My Top Five
11-14 weeks

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Disclosure of Commercial Interest - None
My Top Five

Why Does it Have to Change?

Keeping up with the Neighbours

#@** Did I Really Miss That?

Too Much

Sex Matters!
My Top Five

Why Does it Have to Change?  →  Early Anatomy?
Shift in Thinking

- 11-14 wk NT screen TAS
- 11-14 wk anatomy TAS/TV US
- 14-16 wk anatomy TAS/TV US
- 18-22 week TAS/TV US

Anatomic Evaluation Anytime
Rapid Shift into 1st Trimester
Early Anatomic Scan (EAS)

- See Patients Earlier
  - Guidelines require offer combined MSS / NT

- Transvaginal Ultrasound
  - High acceptance/familiarity by patient/physician

- Desire avoid late termination
  - > physical & psychological morbidity
Detailed early anatomy by TVUS - To Whom?

- Offer those at most risk in current pregnancy
  - Increased NT or abnormality at 11-14 wk TAS
  - Maternal Indications:
    - Known inherited or recurrent conditions
    - Maternal exposures or disease with fetal risk
    - ? High BMI patients
      - Decreased DR but increased incidence congen anomalies
Effects EAS by TVS?

- Increased cost to health care system
  - Instigate additional interim examinations (FP & FN)
  - Still perform routine 18-22 wk

- Require different expertise
  - Learning curve – embryology, new & restriction planes

- Safety Concerns (Power output in mW/s SPTA)
  - $2D/3D \rightarrow 73 \, M \, mode \rightarrow 234 \, CDS \rightarrow 1140$ for pulsed spectral Doppler

- Bypass the “natural selection process”
<table>
<thead>
<tr>
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<th>Risk Fetal Death (%)</th>
<th>Risk Aneuploidy After 12 wks</th>
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<td><strong>T21</strong></td>
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*Nicolaides Prenatal Diagnosis Jan 2011*
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- **Women > 35 years**
  - 20% pregnant women
  - Burden 50% all T21

_Nicolaides Prenatal Diagnosis Jan 2011_
1st compared with 2nd trimester survey

- **Largest prospective trial**
  - Randomized 39,572 women
  - Either 12–14 weeks or 15–22 weeks of gestation.
    - conducted in Sweden 1999 – 2002
    - Unselected population

- **Results: DR major malformations**
  - 38% early anatomic survey
  - 47% later anatomic survey (P=.06).
  - Rescans 22% in early group vs 5% later group

- **Conclusion: No DR advantage but termination earlier**
  : Most lethal malformation detected < 15 weeks

Guidelines
Evolution

- **AIUM**: If the TAS is not definitive do TVS

- **ISUOG**: Purpose of the first trimester fetal US includes not only dating... ..... but to detect gross fetal malformations
My Top Five

Why Early Anatomy?

Keeping up with the Neighbors

The 11-14 wk NT, NB, IT....
11-13 wk +6 day NT: Technique

- **CRL 45-84mm**
- **Zoom**
  - Fetal head/thorax occupy whole screen
  - Largest measurement
- **Midsagittal view face**
- **Neutral position**
- **Away from amnion**

Place calipers inner to inner
### Performance of different methods of screening for trisomy 21

<table>
<thead>
<tr>
<th>Method of screening</th>
<th>DR(%)</th>
<th>FPR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>First trimester</td>
<td></td>
<td></td>
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<tr>
<td>MA + fetal NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA + serum free β-hCG and PAPP-A</td>
<td>60–70</td>
<td>5</td>
</tr>
<tr>
<td>MA + NT + free β-hCG and PAPP-A (combined test)</td>
<td>85–95</td>
<td>5</td>
</tr>
<tr>
<td>Combined test + nasal bone or tricuspid flow or ductus venosus flow</td>
<td>93–96</td>
<td>2.5</td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA + serum AFP, hCG (double test)</td>
<td>55–60</td>
<td>5</td>
</tr>
<tr>
<td>MA + serum AFP, free β-hCG (double test)</td>
<td>60–65</td>
<td>5</td>
</tr>
<tr>
<td>MA + serum AFP, hCG, uE3 (triple test)</td>
<td>60–65</td>
<td>5</td>
</tr>
<tr>
<td>MA + serum AFP, free β-hCG, uE3 (triple test)</td>
<td>65–70</td>
<td>5</td>
</tr>
<tr>
<td>MA + serum AFP, hCG, uE3, inhibin A (quadruple test)</td>
<td>65–70</td>
<td>5</td>
</tr>
<tr>
<td>MA + serum AFP, free β-hCG, uE3, inhibin A (quadruple test)</td>
<td>70–75</td>
<td>5</td>
</tr>
<tr>
<td>MA + NT + PAPP-A (11–13 weeks) + quadruple test</td>
<td>90–94</td>
<td>5</td>
</tr>
</tbody>
</table>

MA, maternal age; NT, nuchal translucency; β-hCG, β-human chorionic gonadotrophin; PAPP-A, pregnancy-associated plasma protein-A.

*Prenatal Diagnosis 2011;7-15. Nicolaides*
Primary Purpose of the 11-14 week NT

- Determine fetal aneuploidy risk
- But also,
  - Determine accurate dating for serum biochemistry.
  - Determine early pregnancy loss.
  - Establish chorionicity.
  - Determine anatomic abnormalities.
11-14 wk NT evaluation
Screen for Fetal Aneuploidy Risk – Not Diagnostic

85% DR T21 with a FPR 5%

- 85/100 of the targeted abnormality detected
- 5/100 of normal pregnancies receive FP result
- Positive results NOT mean abnormality but increased risk.
11-14 wk NT evaluation

- Absolute Values
  - 3mm (95th ile)
  - 3.5-4mn (99th ile)

- GA dependant: Normal increase NT value as increase GA
- Into formulas with MA, MSS...
Increased NT – Normal karyotype

Majority normal outcome

Normal NT

Increased NT

Images Courtesy FMF - Fetal Medicine Foundation
Increased NT & Normal karyotype

- But, ~37% adverse outcome
  - 22% structural (prenatal DR 84%)
    - ~all missed cardiac, consider echocardiogram

- Neurodevelopmental delay (NND)
  - Most studies indicate risk ~ general population (1-2%) but some evidence bigger & persistent > risk NND
    - Risk NND with an NT < 4.5mm 25% vs > 6.5mm 81%
    - Persistent risk ~10% vs 5% if resolves

**Mula et al. Increased NT and normal karyotype: perinatal and pediatric outcomes at 2 years of age. UOG 2012:39;34-41.**

*A. Sotiradis et al. UOG 2012:39;10-19*
Distinguish: **Cystic Hygroma**
*(Fluid accumulation extend beyond NT region)*

<table>
<thead>
<tr>
<th>50% Aneuploidy</th>
<th>50% Euploid</th>
</tr>
</thead>
<tbody>
<tr>
<td>T21, T18 &gt; XO</td>
<td></td>
</tr>
<tr>
<td>XO - 90% have cystic hygroma</td>
<td>50% major structural abnormality</td>
</tr>
<tr>
<td>50% are cardiac</td>
<td></td>
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</tbody>
</table>

- **Distinguish : Hydrops Fetalis**
  - Fluid ≥ 2 areas *Subcutaneous edema, pleural fluid, ascites*
  - Cardiac – A wave reversal DV, TR

* * Wald et al. NEJM 1992*
My Top Five

- Why Early Anatomy?
- Keeping up with the Neighbors
- The 11-14 wk NT, NB, IT...
Nasal Bone – Modern Equipment
= sign between tip nose and frontal bone

<table>
<thead>
<tr>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="2015-03-02.png" alt="Image" /></td>
<td><img src="2015-03-02.png" alt="Image" /></td>
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</tbody>
</table>
Nasal Bone (NB) – First Trimester
Independent variable

- Risk aneuploidy
  - Decrease if NB present (3X)
  - Increase if NB absent
    - BUT only after 12 weeks/65mm

<table>
<thead>
<tr>
<th>Absent NB</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euploid</td>
<td>1.5</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.5</td>
</tr>
<tr>
<td>Afro-Caribbeans</td>
<td>8.8</td>
</tr>
<tr>
<td>Orientals</td>
<td>12.5</td>
</tr>
<tr>
<td>T21</td>
<td>65-75</td>
</tr>
</tbody>
</table>

UOG 2003 JD Sonek Nicolaides et al 2003
My Top Five

Why Early Anatomy?

Keeping up with the Neighbors

The 11-14 wk NT, NB, IT....
Why IT with NT?
Intracranial translucency (4th V) with NT

- NT @ 11-14 wks
  - Single most effective marker T21 & major aneuploidy
    - Combined with MA, MSS, NB will ID > 95% major aneuploidy for FPR < 3%

- But Spina Bifida remains challenging
Why IT?

- Most open SB associated with ACM
  - CSF leakage…. Hypotension SAS…. Caudal displacement BS…obliterate CM…..loss IT/4\textsuperscript{th}V
  - Incidence 1/2000
  - IT (become 4\textsuperscript{th}V) still connected to CM

- Problem
  - High NPV if IT visualized but low sensitivity if not visualized, actually technically difficult to obtain
  - Low sensitivity (50%)

**Fong et al UOG 2011; Nicolaides et al UOG 2009**
Intracranial Translucency or 4th Ventricle

- Slightly parasagittal to NT
- Border by 2 echogenic lines between brainstem & CP
- Usually visible
- 1.5-2.5 mm

Chaouli, Nicolaides UOG Feb 2010
Brainstem: Brainstem-Occipital Bone Ratio

*Technique needs validation*

Normal < ratio 0.9  
Abnormal ratio ≥ 1

Image Courtesy Chaoui 2011 UOG
These posterior fossa measurements are challenging & require high degree expertise

Recently, demonstrated BPD < 5\textsuperscript{th} percentile is associated with open SB (LR 10-11x)

- Simple measurement
  - 29/34,951 scans 11-14 with NTD
    - 18 SB; 10 anencephaly, 1 encephalocele
  - The area under the ROC curve for spina bifida aperta was 0.72, with an LR+ of 10.9 and an LR− of 0.48.
  - 50\% of cases of spina bifida aperta had a BPD of less than the fifth percentile compared to 5\% in controls.
    - The positive LR is then 50/5\% or 10,

- Background:
  - 1500 babies born with SB annually USA
  - ~1000 less than prior folic acid fortification

Bernard et al. AJOG 2013
Lots of work going on but direct visualization?

9 wks GA
- 2D Sagittal - cystic protrusion lumbar spine
- 3D sagittal image demonstrates dilation of neural tube elements.

6-12 mHZ - 256 element 3D/4D TV Voluson E8

My Top Five

Why Early Anatomy?

The 11-14 wk NT, NB, IT....

#@** Did I Really Miss That?  →  DO NOT MISS LESIONS
# 11-14 weeks – 3 Major Groups

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<tr>
<th>Always Detect</th>
<th>Potentially Detect</th>
<th>Undetectable</th>
</tr>
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<tbody>
<tr>
<td><strong>Anencephaly</strong></td>
<td>Cardiac</td>
<td>Microcephaly (&gt;30wks)</td>
</tr>
<tr>
<td><strong>Alobar Holosprosencephaly</strong></td>
<td>Skeletal Dysplasias</td>
<td>ACC (&gt; 14-19 wks)</td>
</tr>
<tr>
<td><strong>Body Stalk Anomaly</strong></td>
<td>Limb amputations</td>
<td>VM (infection, hem)</td>
</tr>
<tr>
<td><strong>Exomphalos</strong></td>
<td>Open NTD</td>
<td>Fetal Tumors</td>
</tr>
<tr>
<td><strong>Gastrochisis</strong></td>
<td>Renal agenesis</td>
<td>Hydronephrosis (VUR)</td>
</tr>
<tr>
<td><strong>Megacystis</strong></td>
<td>Facial clefts</td>
<td>Echogenic lung lesions &gt; 16 wks</td>
</tr>
<tr>
<td></td>
<td>Diaphragmatic hernias</td>
<td>Duodenal/Small bowel atresias (&gt; 20wks)</td>
</tr>
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> 45,000 11-14 wk Scans

Prenatal Diagnosis 2011 Challenges in diagnosis of Fetal non-chromosomal abnormalities 11-13 wks. Nicolaides
Exencephaly – Anencephaly Sequence

- **Exencephaly** – Defined by acrania/no calvarium
  - Exposed brain mass will degenerate
  - mechanical trauma and injurious environment
  - T1 diagnosis > 10-11 wks when should see ossification

- **Anencephaly**-
  - Commonest NTD 1/1000 births – recurrence risk 1.9%
  - MS AFP elevated, folic acid preventative ~ 70%
Exencephaly

12 weeks
Lack midline structures
Lack cranial vault ossification

11.3 weeks
Alobar Holoprosencephaly

12 weeks

Characteristic Features
- Monoventricle with absent midline structures
- Fusion of the thalami

Additional Features
- Displaced pancake of cortical tissue

Characteristic facial features including
- Hypotelorism, cleft, proboscis
Alobar Holoprosencephaly

Characteristic Features  Monoventricle, absent midline structures, fusion thalami

Additional Features  Dorsal sac, displaced pancake cortical tissue

Common Facial Features  Hypotelorism, single orbit/proboscis, clefts

Diagnose > 10 weeks because no normal midline structures
Failure cleavage of forebrain
Alobar Holoprosencephaly

57, 119 pregnancies
Risk estimates based on MA, NT, hcg and PAPP-A

- 1/1300 prevalence
  - 2/3 aneuploidy (T18, 13) @ 10% risk recurrence
  - 1/3 euploid @ 1% risk recurrence

Thus perform karyotype despite fatal prognosis

- Check for associated genetic conditions
  - Pallister Hall, Smith-Lemli-Opitz, CHARGE

UOG 2010 Mar Nicolaides et al
Midgut Physiological Herniation vs Omphalocele
Both Insert in Base UC

Normal
- < 10mm < 10wks
- Gone by 12 weeks
- Never contain liver or stomach

Omphalocele
- > 10 mm > 10 wks
- Persists > 12 weeks
- Homogeneous & rounder? Liver (CDS)

Cyr et al, Bowerman et al

Liver
Midgut Physiological Herniation vs Omphalocele
Both Insert in Base UC

If unsure
Repeat exam after 12 wks

Cyr et al, Bowerman et al
Omphalocele

Traditional Grim Prognosis T2

- 70-90% anomalies
  - 17% survival (TOP, spont demise)
  - Aneuploidy 90% no liver vs 10% liver herniated into sac

Better Prognosis 11-14 week

- Abnormal NT or anatomy
  - Risk aneuploidy 70-80%
- Normal NT & anatomy
  - ~ 20% resolve by 16 wks, 2/3 if euploid, but additional abnormalities found in 20% @ 16 wks

*Pandya et al 2012 UOG*
Gastroschisis

- No covering membrane
- Free-floating loops bowel risk for chemical peritonitis
  - Obstructions, atresia, dilations
- Typically RHS cord

13 weeks
Gastroschisis

- < age 25, substance abuse
- 0-3% aneuploidy risk
  - Not recommend karyotype
- 5% structural anomalies
- 90% survival if isolated
  - 1/3 issues short gut, hypomotility
    - Protein loosing enteropathies
- Monitor closely T3 risk
- IUGR, IUFD, olig
- Delivery by 37 weeks
11-14 weeks – Always Detect Group

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Megacystis 1st Trimester

- Megacystis define > 7mm sagittal
  - Urine production with bladder being week 12, should see bladder by wk 13 ~ 98%

- Euploid Group
  - 7 – 15 mm - 90% resolve
    - Transient functional neurogenic bladder
      - Delay in SM autonomic innervation
      - Rescan in 2 weeks, consider karyotype
  
  - > 15 mm ~ all progressive obstructive uropathy
Euploid Megacystis - 12 weeks NT Evaluation

**Transient – Resolved spontaneously**

12mm

**Posterior Urethral Valves**

17 mm

Transient – Resolved spontaneously
Keyhole Sign – Dilation posterior urethra

• Highly sensitive but not specific for PUV
  XY = PUV
  XX = urethral atresia

• Differential Diagnosis
  • VUR – transient finding in 1/3 boys
  • Bladder dyssnergy – thick-walled dilated bladder
  • Megacystic-microcolon-hypoperistalsis (XX)
  • BOO (bladder outlet obstruction)
My Top Five

- Why Early Anatomy?
- The 11-14 wk NT, NB, IT....
- DO NOT MISS LESIONS
- Too Many
- Multips +
Multips +

- Twin rates doubles 1980-2009 from 18.9 to 33.2/1000 births

- Twin rates as much as 1/30 pregnancies in some parts USA

National Center for Health Statistics 2012; Dias T. USOG 2011; 38: 530–532
Excluding prematurity, vast majority of twin complications occur in MC group

MC twin pregnancy ~ 1/250 all pregnancies
- 20 - 30% of twin pregnancies
  - PNMR MC is 2x DC and 4x singleton
  - Neurological morbidity 4-5x DC, 25-30x singleton
  - 1/3 MC twin pregnancies will develop complications
    - Acute or chronic TTTS, discordant growth/malformations

Dias T. USOG 2011; M: 530-532
First Trimester Guidelines - Multiples

- Require fetal number, chorionicity, amnionicity

- NT
  - Discordant in DC consider aneuploidy
  - Discordant in MC consider TTTS
Chorionicity...Chorionicity....Chorionicity

Prior to 14 weeks best time determine chorionicity
Still see no comments or incorrect assignment up to 44% in community practice*

Dichorionic: 2 separate GS or placentas. Lambda sign. Thick membrane. Different gender

*Wan et al Prenat Diagn 200; Dias T. BJOG 2010;117:979–984
Ultrasound Evaluation

- Lambda sign 10-14 wks pregnancy indicates DC
  - Later in pregnancy may lose lambda sign, the membrane may be thin despite DC

- ≥ 14 wks:
  - Discordance fetal gender PPV ~ 100% DC but only 55% twins discordant for gender
### Dichorionic

| 2 separate sacs | Thick membrane, \( \lambda \) |

After 10 weeks reliable signs for DC are combo placental number and lambda sign

### Monochorionic

| 2 YS | 2 amnions | Thin membrane & T |

2 amnions
MC But? Amnioncity

- Membrane thin, hard to see, espec prior 8-10 wks
- YS not considered reliable to distinguish MA vs DA
  - 85% MCDA have 2 YS but 15% single YS
  - Rarely MCMA has 2 YS (example below)
- Variable temporal development YS and Amnion

MCMA
Cord Entanglement T1
2 YS were identified

*UOG 2012 Corbett et al
Learning Points – Too Many 😊

- Chorionicity...chorionicity....chorionicity
  - Stratify group MC for closer surveillance
    - If unsure refer to specialist before 14 weeks.
    - YS is not reliable
My Top Five

Why Early Anatomy?

The 11-14 wk NT, NB, IT....

DO NOT MISS LESIONS

Too Many

Sex Matters

Fetal Gender
Boys and Girls are Different?

Male genitalia develop 7-14 weeks
Increased incidence hypospadias in severe early onset UPI (19%)
Boy or Girl?  
The Angle of the Dangle  
12 wks
Boy or Girl?
The Angle of the Dangle
12 weeks GA

Male angle > 30 degrees, anterior directed genital tubercule
Female angle < 30 degrees with caudally directed genital tubercle

Efrat et al UOG 1999
Boy or Girl?
9 weeks GA
Get out there & make happy patients
Does Sex Really Matter Anymore?

- Review literature - 16 reports
  - ~ 100% sensitivity & specificity ≥ 8-10 wks cffDNA
  - ~ 100% sensitivity & specificity ≥ 13 wks US

- Indications:
  - Recessive X-linked disease - male fetuses are affected
  - CAH - female fetuses virilisation external genitalia

- Definitive prenatal diagnosis only by invasive

Why Does it Have to Change?  
Early Anatomy

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Sex Matters!  
Fetal Gender Determination
THANK YOU

phyllis.glanc@sunnybrook.ca