First Trimester Screening:
Chromosomal Defects and Beyond

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Objectives

- List the first trimester sonographic markers and discuss the background research for each one
- Identify the different chromosomal abnormalities associated with each of the first trimester sonographic markers
- Outline the associations between the markers.
- Discuss the different fetal outcomes, other than chromosomal abnormalities, associated with each first trimester sonographic marker.
- Describe possible future directions for risk-calculation algorithms for outcomes other than Down syndrome based on these first trimester sonographic markers.

Ultrasound Screening at 11-13^{+6} wks.

- Nuchal translucency (continuous variable)
- Nasal bone evaluation (present/absent)
- Doppler of Ductus Venosus (normal/abnormal)
- Tricuspid valve regurgitation (present/absent)
- Fronto-maxillary facial angles (continuous variable)

Calculation of Risk for Chromosome Abnormalities

Background (*a priori*) risk

Maternal age, gestational age, previous history of aneuploidy

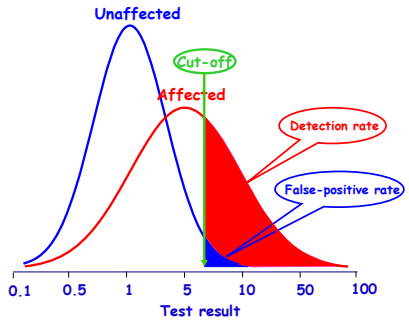
X

Factor(s) derived from screening test(s)

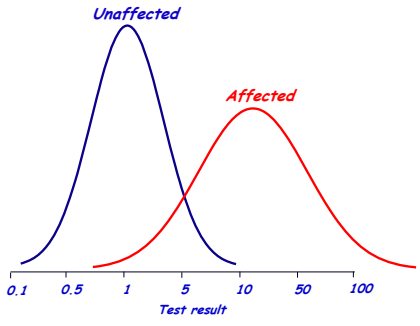
Nuchal Translucency, other markers

= Adjusted risk

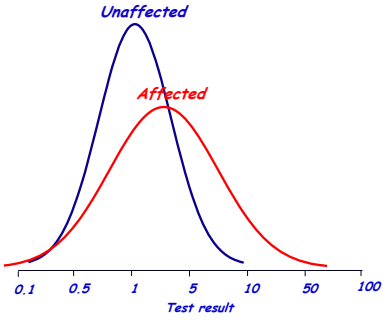
Ultrasound Screening at 11-13^{+6} wks.: Continuous Variables



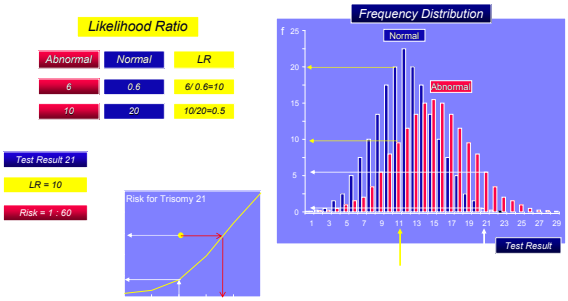
Ultrasound Screening at 11-13^{+6} wks.: Continuous Variables



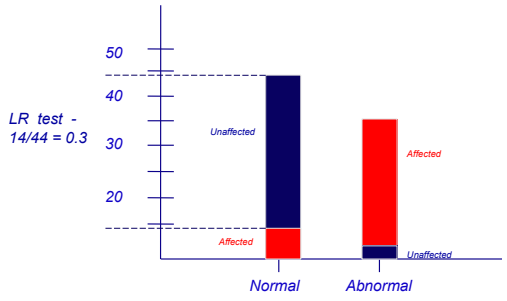
Ultrasound Screening at 11-13^{+6} wks.: Continuous Variables



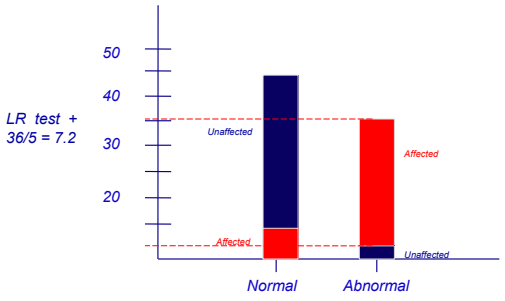
Calculation of Risk for Chromosome Abnormalities



Ultrasound Screening at 11-13^{+6} wks.: Dichotomous Variables



Ultrasound Screening at 11-13^{+6} wks.: Dichotomous Variables



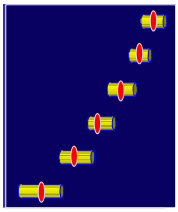
Nuchal Translucency

Ultrasound Screening at 11-13^{+6} wks.

- Nuchal translucency
  - "UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10–14 weeks of gestation" Snijders et al. THE LANCET • Vol 352 •, 1998
  - 96,127 singleton pregnancies, median age 31 (14-49)
  - 306 FMF-credentialed sonographers, 22 centers across UK
  - Cut-off of 1:300 or higher was used
  - Identified 80% of Down syndrome pregnancies (5%SPR)
  - Identified 59%-87% of other chromosome abnormalities

Ultrasound Screening at 11-13^{+6} wks.

Risk group	Median risk	Observed prevalence	
> 1 in 20	1 in 7	1 in 7	(187 / 1305)
1 in 20 – 100	1 in 58	1 in 41	(9 / 2011)
1 in 100 – 300	1 in 197	1 in 159	(32 / 5096)
1 in 300 – 1000	1 in 629	1 in 590	(31 / 18279)
1 in 1000 – 2000	1 in 1504	1 in 1389	(4 / 19445)
< 1 in 2000	1 in 3695	1 in 3846	(13 / 49991)



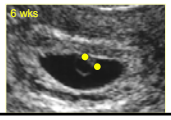
Snijders *et al.* Lancet Vol 352 • August 1, 1998

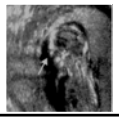
Ultrasound Screening at 11-13^{+6} wks. Pre-standardization

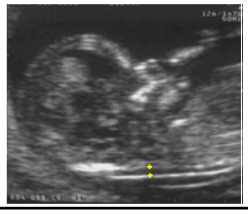
Author	GA (wks)	Screen cut off	N	Sensitivity	FPR
Pajkrt '98	10-14	Risk > 1 in 300	1473	100 %	19.8 %
Theodoropoulos '98	10-14	Risk > 1 in 300	3550	91 %	4.9 %
Szabo '95	9-12	> 3mm	3380	90 %	2.0 %
Schwarzler	10-14	Risk > 1 in 270	4523	83 %	4.7 %
Snijders '98	10-14	Risk > 1 in 300	96127	82 %	8.3 %
D'Ottavio '97	13-15	> 4mm	3509	70 %	1.0 %
Zimmerman '96	10-13	> 3mm	1131	67 %	1.9 %
Haffner '98	10-13	> 2SD	4233	57 %	1.7%
Orlandi '97	9-14	> 95th centile	744	57 %	6.0 %
Whitlow '99	11-15	> 99th centile	6634	57 %	1.0 %
Taipale '97	10-14	> 3mm	9003	54 %	1.0 %
Bewley '95	8-13	> 3mm	1368	33 %	6.0 %
Kornman '96	8-13	> 3mm	537	29 %	6.0 %

Study	n	Gestation	Not measured	NT cut-off	FPR	Detection Tr21
Bewley 1995[1]	1,704	8-13 wks	34%	3.0 mm	6.0%	1 of 3 (33%)
Kornman 1996[2]	923	8-13 wks	42%	3.0 mm	6.3%	2 of 4 (50%)
Haddow 1998[3]	3,991	9-15 wks	17%	95th centile	5.0%	18 of 58 (31%)
Crossley 2002[4]	17,229	10-14 wks	27%	-	5.0%	20 of 37 (54%)
Wald 2003[5]	47,053	6-16 wks	18%	-	5.0%	?29 of 101

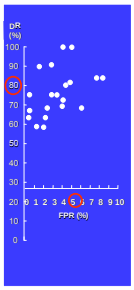
1. No more time than CRL
2. 3 mins per scan; 54% CRL<33mm
3. Teaching by letter
4. Attending a lecture
5. ?training; 6-16w







Study	n	NT cut-off	FPR	Detection Tr21
Pandya 1995	1,763	2.5 mm	3.4%	3 of 4 (75%)
Szabo 1995	3,380	3.0 mm	1.6%	27 of 30 (90%)
Taipale 1997	6,939	3.0 mm	0.7%	4 of 6 (67%)
Schuchter 2001	9,342	2.5 mm	2.1%	11 of 19 (58%)
Chasen 2003	2,248	95th centile	3.4%	9 of 12 (75%)
Snijders 1998	96,127	95th centile	4.4%	234 of 326 (72%)
Pajkrt 1998	3,614	3.0 mm	4.2%	32 of 46 (70%)
Theodoropoulos 1998	3,550	2.5 mm	2.9%	2 of 2 (91%)
Panburana 2001	2,067	95th centile	8.0%	174 of 210 (83%)
Economides 1998	2,256	99th centile	0.4%	6 of 8 (75%)
Schwarzler 1999	4,523	2.5 mm	2.7%	8 of 12 (67%)
Audibert 2001	4,130	3.0 mm	1.7%	7 of 12 (58%)
Zoppi 2001	10,111	95th centile	5.1%	52 of 64 (81%)
Brizot 2001	2,492	95th centile	6.4%	7 of 10 (70%)
Wayda 2001	6,841	2.5 mm	4.1%	17 of 17 (100%)
Gasiorek-Wiens 2001	21,959	95th centile	8.0%	174 of 210 (83%)
Comas 2002	7,345	95th centile	4.9%	38 of 38 (100%)
Whitlow 1999	5,947	99th centile	0.7%	15 of 23 (65%)
Rosenberg 2002	6,234	3.0 mm	2.8%	13 of 21 (62%)
Avgidou 2004	30,559	95th centile	5.2%	144 of 191 (80%)
Total	231,427		4.3%	813 / 1062 (77%)



Measuring NT

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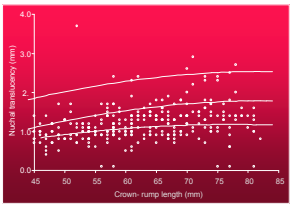
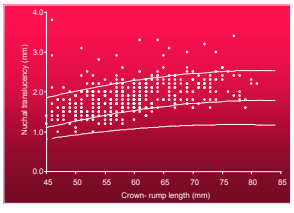
- **Gestation** 11^{+0} to 13^{+6} wks (**CRL 45-84 mm**)
- **Mid-sagittal view** (fetus can be either facing towards or away from the transducer)
- **Image size**: head and upper thorax - **75% of the image** ⟹ measurement accuracy **0.1 mm**
- Fetus **away from amnion**
- Fetus in **neutral position**
- Use **maximum lucency**
- Adjust for **nuchal cord**
- Caliper placement **"on-to-on"**
- See the **whole lucency**

Monitoring NT quality over time





Nasal Bone

Ultrasound Screening at 11-13^{+6} wks.

- Nasal bone evaluation (present or absent)
  - "Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks of gestation: an observational study"
    Cicero et al. THE LANCET • Vol 358 • November 17, 2001
  - Assessed 701 pregnancies before karyotyping
  - Obtained required views of nasal bone in 100%
  - NB absent in 73% of T21 and 0.5% of normals
  - Conclusion: adding NB could increase sensitivity to 85% and decrease invasive testing rate to 1%

Ultrasound Screening at 11-13^{+6} wks.

- Nasal bone evaluation (present or absent)
  - "Nasal bone in first-trimester screening for trisomy 21"
    Cicero et al. AJOG (2006) 195, 109–14
  - 20,418 patients coming in for FTS
  - Association between absent NB and NT, CRL, maternal age and ethnicity were revealed and accounted for in a multivariable model
  - Conclusion: adding NB could reduce invasive testing rate to 2.5% for a 90% detection rate (combined screen)

Nasal Bone

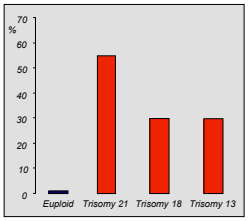
- **Gestation** 11^{+0} to 13^{+6} wks (**CRL 45-84 mm**)
- **Mid-sagittal view (face up only)**
- **Image size**: head and upper thorax - **75% of the image**
- Angle of insonation **perpendicular to the nasal bone**
- Nasal bone is present when **the bone is seen as brighter and thicker than the overlying skin**
- Nasal bone is absent when **the bone is seen as equal to or less echogenic and thinner the overlying skin**
- **No measurement of NB**

Monitoring Nasal Bone quality over time

Tricuspid Flow

Ultrasound Screening at 11-13^{+6} wks.

- Tricuspid Regurgitation (present or absent)



At 11-13^{+6} weeks tricuspid regurgitation is found in about:

- *Euploid fetuses* *1%*
- *Fetuses with trisomy 21* *55%*
- *Fetuses with trisomy 18* *30%*
- *Fetuses with trisomy 13* *30%*

Ultrasound Screening at 11-13^{+6} wks.

- Tricuspid Regurgitation (present or absent) (cont.)
  - Heart Defects were found in 7% of euploid and 45% of aneuploid fetuses referred mainly for increased NT
  - At 11- 13^{+6} weeks, 81% of cardiac defects were dx
  - In euploid fetuses, TR is associated with an 8-fold increase in the risk of a cardiac defect
  - Color-flow was not reliable for the diagnosis of TR at 11- 13^{+6} weeks, pulsed Doppler was used
  - TR is associated with GA

Faiola et al. Ultrasound Obstet Gynecol 2005; 26: 22–27

Ultrasound Screening at 11-13^{+6} wks.

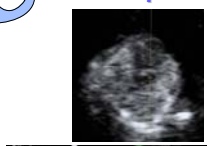
- Tricuspid Regurgitation (present or absent) (cont.)
  - TR is associated with gestational age and NT in euploid and aneuploid pregnancies
  - Prevalence of cardiac defects increases with NT

Table 7 Prevalence of cardiac defects in chromosomally normal fetuses with and without tricuspid regurgitation according to nuchal translucency

	Cardiac defect (n (%))		
NT (mm)	Total	TR +ve	TR −ve
< 3.5	4/181 (2.2)	2/8 (25.0)	2/173 (1.2)
3.5–4.4	6/130 (4.6)	3/9 (33.3)	3/121 (2.5)
≥ 4.5	22/147 (15.0)	10/22 (45.5)	12/125 (9.6)
Total	32/458 (7.0)	15/39 (38.5)	17/419 (4.1)

Faiola et al. Ultrasound Obstet Gynecol 2005; 26: 22–27

Tricuspid Flow



- **Gestation** 11^{+0} to 13^{+6} wks (**CRL 45-84 mm**)
- **4-chamber view** (Spine up or down)
- **Doppler Gate**: open to **2-3mm**
- Angle of insonation: **less than 30 degrees from the direction of the inter-ventricular septum.**
- Tricuspid regurgitation is present when **the velocity is >= 60cm/sec and the jet covers at least half of systole**
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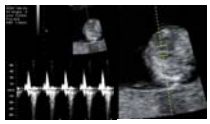
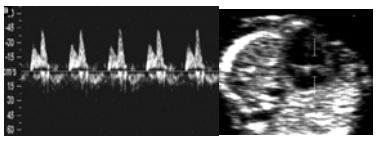
Monitoring Tricuspid Flow Assessment Quality over Time

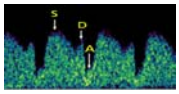




Ductus Venosus Flow

Ultrasound Screening at 11-13^{+6} wks.

- Ductus Venosus (normal / abnormal)
  - "Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow"
    Matias et al. Ultrasound Obstet Gynecol 1998;12:380–384
  - 486 pregnancies before karyotyping
  - Obtained required views of heart in 100% (3-10 mins)
  - Assessed peak velocities in S, D, and A waves



Ultrasound Screening at 11-13^{+6} wks.

- Ductus Venosus (normal / abnormal) (cont.)
  - Only height of the A-wave helped discriminate euploid from aneuploid pregnancies
  - Absent/reversed A-wave flow in 91% of aneuploid and 3% of euploid pregnancies
  - 7/13 euploid fetuses with absent or reversed flow were dx at 14-16weeks with a major heart defect

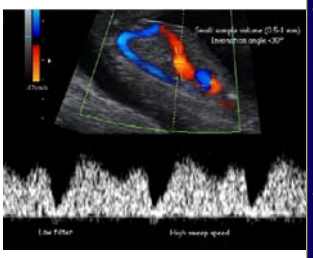
Matias et al. Ultrasound Obstet Gynecol 1998;12:380–384

Ultrasound Screening at 11-13^{+6} wks.

- Ductus Venosus (normal / abnormal) (cont.)
  - Conclusions:
    - In aneuploid fetuses with increased NT, abnormal DV flow can be found in the absence of heart defects
    - It may be a transient finding (first trimester only)
    - if used to screen those at high risk after NT/ fβhCG/ PAPP-A screening, could reduce the invasive testing rate to 0.5% for an 80% detection rate for Down syndrome

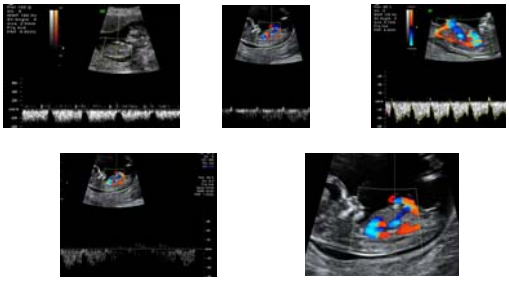
Matias et al. Ultrasound Obstet Gynecol 1998;12:380–384

Ductus Venosus Flow



- **Gestation** 11^{+0} to 13^{+6} wks (**CRL 45-84 mm**)
- **Mid-sagittal view:** Fetal thorax and abdomen fill the image
- **Doppler Gate**: between 0.5 and 1.0 mm
- Angle of insonation: **less than 30 degrees from the direction of the flow**
- **Filter**: 50-70Hz
- **Sweep speed:** 2-3 cm/sec
- Hint: Use 1st trimester color, not ❤

Monitoring Ductus Venosus Flow Assessment over Time



Frontomaxillary Facial Angle

Ultrasound Screening at 11-13^{+6} wks.

- FMFA (continuous variable)
  - "Frontomaxillary facial angle in chromosomally normal fetuses at 11^{+0} to 13^{+6} weeks"
    Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 737–741
  - 611 euploid fetuses, 500 (82%) successfully acquired appropriate view for 3D volume collection (15 min.)
  - In 150, the angle was measured by both 2D and 3D (with blinding)
  - In 50, 3D volumes were used to measure the angle twice by the same examiner and once by another (with blinding)

Ultrasound Screening at 11-13^{+6} wks.

- FMFA (continuous variable) (cont).
  - FMFA decreases with GA
  - Independent of NT, biochem
  - Intra- and inter-operator

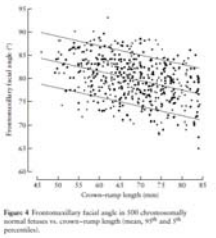


Figure 4 Frontomaxillary facial angle in 500 chromosomally normal fetuses vs. crown–rump length (mean, 95th and 5th percentiles).

Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 737–741

Ultrasound Screening at 11-13^{+6} wks.

- FMFA (continuous variable) (cont).
  - Independent of NT and biochemistry
  - Intra- and inter-operator variability <5% in 95% of cases
  - Difference in FMFA measurements acquired by 2D and 3D was < 8% in 95% of cases
  - No difference in delta FMFA measurements by ethnicity

Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 737–741

Ultrasound Screening at 11-13^{+6} wks.

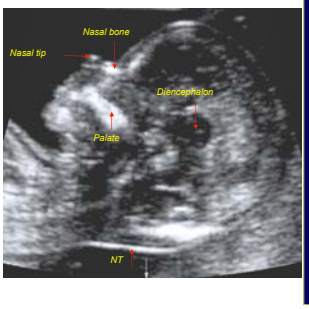
- FMFA (continuous variable)
  - "Frontomaxillary facial angle in fetuses with trisomy 21 at 11 to 13^{+6} weeks"
    Sonek et al. Ultrasound Am J Obstet Gynecol 2007;196;271.e1-271.e4
  - 300 euploid fetuses, 100 with Down syndrome
  - FMFA was measured using 3D only
  - No difference in median FMFA in those euploid and aneuploid fetuses with or without nasal bones

Ultrasound Screening at 11-13^{+6} wks.

- FMFA (continuous variable) (cont.)
  - FMFA was, on average, >10 degrees larger in Down syndrome cases than in the euploid
  - In 69% of Down syndrome cases, the FMFA was above the 95%tile of the euploid
  - In 40% it was greater than the upper limit for euploid (90 degrees)
  - No significant intra- or inter-operator differences

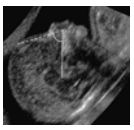
Sonek et al. Ultrasound Am J Obstet Gynecol 2007;196;271.e1-271.e4

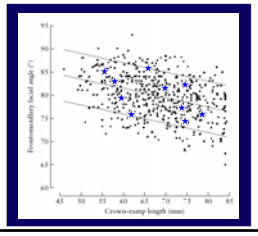
Fronto-Maxillary Facial Angles (FMFA)



- **Gestation** 11^{+0} to 13^{+6} wks (**CRL 45-84 mm**)
- **Mid-sagittal view:** Echogenic nose tip & rectangular palate anteriorly, diencephalon centrally, NT posteriorly
- **Magnification**: Fetal head and thorax fill the image
- **Angle measurement:** Along superior surface of palate, then from front of palate to frontal bone/ metopic suture line under skin

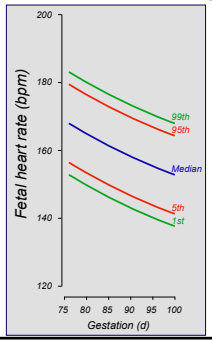
Monitoring FMFA quality over time



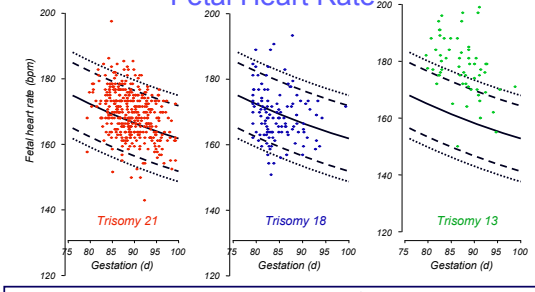
Fetal Heart Rate

Ultrasound Screening at 11-13^{+6} wks.: Fetal Heart Rate



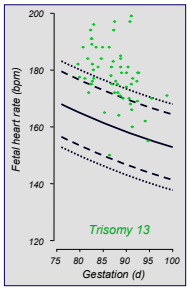
- In normal pregnancy, the FHR:
  - Averages about 110 bpm at 5 weeks
  - Increases to 170 bpm at 10 weeks
  - Gradually decreases to 150 bpm by 14 weeks

Ultrasound Screening at 11-13^{+6} wks.: Fetal Heart Rate



- *In trisomy 21 the FHR is mildly increased and is above the 95th centile in about 15% of cases*
- *In trisomy 18 the FHR is mildly decreased and is below the 5th centile in about 15% of cases*
- ***In trisomy 13 the FHR is substantially increased , above the 95th centile in 85% of cases***

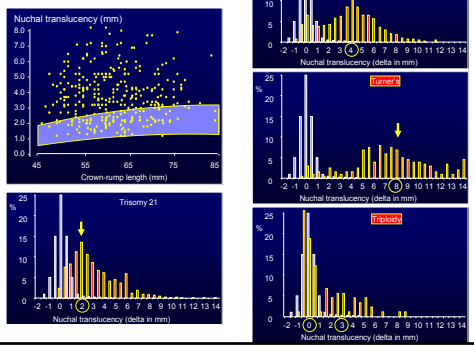
Ultrasound Screening at 11-13^{+6} wks.: Fetal Heart Rate



- *Inclusion of FHR in first-trimester combined sonographic and biochemical screening for chromosomal abnormalities has a small impact on the detection of trisomies 21 and 18 but a major improvement in the detection of trisomy 13*
- *In addition, inclusion of FHR is important in distinguishing between trisomy 18 and 13, which are otherwise similar in presenting with increased fetal NT and decreased maternal serum free β-hCG and PAPP-A*

Beyond Down Syndrome:
Other Chromosome Abnormalities

NT is a marker for other aneuploidies

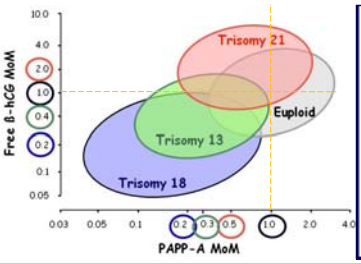


Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

- Screening with NT will allow for detection of 90% (3%FPR) of other chromosome abnormalities
- Detection for triploidy is around 85% (3%FPR) using a combination of algorithms for T21 and for trisomies 18 and 13, mostly due to the contribution of the biochemistry

Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

- 1st trimester biochemistry is associated with other chromosome abnormalities



- *In euploid pregnancies the average free ß-hCG is 1.0 MoM and PAPP A is 1.0 MoM*
- *In chromosomal defects the values are*

	free ß-hCG	PAPP-A
Trisomy 21	2.0	0.5
Trisomy 18	0.2	0.2
Trisomy 13	0.4	0.3
Turner	1.2	0.5
Triploidy		
Digynic	0.2	0.1
Diandric	9.0	0.7

Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

- Nasal bone absence is associated with other chromosome abnormalities
  - 21,074 cases
  - 33 sonographers
  - All w/ FMF nasal bone certificates

Table 1 Prevalence of absent nasal bone in chromosomally normal and abnormal fetuses at 11 to 13^{+6} weeks

Fetal karyotype	N	Absent nasal bone
Normal	20,165	113 (0.6%)
Trisomy 21	140	87 (62.1%)
Trisomy 18	40	22 (55.0%)
Trisomy 13	19	6 (31.6%)
Turner syndrome	13	5 (38.5%)
Triploidy	11	1 (9.1%)
Other*	30	4 (13.3%)
Total	20,418	238 (1.2%)

* Trisomies or sex chromosome aneuploidies other than above, unbalanced translocations, deletions, mosaics.

Cicero et al. American Journal of Obstetrics and Gynecology (2006) 195, 109–14

Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

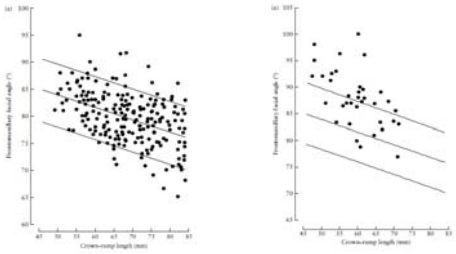
- Tricuspid regurgitation is associated with other chromosome abnormalities

		Tricuspid regurgitation		
Karyotype	Total	Total (n (%))	Cardiac defect (n (%))	No cardiac defect (n (%))
Normal	458	39 (8.5)	15 (46.9)	24 (5.6)
Trisomy 21	126	82 (65.1)	39 (97.5)	43 (50.0)
Trisomy 18	68	37 (54.4)	28 (68.3)	9 (33.3)
Trisomy 13	15	7 (46.6)	5 (55.6)	2 (33.3)
Turner	28	4 (14.3)	4 (25.0)	—
Other	23	7 (30.4)	5 (45.5)	2 (16.7)

Faiola et al. Ultrasound Obstet Gynecol 2005; 26: 22–27

Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

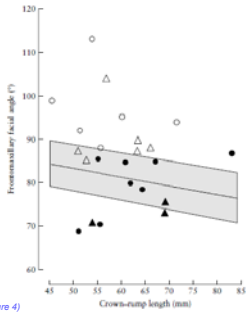
- FMFA is associated with trisomy 18



Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 928–933 (figure 3a,4a)

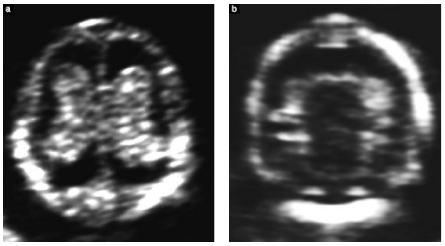
Ultrasound Screening at 11-13^{+6} wks.: Associations with other aneuploidies

- FMFA is associated with trisomy 13 in those cases with holoprosencephaly



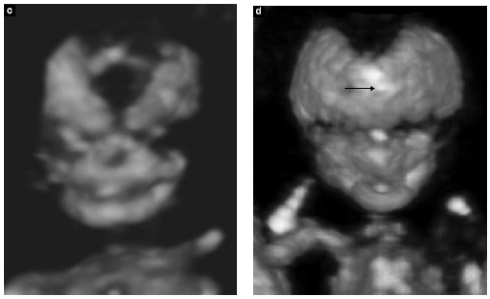
Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 819–823 (figure 4)

FMFA are associated with trisomy 13 in those cases with holoprosencephaly



Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 819–823 (figure 2)

FMFA are associated with trisomy 13 in those cases with holoprosencephaly



Borenstein et al. Ultrasound Obstet Gynecol 2007; 30: 819–823 (figure 2)

Associations Between First Trimester Markers

Associations between First Trimester Markers

- In addition to being related to aneuploidy, some first trimester markers are associated with:
  - Other first trimester markers
  - Characteristics of the mother and/or fetus
  - These associations must be accounted for in the risk calculation algorithm to avoid falsely under- or over-estimating the new risk given to the woman

Associations between First Trimester Markers

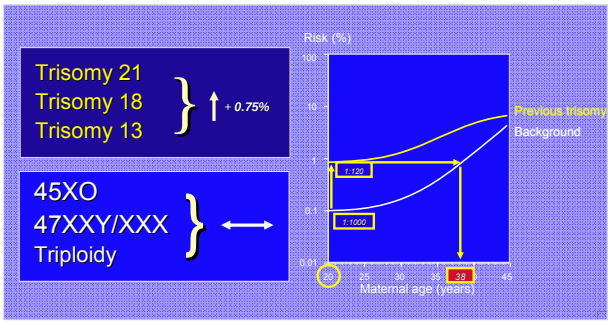
- A woman's *a priori* risk is associated with:
  - Her age
  - Her previous obstetric history
  - Gestational age of the fetus

Associations between First Trimester Markers: A priori risk is related to maternal age

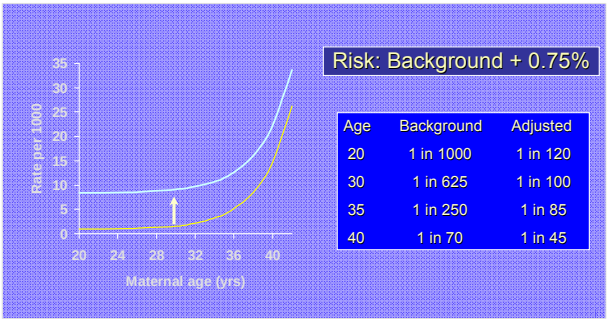
Table 2. Estimated risk for trisomies 21, 18 and 13 (1/number given in the table) in relation to maternal age and gestation.

Maternal age (yrs)	Trisomy 21 Gestation (wks)				Trisomy 18 Gestation (wks)				Trisomy 13 Gestation (wks)			
	12	16	20	40	12	16	20	40	12	16	20	40
20	1068	1200	1295	1527	2484	3590	4897	18013	7826	11042	14656	42423
25	946	1062	1147	1352	2200	3179	4336	15951	6930	9778	12978	37567
30	626	703	759	895	1456	2103	2869	10554	4585	6470	8587	24856
31	543	610	658	776	1263	1825	2490	9160	3980	5615	7453	21573
32	461	518	559	659	1072	1549	2114	7775	3378	4766	6326	18311
33	383	430	464	547	891	1287	1755	6458	2806	3959	5254	15209
34	312	350	378	446	725	1047	1429	5256	2284	3222	4277	12380
35	249	280	302	356	580	837	1142	4202	1826	2576	3419	9876
36	196	220	238	280	456	659	899	3307	1437	2027	2691	7788
37	152	171	185	218	354	512	698	2569	1116	1575	2090	6050
38	117	131	142	167	272	393	537	1974	858	1210	1606	4650
39	89	100	108	128	208	300	409	1505	654	922	1224	3544
40	68	76	82	97	157	227	310	1139	495	698	927	2683
41	51	57	62	73	118	171	233	858	373	526	698	2020
42	38	43	46	55	89	128	175	644	280	395	524	1516

Associations between First Trimester Markers: Previous Obstetric History



Associations between First Trimester Markers: Previous Obstetric History



Age	Background	Adjusted
20	1 in 1000	1 in 120
30	1 in 625	1 in 100
35	1 in 250	1 in 85
40	1 in 70	1 in 45

Associations between First Trimester Markers: Previous Obstetric History

EXAMPLE CALCULATION

Prior Risk: 1 in 1000 (20 year old)
1/1000 = 0.001 or 0.1%

Previous history of trisomy adds 0.75%
0.1% + 0.75% = 0.85% or 0.0085

0.0085 = 85/10,000 = 1/118

Associations between First Trimester Markers: *a priori risk* is related to gestational age

Table 2. Estimated risk for trisomies 21, 18 and 13 (1/number given in the table) in relation to maternal age and gestation.

Maternal age (yrs)	Trisomy 21 Gestation (wks)				Trisomy 18 Gestation (wks)				Trisomy 13 Gestation (wks)			
	12	16	20	40	12	16	20	40	12	16	20	40
20	1068	1200	1295	1527	2484	3590	4897	18013	7826	11042	14656	42423
25	946	1062	1147	1352	2200	3179	4336	15951	6930	9778	12978	37567
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33	383	430	464	547	891	1287	1755	6458	2806	3959	5254	15209
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35	249	280	302	356	580	837	1142	4202	1826	2576	3419	9876
36	196	220	238	280	456	659	899	3307	1437	2027	2691	7788
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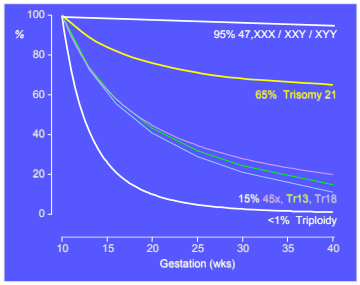
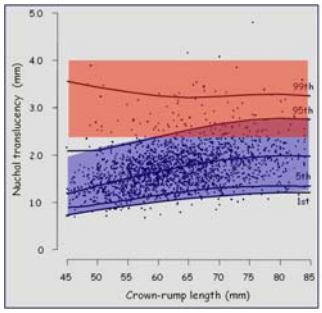
38	117	131	142	167	272	393	537	1974	858	1210	1606	4650
39	89	100	108	128	208	300	409	1505	654	922	1224	3544
40	68	76	82	97	157	227	310	1139	495	698	927	2683
41	51	57	62	73	118	171	233	858	373	526	698	2020
42	38	43	46	55	89	128	175	644	280	395	524	1516

Associations between First Trimester Markers: A priori risk is related to gestational age



- *The risk of fetal death in chromosomally abnormal fetuses is higher than in normal fetuses*
- *The rate of fetal death is different for different chromosomal defects*

Associations between First Trimester Markers: NT is related to gestational age



In the distribution of NT thickness in chromosomally normal fetuses:

• The median, 1st, 5th and 95th centiles increase with fetal crown rump legth (CRL)

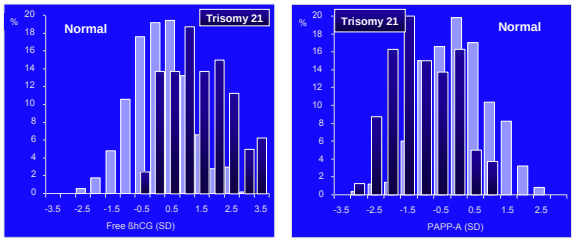
• The 99th centile is about 3.5 mm and does not change with CRL

The best way to explain these findings comes from the suggestion that fetal NT follows a mixture of two distributions:

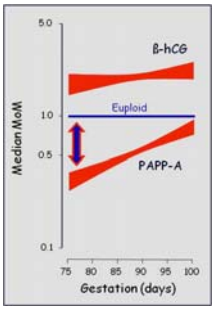
- ***One which is CRL-dependent***
- ***Another which is CRL-independent***

*Wright et al Ultrasound Obstet Gynecol 2008; **31: 376–383***

Associations between First Trimester Markers: First Trimester Biochemistry



Associations between First Trimester Markers: First Trimester Biochemistry and GA



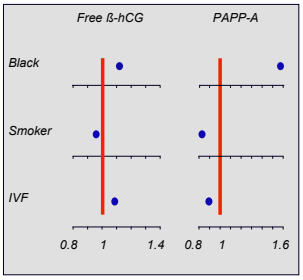
In trisomy 21 pregnancies:

• Free ß-hCG is higher than in normal pregnancies and the difference between the two is higher at 13 than at 11 weeks

• Serum PAPP-A is lower than in normal pregnancies and the difference between the two is higher at 11 than at 13 weeks

• The difference from normal pregnancies in PAPP-A at 11 weeks is greater than the difference in ß-hCG at 13 weeks and therefore the overall performance of biochemical screening is better at 11 than at 13 weeks

Associations between First Trimester Markers: First Trimester Biochemistry and Maternal Factors



• In Black women the PAPP-A level is about 60% higher than in White women. Failure to take into account ethnic origin would result in substantial underestimate of the true risk of trisomy 21 in Black women

• In women who smoke and those conceiving by IVF serum PAPP-A is decreased and this could be misinterpreted for increased risk for trisomy 21 and a substantial increase in false positive rates

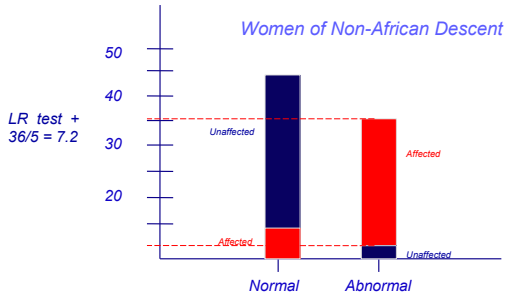
•In the calculation of accurate patient-specific risks it is necessary to make adjustments in the measured free ß-hCG and PAPP-A.

Associations between First Trimester Markers

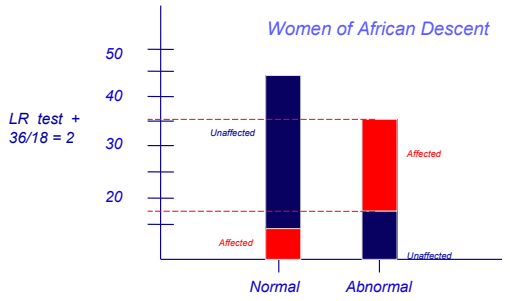
- Absence of the nasal bone is related to:
  - Delta NT
  - Gestational age
  - Slightly with maternal age
  - Maternal ethnicity (African descent)

Cicero et al. AJOG (2006) 195, 109–14

Associations between First Trimester Markers: Nasal bone and maternal ethnicity



Associations between First Trimester Markers: Nasal bone and maternal ethnicity

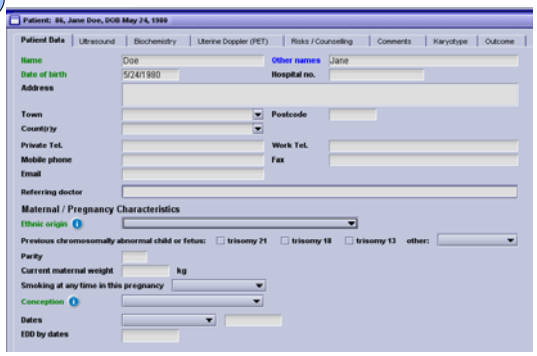


Associations between First Trimester Markers

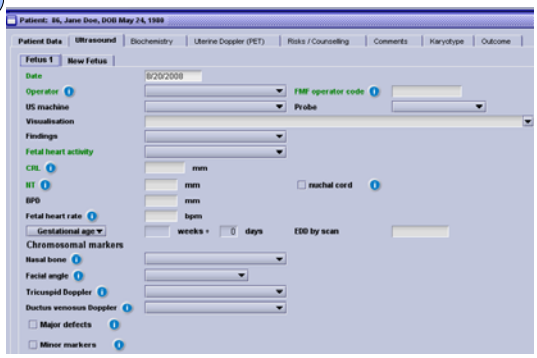
- Presence of tricuspid regurgitation* or abnormal ductus venosus flow** are related to:
  - Delta NT
  - Gestational age
  - Presence of cardiac defects

*Faiola et al. Ultrasound Obstet Gynecol 2005; 26: 22–27
** Maiz et al. Ultrasound Obstet Gynecol 2008; 31: 256–260

Associations between First Trimester Markers

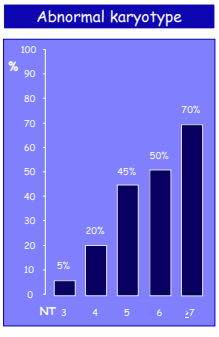


Associations between First Trimester Markers



Beyond Chromosome Abnormalities

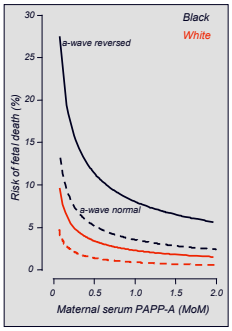
Beyond Chromosome Abnormalities: Increased NT and Poor Pregnancy Outcome



Nuchal translucency	Normal karyotype	
	Fetal death	Major defects
<95th centile	1.3%	1.6%
95th-99th centiles	1.3%	2.5%
3.5-4.4 mm	2.7%	10.0%
4.5-5.4 mm	3.4%	18.5%
5.5-6.4 mm	10.1%	24.2%
≥6.5 mm	19.0%	46.2%

Increased NT is associated with:
- All major chromosomal abnormalities
- More than 50 defects & genetic syndromes
- The risk increases with NT thickness

Beyond Chromosome Abnormalities: Abnormal DV and Fetal Death

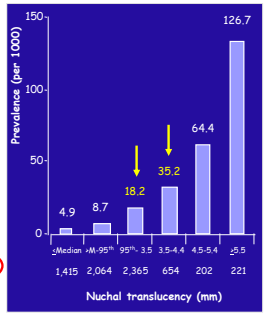


- *The risk of miscarriage or fetal death between 11 weeks and delivery is about 2%*
- *The prevalence of reversed a-wave at 11-13+6 weeks is >10% in pregnancies resulting in fetal death and <4% in those resulting in live birth*
- *The risk of fetal death is increased if:*
  - *DV a-wave is reversed*
  - *PAPP-A is low*
  - *The mother is Black*
  - *The mother is obese*

Beyond Chromosome Abnormalities: Increased NT and Heart Defects

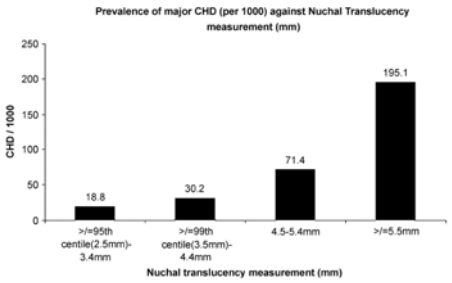
Screening for Major Heart Defects

Author	N	CHD n (/1,000)	FPR	DR
Josefsson et al 1998	1,460	13 (8.9)	8.9%	38.5%
Bilardo et al 1998	1,590	4 (2.5)	2.8%	50.0%
Hyett et al 1999	29,154	50 (1.7)	6.2%	56.0%
Schwarzler et al 1999	4,474	9 (2.0)	2.6%	11.1%
Michailidis et al 2001	6,606	11(1.7)	3.5%	36.4%
Mavrides et al 2001	7,339	26 (3.5)	3.5%	15.4%
Ovros et al 2002	3,655	20 (5.5)	2.5%	45.0%
Hafner et al 2003	12,978	27 (2.1)	5.0%	25.9%
Total	67,256	160 (2.4)	4.9%	37.5%



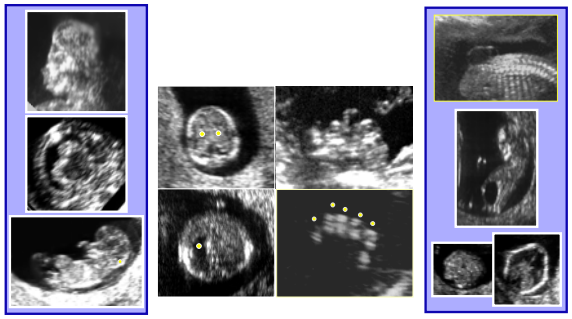
Atzei et al 2005, n=6,921

Beyond Chromosome Abnormalities: Increased NT and Heart Defects



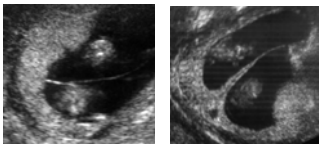
Clur et al. Prenat Diagn 2008; 28: 347–354

Beyond Chromosome Abnormalities: Fetal Structural Abnormalities

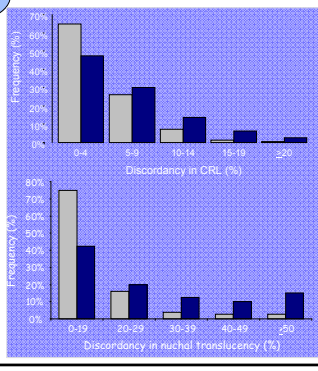


Beyond Chromosome Abnormalities: TTTS

- Twin-to-Twin Transfusion Syndrome
  - Affects 10% of monochorionic pregancies
  - 2/3 of monozygotic twins are monochorionic
  - All monochorionic twins are monozygotic



Beyond Chromosome Abnormalities: TTTS



CRL (%)	Normal	Severe TTTS	LR+ve
0-4	64.7%	47.5%	0.7
5-9	26.3%	30.0%	1.1
10-14	7.2%	13.8%	1.9
15-19	1.3%	6.3%	4.6
≥20	0.4%	2.5%	5.6
≥10	8.9%	22.6%	2.5

NT (%)	Normal	Severe TTTS	LR+ve
0-19	74.8%	42.5%	0.6
20-29	16.0%	20.0%	1.3
30-39	3.8%	12.5%	3.3
40-49	2.7%	10.0%	3.7
≥50	2.7%	15.0%	5.6
≥30	9.2%	37.5%	4.1

Beyond Chromosome Abnormalities: Extreme Values of First Trimester Biochemistry

- Extremely Low fβhCG and IUGR

MoM	Percentile	Total (n)	Adjusted odds ratio (95% CI)
Free β-hCG			
<0.21	<1st	56	2.7 (1.3-5.9)†
<0.38	<5th	269	1.3 (0.8-2.0)
>2.30	>95th	323	1.1 (0.7-1.7)
>3.06	>99th	63	1.1 (0.4-3.0)

- Extremely low fβhCG and Preterm Birth

MoM	Percentile	Total (n)	Adjusted odds ratio (95% CI)
Free β-hCG			
<0.21	<1st	69	1.1 (0.2-8.2)
<0.38	<5th	359	1.1 (0.5-2.8)
>2.30	>95th	380	1.7 (0.8-3.5)
>3.06	>99th	75	2.0 (0.5-8.5)

Krantz et al. American Journal of Obstetrics and Gynecology (2004) 191, 1452-8 Tables IV and V

Beyond Chromosome Abnormalities: Extreme Values of First Trimester Biochemistry

- Extremely Low PAPP-A and IUGR

MoM	Percentile	Total (n)	Adjusted odds ratio (95% CI)
PAPP-A			
<0.29	<1st	54	5.4 (2.8-10.3)†
<0.45	<5th	270	2.7 (1.9-3.9)†
>2.07	>95th	293	1.0 (0.6-1.6)
>3.92	>99th	64	1.0 (0.4-2.8)

- Extremely low PAPP-A and Preterm Birth

MoM	Percentile	Total (n)	Adjusted odds ratio (95% CI)
PAPP-A			
<0.29	<1st	71	2.5 (0.6-10.5)
<0.45	<5th	356	2.3 (1.1-4.7)†
>2.07	>95th	392	1.4 (0.6-3.0)
>3.92	>99th	78	2.0 (0.5-8.3)

Krantz et al. American Journal of Obstetrics and Gynecology (2004) 191, 1452-8 Tables IV and V

Beyond Chromosome Abnormalities: Extreme Values of NT

- Increased NT and Preterm Birth

MoM	Percentile	Total (n)	Adjusted odds ratio (95% CI)
Nuchal translucency			
<0.41	<1st	71	1.1 (0.2-8.3)
<0.55	<5th	369	1.6 (0.7-3.4)
>1.47	>95th	372	1.6 (0.7-3.5)
>1.96	>99th	75	3.5 (1.1-11.3)†

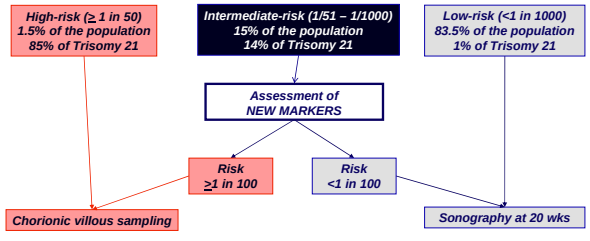
Krantz et al. American Journal of Obstetrics and Gynecology (2004) 191, 1452-8 Tables IV and V

Risk Calculaton Algorithms: Future Directions

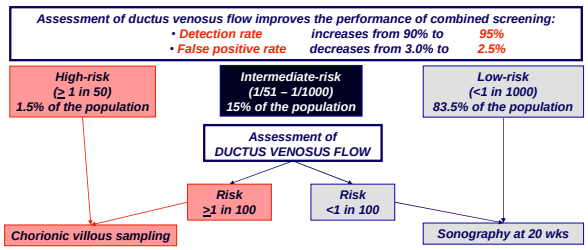
Risk Calculation Algorithms: Future Directions

- Two strategies for including new markers into first trimester screening
  - Do everything on everyone always
  - Do two-stage screening
    - Identify an intermediate risk group after initial NT and biochemistry
    - Look at additional ultrasound markers to push these women into high-risk or low-risk group

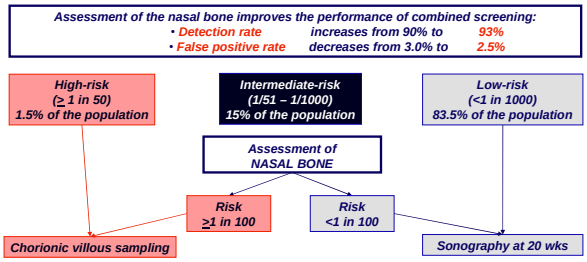
Risk Calculation Algorithms: 2-Stage



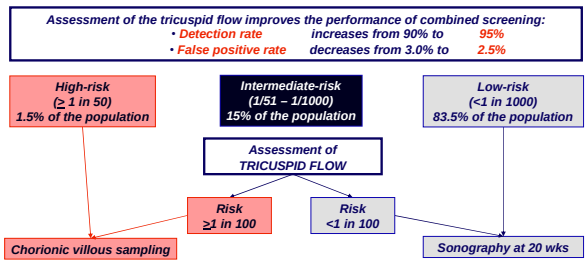
Risk Calculation Algorithms: 2-Stage Adding Ductus Venosus



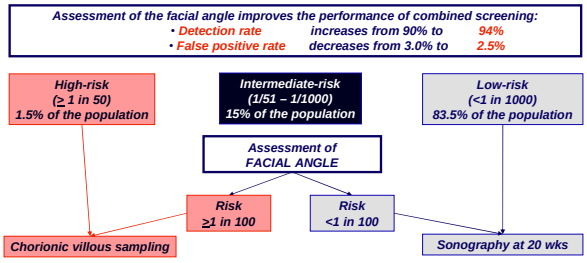
Risk Calculation Algorithms: 2-Stage Adding Nasal Bone



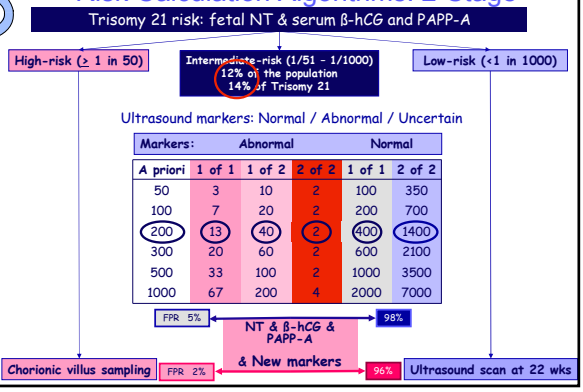
Risk Calculation Algorithms: 2-Stage Adding Tricuspid Flow



Risk Calculation Algorithms: 2-Stage Adding Facial Angles



Risk Calculation Algorithms: 2-Stage



Thank you for the opportunity to address you today!