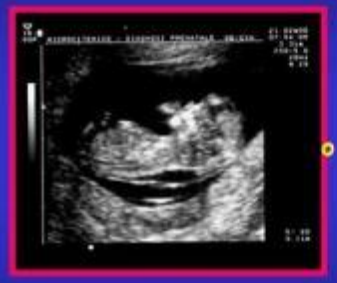
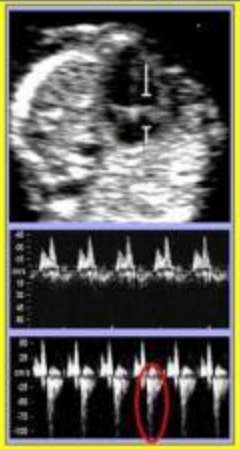


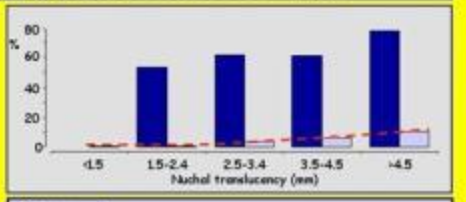
Figure 1 Holosystolic regurgitation is seen on pulsed Doppler examination of the tricuspid valve in a fetus at 12 weeks' gestation. The velocity of over 1 m/s allows clear distinction from arterial flow, which is usually less than 50 cm/s at this gestational age.

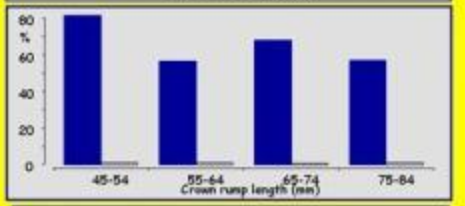
- Tricuspidal regurgitation (TR) has been found in about 30% of cases with enlarged nuchal translucency (NT)
- When NT is enlarged and TR is present, there is a chromosomal abnormality in 80% of cases

Huggon 2003

Tricuspid regurgitation at 11-13+6 wks







Trisomy 21 n=77	Normals n=12,796
65%	1%

Nicolaides et al. 2008

LEFT ATRIOVENTRICULAR VALVE SPECTRAL DOPPLER IN 1ST TRIMESTER FETUSES WITH ENLARGED NT

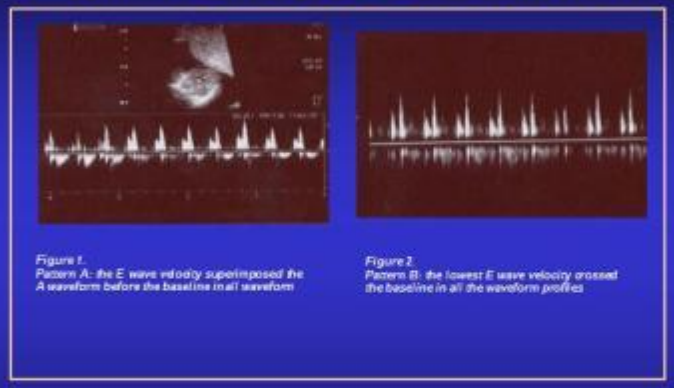


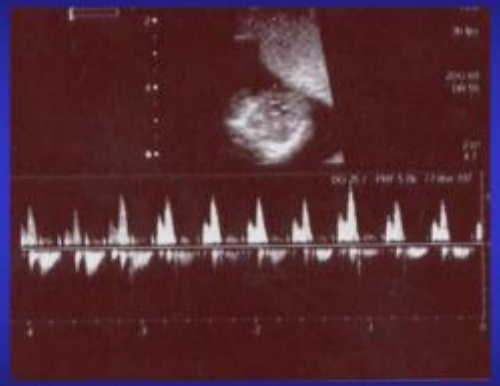
Figure 1.
Pattern A: the E wave velocity superimposed the A waveform before the baseline in all waveform

Figure 2
Pattern B: the lowest E wave velocity crossed the baseline in all the waveform profiles

Evaluation of left atrioventricular valve Doppler in trisomy 21 fetuses with enlarged NT shows more frequently a specific pattern (type B), that may be suggestive of an altered myocardial function.

Zoppi, Ultrasound Obstet Gynecol 2006

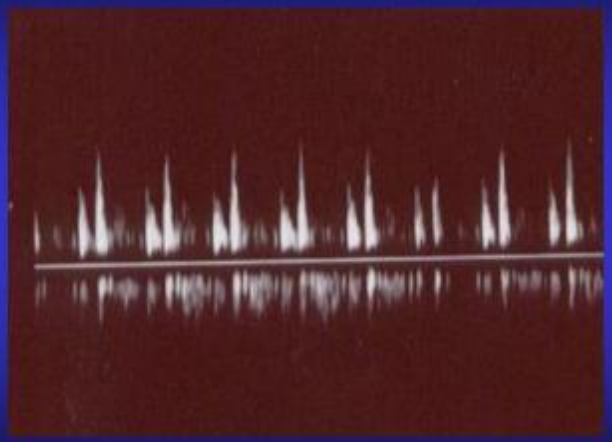
LEFT ATRIOVENTRICULAR VALVE SPECTRAL DOPPLER IN 1ST TRIMESTER FETUSES WITH ENLARGED NT



Pattern A: the E wave velocity superimposed the A waveform before the baseline in all waveform

Zoppi, Ultrasound Obstet Gynecol 2006

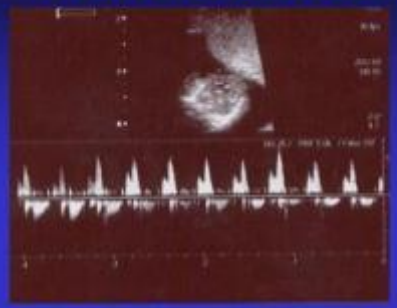
LEFT ATRIOVENTRICULAR VALVE SPECTRAL DOPPLER IN 1ST TRIMESTER FETUSES WITH ENLARGED NT



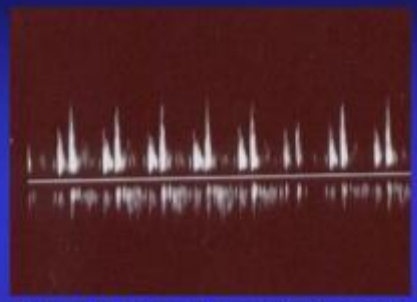
Pattern B: the lowest E wave velocity crossed the baseline in all the waveform profiles

Zoppi, Ultrasound Obstet Gynecol 2006

LEFT ATRIOVENTRICULAR VALVE SPECTRAL DOPPLER IN 1ST TRIMESTER FETUSES WITH ENLARGED NT



Pattern A: the E wave velocity superimposed the A waveform before the baseline in all waveform



Pattern B: the lowest E wave velocity crossed the baseline in all the waveform profiles

Left AV Doppler in trisomy 21 fetuses with enlarged NT shows more frequently (70% VS 6%) pattern type B

Zoppi, Ultrasound Obstet Gynecol 2006

FIRST TRIMESTER CONTINGENT SCREENING

>90% Sensitivity- 2% False positive rate

COMBINED TEST

Risk >1 in 100 (2% screen+)

Risk >1 in 100 < 1 in 1000) (16% screen+)

Risk <1 in 1000 (82% screen+)

ULTRASOUND EXAMINATION IN EXPERT CENTRES FOR NASAL BONE OR DUCTUS VENOSUS OR TRICUSPID REGURGITATION

Positive

Negative

CVS

No CVS no other screening

Nicolaides UOG 2005

Nuchal translucency measurement at different crown-rump lengths along the 10- to 14-week period for Down syndrome screening

Maria A. Zoppi, Rosa M. Ibba, Marcella Floris, Fabiola Manca, Carolina Axiana and Giovanni Monni*

Table 3—Sensitivity, specificity, likelihood ratio (LR) for Down syndrome (NT >/= 1.5 MoM cut-off)

Group	Sensitivity	95th CI	Specificity	95th CI	LR	95th CI
38–44 mm	86.7%	62.1–96.3	89.3%	87.6 to 90.7	8.1	6.3 to 10.3
45–54 mm	71.2%	60.0–80.3	95.0%	94.5 to 95.3	14.1	11.9 to 16.7
55–70 mm	80.6%	65.0–90.2	95.0%	94.5 to 95.5	16.3	13.4 to 19.7
71–84 mm	62.5%	30.6–86.3	99.4%	95.1 to 97.3	17.1	9.3 to 31.5
All	75.0%	67.0–81.6	94.6%	94.3 to 94.9	14	12.5 to 15.7

Table 4—Sensitivity, specificity, likelihood ratio (LR) for Down syndrome (NT >/= 2.0 MoM cut- off)

Group	Sensitivity	95th CI	Specificity	95th CI	LR	95th CI
38–44 mm	80%	54.8–92.9	94.0%	92.6 to 95.0	13.2	9.6 to 18.2
45–54 mm	63.0%	51.5–73.2	97.7%	97.4 to 97.9	27.1	21.9 to 33.5
55–70 mm	66.7%	50.33–79.8	98.7%	98.4 to 98.9	50.1	36.9 to 68.1
71–84 mm	50.0	21.5–78.5	99.4%	98.8 to 99.7	84.1	30.5 to 231.5
To All	65.2%	56.7–72.7	97.8%	97.6 to 98.0	30.0	25.7 to 35.1

A TEST MORE SENSIBLE…….

(NT MEASURED AT THE BEGINNING OF THE 11- 14 WEEKS PERIOD)

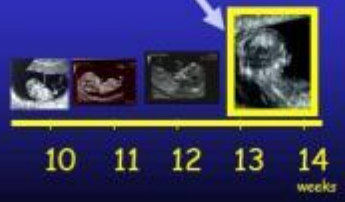
- 35 year- old (or more aged) woman with a traditional indication for invasive prenatal diagnosis for karyotype analysis, that would like to perform a more informed choice….

A MORE SPECIFIC TEST

(NT MEASURED AT THE END OF THE 11- 14 WEEKS PERIOD)

- Woman with infertility problems, precious pregnancy.

When the priority is to avoid any risk of complicance of an unnecessary invasive procedure performed on a probably healthy fetus……



TRANSABDOMINAL FETAL CARDIAC EXAMINATION IN CASES WITH ENLARGED NT FOR CHROMOSOMAL ABNORMALITY SCREENING

	All	Chromosomal abnormalities	Normal karyotype
Fetuses with NT enlarged	202	47 (23%)	155 (77%)
Median CRL	59.5 mm		
TA heart US "not normal"	40 (18%)	26 (55%)	15 (10%)

Zoppi et al, ISUOG Annual Congress 2006

ENLARGED NUCHAL TRANSLUCENCY IN THE SAME WOMAN IN DIFFERENT PREGNANCIES

	All fetuses	Normal karyotype
Fetuses	38,164	
Enlarged NT	1,749 (5%)	1,503 (4%)
NT enlarged in more than one pregnancy		23 (8.8%)

Zoppi et al, ISUOG Annual Congress 2006

CHROMOSOMAL ABNORMALITIES AND NT IN 115 MULTIPLE PREGNANCIES (252 FETUSES)

Chromosomal abnormalities	*Maternal age*	*Pregnancy*	*NT*
Trisomy 21	39	dichorionic	>95th
Trisomy 21	33	tetrachorionic	>95th
47, XXY	37	trichorionic	<95th

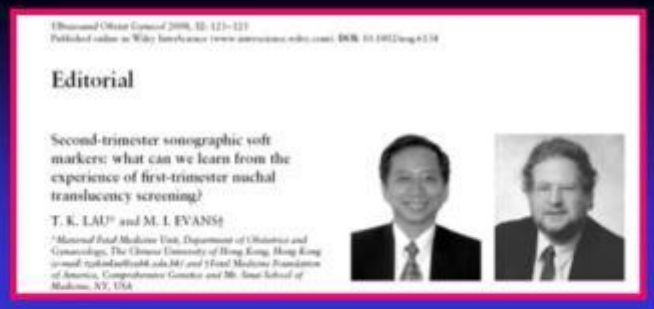
Monni, Croat Med J 2000

NT AND EMBRYO REDUCTION AT 11 WEEKS OF GESTATION IN QUADRUPLETS

	Fetus 1	Fetus 2	Fetus 3	Fetus 4
CRL (mm)	44.7	44.2	45.8	44.4
NT (mm)	0.7	0.9	2.3	0.9
Estimated risk	1 in 1809	1 in 1830	1 in 210	1 in 1806
Karyotype	46, XY*	46, XX *	47, XX +21**	46, XY**

* *AF at 15 weeks*
** *AF and FBS at 11 weeks before ER*

Monni, Ultrasound Obstet Gynecol 1999



Editorial

Second-trimester sonographic soft markers: what can we learn from the experience of first-trimester nuchal translucency screening?

T. K. LAU* and M. I. EVANS†

Effort should be focused on:

- The development of a well-defined protocol for the evaluation of these few strong markers, including how to do it, when to do it, and who should do it
- The development of an algorhytm for incorporating these markers into existing screening programs
- The confirmation of their efficacy as screening markers by large prospective studies in an unselected population

Editorial

Second-trimester sonographic soft markers: what can we learn from the experience of first-trimester nuchal translucency screening?

T. K. LAU* and M. I. EVANS†

It should be remembered that

- A service without quality is worse than no service at all
- The screening procedure should not be merely a test but must be a comprehensive program
- The basic principle of Medicine – "First do not harm" - should always be observed