THE 11-14 WEEK OBSTETRICAL SCAN

Jude P. Crino, M.D.

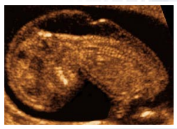
JOHNS HOPKINS MEDICINE
JOHNS HOPKINS HEALTH SYSTEM

ANEUPLOIDY SCREENING AT 11-14 WEEKS

The skin is deficient in elasticity giving the appearance of being too large for the body…….. The face is flat and the nose is small.

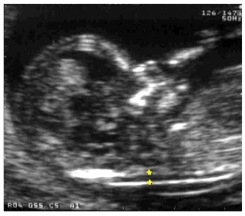
Observations on an ethnic classification of idiots
Langdon Down 1866

Langdon Down 1828-1896



Courtesy Kypros Nicolaides, M.D.

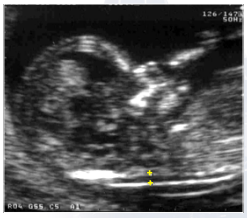
FIRST TRIMESTER NUCHAL TRANSLUCENCY



SECOND TRIMESTER NUCHAL FOLD

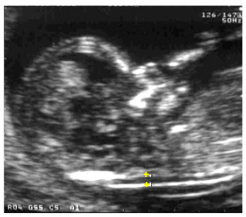
NUCHAL TRANSLUCENCY

- First trimester correlate of nuchal fold
- Specific measurement technique
- Standardized training
- Quality assurance



Training and quality assurance in the 11-14 weeks scan

Measurement of nuchal translucency

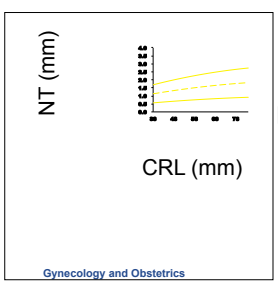


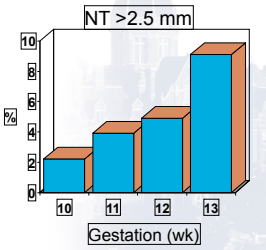
- *Gestation 11-14 wks*
- *Crown-rump length 45-84 mm*
- *Mid-sagittal view*
- *Image size: head and thorax*
- *Neutral position*
- *Away from amnion*
- *Maximum lucency*
- *Callipers on-to-on*

NUCHAL TRANSLUCENCY CUTOFF VALUES

- NT increases w/ gestational age
  - 17% per week
- If single cutoff used false pos rate increases w/ advancing gest age

NUCHAL TRANSLUCENCY AND GESTATIONAL AGE



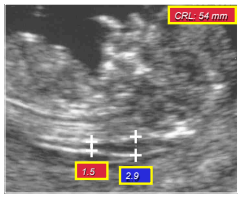


CONVERSION OF NT TO DOWN SYNDROME RISK

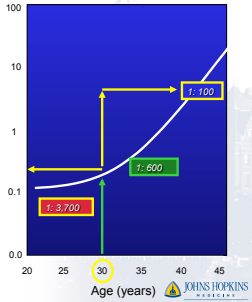
- NT measurement is compared to expected normal median value for crown-rump length or gest age
- The deviation in fetal NT from the expected value is converted into a likelihood ratio
  - delta value method – based upon difference in mm from normal regressed median for CRL
  - MoM-Gaussian method – uses multiples of the expected median (MoM) for gest age
- Risk for trisomy 21 = *a priori* maternal age and gestation-related risk X likelihood ratio

Risk (%)

Calliper placement



Which is the correct measurement?



Screening for trisomy 21

Effectiveness of different methods of screening

100,000 pregnancies

Trisomy 21 N=200

Method of screening	*DR*	*Detected*
Maternal age	*30%*	*60*
Nuchal translucency (NT) at 12 wks	*75%*	*150*
Quadruple screen at 16 wks	*80%*	*160*
Fetal NT & ß-hCG & PAPP- A at 12 wks	*85%*	*170*

Screen positive 5% N=5,000

Courtesy Kypros Nicolaides, M.D.

FIRST TRIMESTER SERUM ANALYTES

	TRISOMY 21	TRISOMY 18
PAPP-A	↓	↓
BETA HCG	↑	↓
INHIBIN A	↑	↔

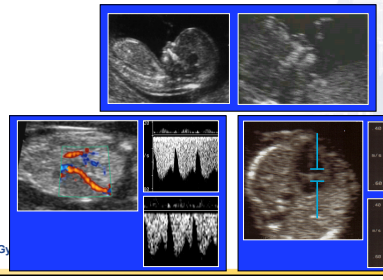
STRATEGIES TO IMPROVE TEST PERFORMANCE
↑ detection, ↓ false pos rate

- First trimester contingent screening using additional sonographic markers
- Combining 1st and 2nd trimester tests
  - integrated
  - sequential

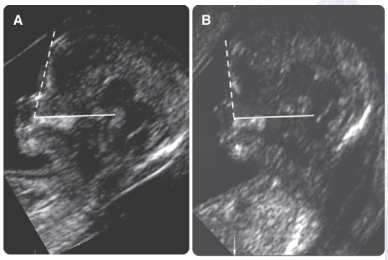
Screening for trisomy 21

Additional sonographic markers at 11-13+6 wks

	Trisomy	Normal
Absent NB	60-70%	2%
Abnormal ductus	70-80%	5%
Tricuspid regurgitation	70%	7%



FRONTOMAXILLARY FACIAL ANGLE



Ultrasound images of facial angle in **A**, a euploid fetus and **B**, 1 with trisomy 21.

 AJOG 2007;196:271.e1

SCREENING FOR ANEUPLOIDY OTHER THAN TRISOMY 21

	Free ß-hCG	PAPP-A	Increased NT	Crown-rump length	Fetal heart rate	Ultrasound markers
Trisomy 18	↓	↓	75%	↓	↓	Omphalocele Single umb. artery
Trisomy 13	↓	↓	72%	↔	↑	Megacystis Holoprosencephaly
Turner's	↔	↔	87%	↔	↑	
Triploidy	↓↓/↑↑	↓↓/↔	59%	↓	↓	Small / molar placenta

 Courtesy Kypros Nicolaides, M.D.

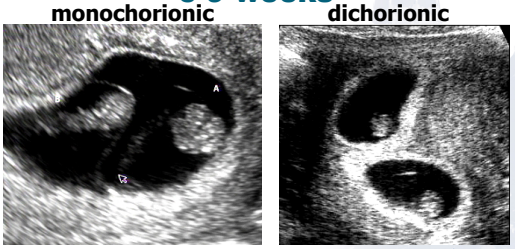
ADDITIONAL BENEFITS OF FIRST TRIMESTER SCREENING

- First trimester dating
- Early diagnosis of multiples and chorionicity
- Early diagnosis of some structural anomalies
- Serum screening for adverse outcomes
- Screening for congenital heart disease

MULTIPLE GESTATION
Assessment of Chorionicity

6-9 weeks

monochorionic **dichorionic**

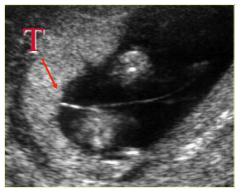


MULTIPLE GESTATION
Assessment of Chorionicity

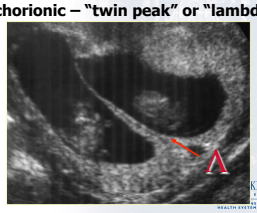
10-14 weeks

- Dividing membrane
  - appearance of base

monochorionic – "T"



dichorionic – "twin peak" or "lambda"



MULTIPLE GESTATION
Assessment of Chorionicity

Frequency of lambda sign in dichorionic pregnancies

	Fused placenta	Separate placenta	Total
N	67	34	101
10-14 weeks	100%	100%	100%
16 weeks	100%	91%	97%
20 weeks	93%	74%	87%

Obstet Gynecol 1999;94:450

Gynecology and Obstetrics

MULTIPLE GESTATION
Assessment of Chorionicity

Ultrasound diagnosis	*Placental pathology*	
	Monochorionic (n)	*Dichorionic (n)*
Monochorionic		
At < 14 weeks	21	1
At ≥ 14 weeks	10	3
Total	31	4
Dichorionic		
At < 14 weeks	0	74
At ≥ 14 weeks	3	26
Total	3	100

Ultrasound Obstet Gynecol 2002;19:350

Gynecology and Obstetrics

The 11-14 weeks scan

Increased NT – Normal karyotype

Courtesy Kypros Nicolaides, M.D.

Gynecology and Obstetrics

OUTCOME OF INCREASED NUCHAL TRANSLUCENCY

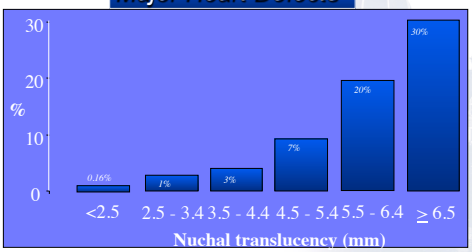
Nuchal translucency	Chromosomal Defects	Fetal death	Major fetal abnormalities	Alive and well
<95th centile	0.2%	1.3%	1.6%	97%
95th-99th centiles	3.7%	1.3%	2.5%	93%
3.5-4.4 mm	21.1%	2.7%	10.0%	70%
4.5-5.4 mm	33.3%	3.4%	18.5%	50%
5.5-6.4 mm	50.5%	10.1%	24.2%	30%
≥6.5 mm	64.5%	19.0%	46.2%	15%

Snijders et al 1998; Souka et al 1998; 2001; Michailidis & Economides 2001

Gynecology and Obstetrics

OUTCOME OF INCREASED NUCHAL TRANSLUCENCY

Major Heart Defects



Gynecology and Obstetrics

INCREASED NT NORMAL KARYOTYPE

- Craniosynostosis
- Iniencephaly
- Agnathia/micrognathia
- Cardiac defects
- Diaphragmatic hernia
- Omphalocele
- Megacystis
- Renal agenesis
- Polycystic kidneys
- Multicystic kidneys
- Nephrotic syndrome
- Body stalk anomaly
- Congenital lymphedema

- Beckwith-Wiedemann syndrome
- GM1-gangliosidosis
- Mucopolysaccharidosis type VII
- Smith-Lemli-Opitz syndrome
- Vitamin D resistant rickets
- Zellweger syndrome

- Brachmann-de Lange syndrome
- Charge association
- di George syndrome
- EEC syndrome
- Fryn syndrome
- Noonan syndrome
- Perlman syndrome
- Stickler syndrome
- Treacher-Collins syndrome
- Trigonocephaly C syndrome
- VACTERL association

- Achondrogenesis
- Achondroplasia
- Asphyxiating thoracic dystrophy
- Blomstrand osteochondrodysplasia
- Campomelic dysplasia
- Hypophosphatasia
- Jarcho-Levin syndrome
- Nance-Sweeney syndrome
- Osteogenesis imperfecta
- Roberts syndrome
- Short-rib-polydactyly syndrome
- Sirenomelia
- Thanatophoric dysplasia

- Akinesia deformation sequence
- Myotonic dystrophy
- Spinal muscular atrophy

- Blackfan Diamond anaemia
- Dyserythropoietic anaemia
- Thallasemia-α
- Parvovirus B19 infection

Ultrasound Obstet Gynecol 2001;18:9-17

ANATOMICAL SURVEY AT 11-14 WEEKS

The 11-13+6 week anomaly scan

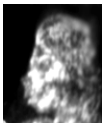
- What are the embryological limitations?
- What abnormalities can be detected?
- What are the sonographic limitations?
- Develop a protocol for an early anatomic survey

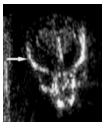
The 11-13+6 week anomaly scan

CNS views

The 11-13+6 week anomaly scan

Acrania / anencephaly





47 cases, prevalence 1 / 1,200
First 31 8 missed
Last 16 0 missed

In the first trimester the brain may appear normal!

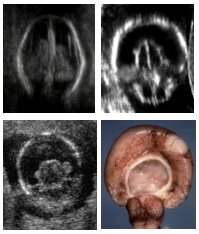
Onset of ossification of the skull 11 wks

Johnson et al 1996

Acrania / anencephaly

The 11-13+6 week anomaly scan

Holoprosencephaly



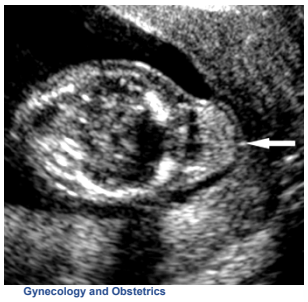
26 cases, prevalence 1 / 3,500

	Prevalence	T13
12 wks	1 : 3,500	65%
20 wks	1 : ~ 7,000	40%
Birth	1 : ~10,000	?

Encephalocele

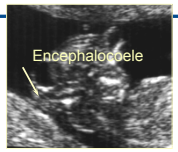
- Seen after 10 weeks
- Bony defect

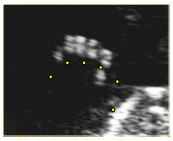
Encephalocele



- 75% occipital
- 25% frontal or parietal

Meckel Gruber Syndrome





- AR lethal disorder
- polydactyly
- echogenic kidneys

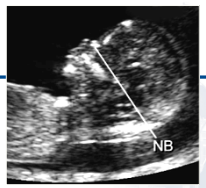
Low risk group: 1 in 20,000

High risk group:
Recurrence 2/6
None missed

Sepulveda et al 1996

Face

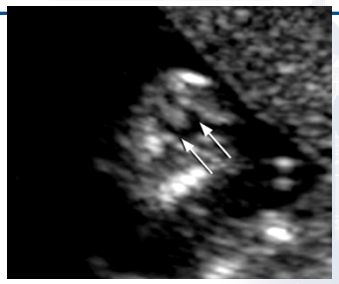
- Profile
- Nasal bone
- Orbits



Face

- Maxilla
- Mandible

Bilateral cleft lip



Spine

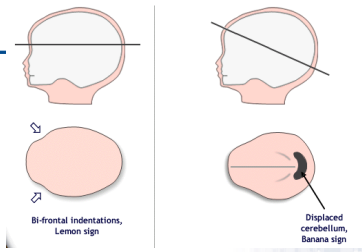
- Vertebrae: neck to pelvis
- Skin intact

Spina bifida

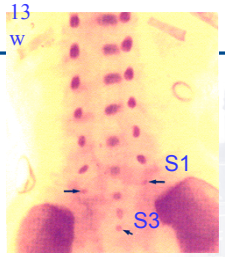
29 cases in 61,972 singleton pregnancies
Prevalence of 1 / 2,000
None diagnosed in first trimester
Increased NT in 1 of 29 cases

High risk group:
Lemon sign: 3 of 3

Sebire et al 1997

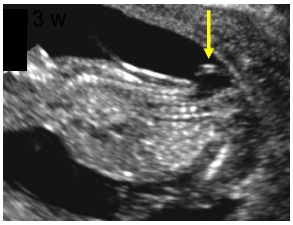


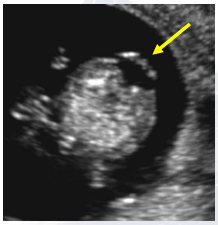
Cranial signs not fully evaluated in 1st trimester



Cannot rule out spina bifida in lumbosacral region before 18 w

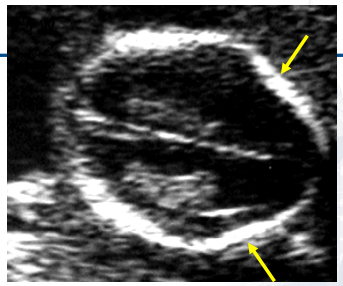
Lumbosacral meningocele





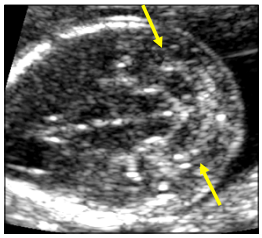
Sagittal

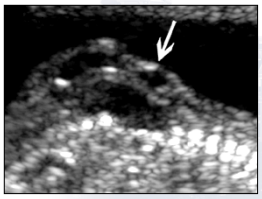
Axial



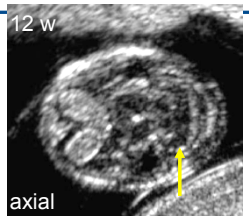
Lemon sign

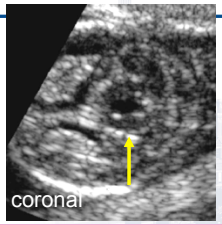
Chiari II malformation
Banana sign & meningomyelocele





Posterior fossa

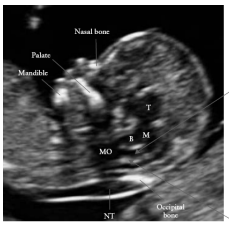


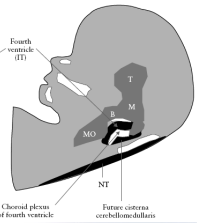


Cerebellar vermis may not close over 4th ventricle until 18 w

Intracranial translucency

Normal

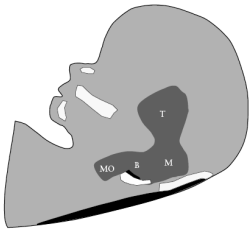




Ultrasound Obstet Gynecol 2009;34:249

Intracranial translucency

Spina bifida



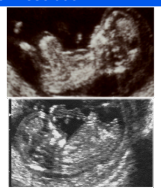
Ultrasound Obstet Gynecol 2009;34:249

The 11-13+6 weeks scan

Omphalocele

Physiological Omphalocele

8 wks Onset of herniation
10 wks Herniation in all cases
11 wks Resolution



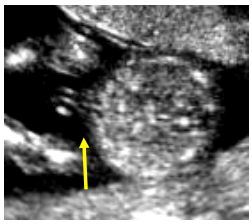
Midline defect with bowel herniation into the base of the cord

Prevalence: 1 / 4,000 births
Cause: Sporadic

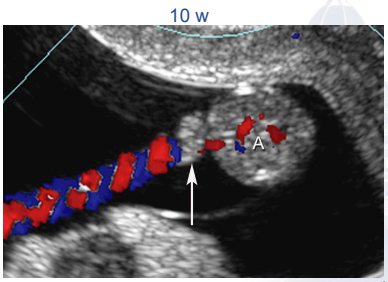
Other defects: Trisomies 18 &13
Beckwith syndrome

Treatment: Surgical
Prognosis: 80% survival

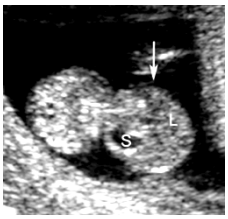
Normal cord insertion



Physiologic midgut herniation



Omphalocele



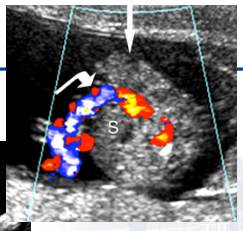
Diagnosed when:
CRL > 45 mm
Mass > 7mm
Contains Liver/stomach

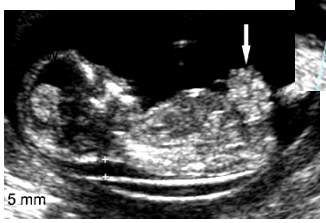
Gastroschisis

Birth prevalence 1 : 5,000

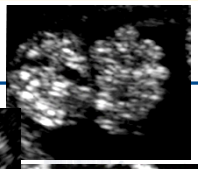
- Sporadic
- Not associated with aneuploidy
- Very few diagnosed in 1st trimester

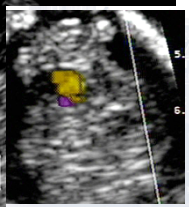
Gastroschisis





Gastroschisis





Body Stalk Anomaly

Birth prevalence 1 : 14,000
Sporadic, lethal

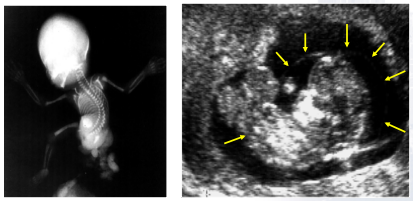
- Major abdominal wall defect
- Short cord
- Kyphoscoliosis

- Early amnion rupture
- Many present with increased NT

Daskalakis et al 1997

The 11-13^{+6} weeks scan

Body stalk defect /
Amniotic band syndrome



Diaphragmatic Hernia

Birth prevalence 1 : 4,000

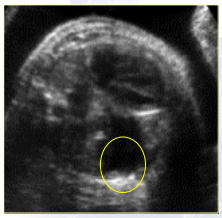
- Development completed by 9 weeks
- Intrathoracic herniation of abdominal viscera may occur when gut returns to abdomen at 10-12 weeks
- May be delayed until 2nd or 3rd trimester

Diaphragmatic Hernia

Bowel in chest, mediastinal shift, pleural effusion, polyhydramnios

Isolated hernia	50%
Chromosomal defects	20%
Other abnormalities	30%

Survival of isolated 50%



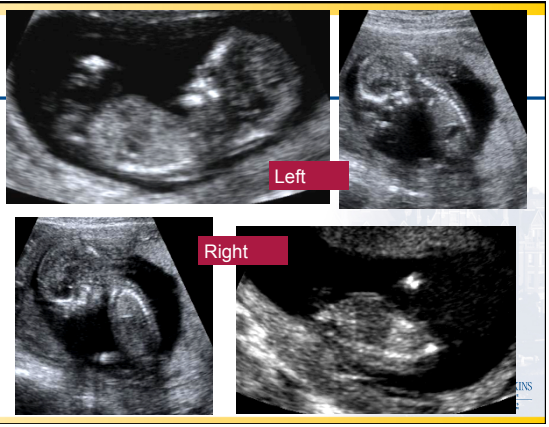
Diaphragmatic Hernia

19 cases
1 / 4,000

NT>95th 7 of 19

5 of 6 NND

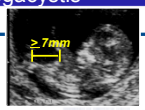
Sebire et al 1997

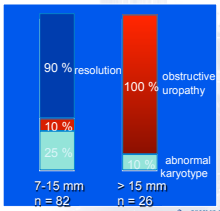


The 11-13+6 weeks scan

Normal bladder

Megacystis





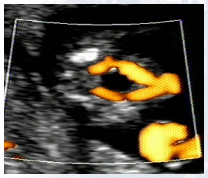
10 wks: visible in 50%

11 wks: visible in 98%

12 wks: visible in all

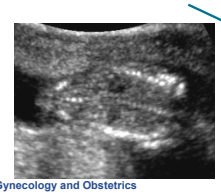
Liao et al 2003

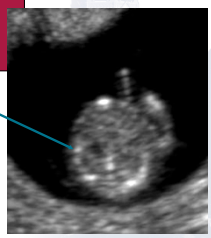
Normal bladder



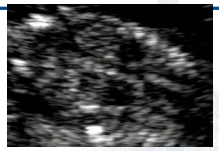
Kidneys

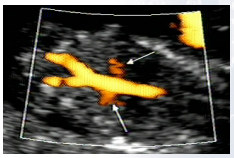
- Visible in all by 12 weeks
- May appear echogenic
- Look for rim of fat





Kidneys



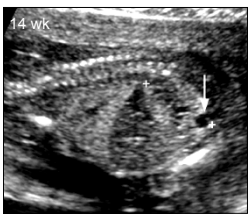


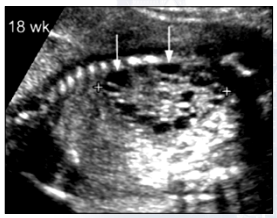
Renal Agenesis

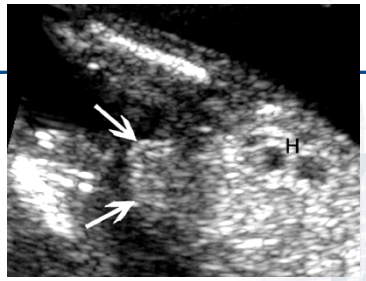
Birth prevalence 1 : 4000

- Absence of kidneys
- Absence of bladder
- 1st trimester - normal fluid

Multicystic dysplastic kidney

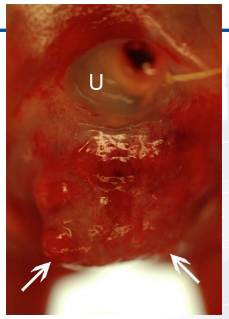




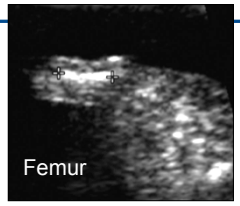


No bladder seen
Irregular mass lower anterior abdominal wall

Cloacal exstrophy



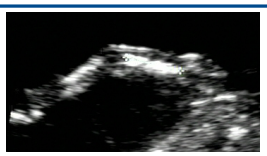
FETAL SKELETON

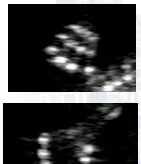


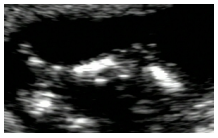
10 wk: Ossification centers of long bones seen
11 wk: Long bones measured with accuracy
Limb movements readily seen

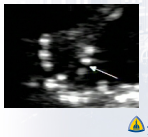
Extremities

- 4 limbs
- Movements

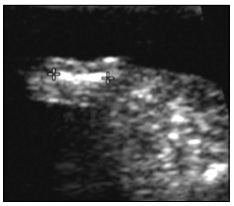


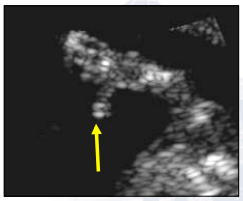






Lethal skeletal dysplasia

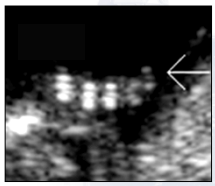




Short femur Hitch-hiker thumb

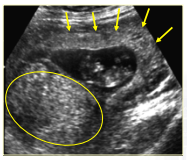
Diastrophic dysplasia

Club foot & polydactyly



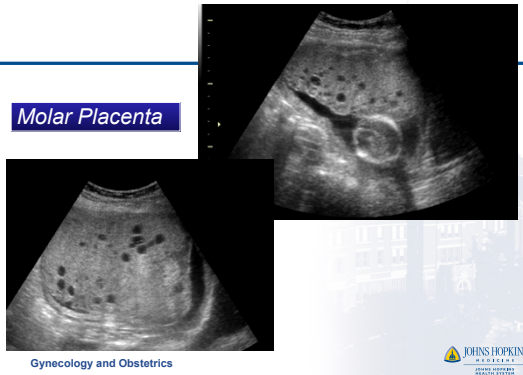
The 11-13^{+6} weeks scan

Molar Placenta (1 in 2,500)



- Complete mole / normal twin
- Partial mole
- Mesenchymal dysplasia

Molar Placenta

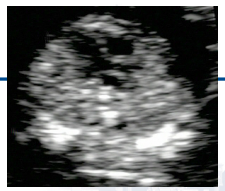


Successful examination of fetal anatomy at 11-13^{+6} weeks

Transabdominal and / or transvaginal scan

CRL (mm)	n	Head/ Brain	Face	Spine	Heart	Abdomen	Stomach	Kidneys	Bladder	Extremities
45-54	174	100%	98%	99%	25%	100%	95%	71%	98%	100%
55-64	400	100%	99%	99%	46%	100%	99%	85%	99%	100%
65-74	413	100%	99%	100%	58%	100%	100%	94%	100%	100%
75-84	157	100%	100%	100%	67%	100%	100%	96%	100%	100%
Total	1,144	100%	99%	99%	50%	100%	99%	88%	99%	100%

Souka et al 2004



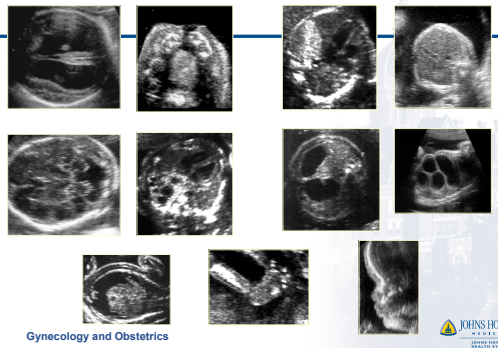
The 11-13^{+6} weeks scan

Screening for structural defects

Author	N	Anomalies	Prenatal diagnosis	
			Total	11-13^{+6} weeks
Hernandi and Torocsik, 1997	3,991	40	30 (75.0%)	11 (27.5%)
Economides et al, 1998	1,632	13	10 (76.9%)	7 (53.8%)
Carvalho et al, 2002	2,853	66	52 (78.8%)	25 (37.8%)
Total	**8,476**	**119**	**92 (77.3%)**	**43 (36.1%)**

Head	Acrania, encephalocele, holoprosencephaly, ventriculomegaly
Spine	Spina bifida, kyphoscoliosis
Thorax	Lungs: CDH, CCAM, sequestration; heart defects
Abdomen	Omphalocele, gastroschisis, GI obstruction, renal defects
Extremities	Skeletal dysplasias, amputations, arthrogryposis

What anomalies do we miss?



11-14 WEEK SONOGRAM SUGGESTED GUIDELINES

- Crown-rump length
- Heart rate
- Nuchal translucency
- BPD level
- Profile
- TRV chest at heart
- TRV abdomen
- Abdominal CI
- Stomach
- Bladder
- Sag/ coronal spine
- Four extremities
- Hands
- Feet

The future…

FUTURE DIRECTIONS

- Integrating first trimester screening and cfDNA in aneuploidy screening strategies
- First trimester preeclampsia screening

CELL FREE DNA

CELL FREE DNA TERMINOLOGY

- NIDT – noninvasive DNA testing
- NIPD – noninvasive prenatal diagnosis (Y chromosome specific sequences, RHD)
- NIPT – noninvasive prenatal testing
- NIPS – noninvasive prenatal screening

SOURCES OF FETAL DNA IN MATERNAL BLOOD

- Fetal cells
  - 1 in 1 billion of total cell population
  - Require isolation via mechanical and/or biochemical means
- Cell free DNA (cfDNA)
  - Maternal blood contains both maternal and fetal cfDNA
  - 2-20% of total cfDNA is fetal

CELL FREE DNA

- Released through apoptosis
  - Fetal cfDNA likely arises from cytotrophoblast cells of placenta
- Released into bloodstream as small DNA fragments (140-200 bp)
- Reliably detected after 7 weeks of gestation
- Undetectable within hours postpartum

TEST COMPARISON

	verifi® Verinata	Harmony Ariosa	MaterniT21 Sequenom	NIPT Natera
Result Types	•Aneuploidy Detected •Aneuploidy Suspected •No Aneuploidy Detected	**Risk score** incorporating maternal, gestational age	•Positive •Negative	**Risk score** incorporating maternal, gestational age
Assay Failure Rate	**<0.7%**	4.6 – 4.9%	1%	5.9 – 12.6%
Sample	**1 tube** maternal blood	2 tubes maternal blood	2 tubes maternal blood	2-4 tubes maternal blood (best with paternal sample)
Egg Donors	Yes (with data)	No	Yes	No
Test Menu	T21, T18, T13 Optional sex chromosome aneuploidies (Published data)	T21, T18, T13 Y chromosome (optional)(not published)	T21, T18, T13 Mandatory sex chromosome aneuploidies (not published)	T21, T18, T13 Sex chromosome aneuploidies (only MX published)
Published Clinical Validation	Large-scale, blinded clinical validation	Large-scale, blinded clinical validation	Large-scale, blinded clinical validation	Small, blinded clinical validation

TEST COMPARISON SENSITIVITY

	T21	T18	T13
Ariosa	>99	>98	80
Natera	>99	>99	>99
Sequenom	99.1	>99.9	91.7
Verinata	>99.9	97.4	87.5

POSITIVE SCREENING TEST FETAL KARYOTPE

Detectable by NIPT	
Trisomy 21	1592 (53.2)
Trisomy 18	511 (17.1)
Trisomy 13	139 (4.6)
Sex chromosome aneuploidy	247 (8.3)
Total	2489 (83.2)

POSITIVE SCREENING TEST FETAL KARYOTPE

Not Detectable by NIPT	
Mosaicism	186 (6.2)
Other trisomy	92 (3.1)
Insertion/Deletion	88 (2.9)
Structural abnormality	100 (3.3)
Balanced rearrangement	97 (3.2)
Unbalanced rearrangement	3 (0.1)
Triploidy	29 (1)
Marker	9 (0.3)
Total	504 (16.8)

FTS AND cfDNA SCREENING STRATEGIES

Table I. Comparison of the different strategies of screening in a population of 10,295 pregnant women in Li et al's study.[119]

Strategy	Total cost of screening over 6 years (S$) (a)	No. of screened positive cases (b)	Cost of CVS/ amniocentesis for screened positive cases (S$) (c)	Total costs = (a) + (c)	No. of T21/T18/ T13 cases detected	Average cost per patient (S$)
FTS for all	3,088,500	288	432,000	3,520,500	43	342
NIPT for all	10,295,000	49 + 31 = 80	120,000	10,415,000	49	1,011
FTS for all and NIPT for patients with risk of 1:101 to 1:1,000	3,088,500 + 666,000 = 3,921,500	167 + 13 = 180	270,000	4,191,500	47	407

Assumptions for NIPT: there is 100% detection rate for T21, T18 and T13, with a 0.3% false positive rate; cost is S$300 per combined FTS, S$1,000 per NIPT and S$1,500 per CVS or amniocentesis. CVS: chorionic villus sampling; FTS: first trimester screening; NIPT: noninvasive prenatal testing; T: trisomy

Gynecology and Obstetrics

Singapore Med J 2015;56:1

CONTINGENT cfDNA ON COMBINED FTS IN THE UK

- Initial combined FTS
- High risk result (≥ 1:100) offered CVS, cfDNA, or no further testing
- Intermediate risk result (1:101-1:2500) offered cf DNA or no further testing
- Low risk result (< 1:2500) not offered additional testing

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Ultrasound Obstet Gynecol 2016;47:45

CONTINGENT cfDNA ON COMBINED FTS IN THE UK

- Overall detection rates
  - 91.5% trisomy 21
  - 100% trisomy 18
- FTS detection rate (FPR 3.4%)
  - 87% trisomy 21
  - 93% trisomy 18
- cfDNA detection rate (FPR 0.25%)
  - 98% trisomy 21
  - 82% trisomy 18

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CONTINGENT cfDNA ON COMBINED FTS IN THE UK

- 43% reduction in rate of invasive testing
- 74.4% trisomy 21 termination rate
  - 92.6% who chose invasive testing
  - 35.7% who chose cfDNA
- 31.9% trisomy 21 live birth rate
- Prenatal detection of trisomies depends upon test performance and patient choice

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FIRST TRIMESTER PREECLAMPSIA SCREENING

Table 1. Estimated detection rates of all preeclampsia and preeclampsia requiring delivery before 37 and 34 weeks gestation, at false-positive rates of 5 and 10%.

Screening test	FPR (%)	Detection rate, % (95% CI)		
		PE <34 weeks	PE <37 weeks	All PE
Maternal characteristics plus	5	42 (33–51)	36 (30–42)	30 (27–33)
	10	58 (49–67)	50 (44–56)	41 (38–44)
Ut-PI	5	57 (47–66)	46 (40–53)	33 (30–36)
	10	70 (61–78)	59 (53–65)	44 (41–47)
MAP	5	49 (40–58)	45 (39–52)	35 (31–37)
	10	65 (56–73)	60 (54–66)	48 (45–51)
PAPP-A	5	48 (38–57)	42 (36–48)	31 (28–34)
	10	60 (51–69)	55 (49–61)	44 (40–47)
PlGF	5	57 (48–66)	50 (44–56)	35 (32–38)
	10	73 (64–81)	66 (60–72)	47 (43–50)
MAP and Ut-PI	5	63 (54–72)	53 (47–59)	38 (35–41)
	10	80 (71–86)	70 (65–76)	52 (49–55)
PAPP-A and PlGF	5	57 (48–66)	49 (43–56)	33 (30–36)
	10	77 (69–84)	67 (61–73)	48 (45–51)
Ut-PI, MAP and PAPP-A	5	67 (58–75)	56 (50–62)	38 (34–40)
	10	80 (71–86)	68 (62–74)	52 (48–55)
Ut-PI, MAP and PlGF	5	80 (72–87)	66 (60–72)	42 (38–45)
	10	89 (81–94)	77 (71–82)	54 (51–57)
Ut-PI, MAP, PAPP-A and PlGF	5	76 (68–83)	63 (57–69)	40 (36–43)
	10	88 (81–93)	75 (69–80)	54 (50–56)

FPR: False-positive rate; MAP: Mean arterial pressure; PE: Preeclampsia; Ut-PI: Uterine artery pulsatility index.

Gynecology and Obstetrics

Womens Health 2016;12:199

THANK YOU

JOHNS HOPKINS MEDICINE
JOHNS HOPKINS HEALTH SYSTEM