

Objectives

- Review rationale for early fetal anatomic evaluation
- Review factors that affect detection rates
- Review anomalies we should see
- Review anomalies we could see
- Consider First Trimester Sex Determination
- Discuss Other Things: Pre-eclampsia

Anatomic Evaluation Over Time

- NIPT (cffDNA) 10 weeks
- 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

Drivers:

1. See patients earlier (NT, FTS....)
2. High acceptance TVS
3. Desire avoid later terminations



Common Numbers Counsel in DS

- 60 • 2nd trimester anatomy
- 75 • Nuchal translucency scan
- 90 • Combined test (NT, MA, PAPP-A, bHCG)
- 99.5 • Cell free fetal DNA (cffDNA) or NIPT
- 100 • Invasive testing CVS or amniocentesis

- DS commonest aneuploidy, advanced maternal age main risk factor
- Risk miscarriage invasive testing 0.2% (1/500)

Adapted from <https://www.linkedin.com/pulse/common-numbers-have-mind-when-counseling-down-alexandros-sotiadiis>

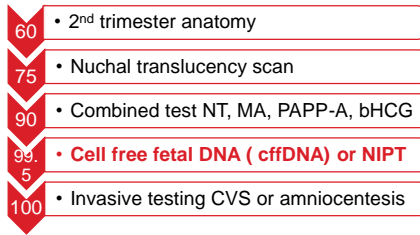
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What is Role of NT scan after NIPT (cffDNA) ?

- Continues to be large variability in actual practice but overall recommend still perform US with NT @ 11-14 wk
 - **ACOG** : NT not necessary however US is useful to confirm viability and # fetuses, assign GA, and identify some major fetal anomalies
 - **ISUOG** : US still offered, NT measured but not the serum tests, look anatomy
 - **SMFM** : NT measured, further research is needed to determine the optimal approach.

Practice Bulletin No. 145: Screening for Fetal Aneuploidy. Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine. Obstet Gynecol. 2014 May; 127(5):e123-37. [DOI: 10.1097/AOG.0000000000000000](#). Statement on the Impact of cffDNA Anomaly Testing on Screening Practice and Practice Bulletin No. 145: Screening for Fetal Aneuploidy. Committee on Practice Bulletins—Obstetrics, Committee on Genetics, and the Society for Maternal-Fetal Medicine Obstet Gynecol. 2016 May; 127(5):e123-37. [DOI: 10.1097/AOG.0000000000000000](#). Statement on the Impact of cffDNA Anomaly Testing on Screening Practice.

US after NIPT? From DS to Anomaly Detection

- Most agree NIPT restrict high+/- intermediate risk after FTS (NT, serum, MA)
- BUT, increasing # pregnant women bypass system directly buy NIPT

Alfirevic, Z., et al. "Women who choose cell-free DNA testing should not be denied first trimester anatomy scan." *BJOG: An International Journal of Obstetrics & Gynaecology* 124.8 (2017): 1159-1161. Syngelaki A, Nicolaides et al Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. *Prenat Diagn* 2011;31:90-102; Karim LJ, Papageorghou AT. Systematic review of first trimester ultrasound screening in detecting fetal structural anomalies and factors affecting screening performance. *UOG* 2016

Role 11-14 wk US after NIPT? From DS to Anomaly Detection

- NIPT diagnose common trisomy's (T21, 18, 13)
- Not diagnose non-chromosomal anomalies (cardiac, anencephaly)
- DR overall > 90% major anomalies
- DR overall 30% low-risk/60% high risk gps
- Enlarged NT with normal NIPT overall 37% adverse outcome, 22% structural
- Bromley 2014 92.3% new detect anomalies in midT2 with normal NT

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What do we Need for Performance Detailed First Trimester Anatomy @ 11-14 wks?

- Standardized protocol
 - Success of NT & mid T 2with standardization
 - France implementation national screen NT 2011-2014 associated with systematic undermeasurement NT, reduction in DS DR 10%
 - Karim et al 2017 demonstrated standardized anatomy protocols 11-14 wks improves sensitivity in both low and high risk groups
- Learning curve: sonoembryology, TV anatomy (limited planes, new planes, restricted planes

Fries, Nicolas, et al. "Impact of a shift in NT measurements on the detection rate of first trimester Down syndrome screening: A population-based study." *Prenatal diagnosis* 36.2 (2016): 106-109. Akarim 2017

Should we provide First Trimester Anatomy Detailed?

Upside	Downside
<ul style="list-style-type: none"> □ Provide early access <ul style="list-style-type: none"> □ Invasive testing, TOP □ Consultations, tertiary care for ongoing pregnancies 	<ul style="list-style-type: none"> □ Not all structures fully developed □ Some anomalies may resolve □ Additional cost <ul style="list-style-type: none"> □ Still perform midT2 scan □ Adding NIPT

Alfirevic, Z., et al. "Women who choose cell-free DNA testing should not be denied first trimester anatomy scan." *BJOG: An International Journal of Obstetrics & Gynaecology* 124.8 (2017): 1159-1161. Syngelaki A, Nicolaides et al Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. *Prenat Diagn* 2011;31:90-102; Karim LJ, Papageorghou AT. Systematic review of first trimester ultrasound screening in detecting fetal structural anomalies and factors affecting screening performance. *UOG* 2016

SOGC: #352-Technical Update 2017: The Role of Early Comprehensive Fetal Anatomy Ultrasound Examination

- Considered in high-risk or potentially challenge at routine evaluation
 - **Anatomic details early fetal anatomy scan is comparable to routine second trimester anatomy scans at 18 to 22 weeks.**
 - The best timing ≥13 weeks' gestation
- **Appropriate training** of the operator required

Nevo O, Brown R, Glanc P, Lim K. No. 352-Technical Update: The Role of Early Comprehensive Fetal Anatomy Ultrasound Examination. JGOC 2017;38(12):1203-11.

Obese Gravida
Special Subgroup Pregnant Women

- Affect 1/3 women in reproductive age group in USA
 - Increased risk for congenital anomalies
 - Decreased DR & increased suboptimal/incomplete studies **despite** delay or repeat studies

Should an Early Anatomy Ultrasound Scan Be Offered Routinely to Obese Pregnant Women?

- Prospective TVS study 15 wks, > 42% morbidly obese
- Direct comparison 26 elements routine mid T2 to early anatomy
- Completion rates low (14%) as compared to mid T2 (60%) but combined rates > 90% which approaches average weight
 - CSP NWS 68% whereas 4 chamber 100% with > 90% ROT, LOT, 3VV

BMI Obesity Class (kg/m ²)	%
Class 1 (30-34.9)	27.8
Class II (35-39.9)	29.9
Class III (≥ 40)	42.4

Glanc, Phyllis, et al. "Should an Early Anatomy Ultrasound Scan Be Offered Routinely to Obese Pregnant Women?." JGOC 40, 10 (2018): 1286-1294.

2013 ISUOG Practice Guideline
Performance First Trimester Fetal Ultrasound*

Organizational step	Proper (and/or normal)
Head	Brain Lateral horns Midline cleft Midline pharyngeal masses Normal appearance Skull/parietal thickness (if abnormal after external contour and internal cerebral structure available)
Face	Face with line Mandible Normal profile/mandible Mouth line Cleft lip/palate and cleft
Spine	Intact overlying skin Normalized long back No curvature or mass
Chest	Cardiac regular activity Basic anatomical disorders
Abdomen	Stomach present in left upper quadrant Bladder Kidney
External wall	Normal anal meconium No umbilical defects
Extremities	Four limbs with well formed segments Hands and feet with normal contours No and normal
Placenta	Placental cord
Uterus	Thin-walled and

PRACTICAL PERSPECTIVE

Landmark study by Nicolaides et al 2011
Prospective 45,000 11-14 weeks screens suggests 3 groups Fetal Anaomlies 1st Trimester Anatomy
DO NOT MISS
USUALLY MISS
RARELY DETECT

Always Detect "Should See"	Potentially Detect "Could See"	Rarely Detect "Won't See"
Anencephaly	Cardiac Defects	Renal Anomalies
Alobar holoprosencephaly	Open NTD	Ventriculomegaly
Omphalocele	Facial Anomalies	Agensis of the Corpus Callosum
Gastroschisis	Diaphragmatic Hernia	Echogenic Lung Lesions
Limb Body Wall Complex/OEIS/Pentalogy of Cantrell	MSK Anomalies	Bowel Atresias
Megacystis		

**CNS
ALWAYS DETECT GROUP**

Exencephaly & Alobar
Holoprosencephaly

? Diagnosis (11.3 wks)

Normal	Exencephaly
<p>12 weeks</p>	<p>11.3 weeks</p> <p style="text-align: center;">Lack midline structures Lack cranial vault ossification - acrania Normal volume - disorganized</p>

**Acrania - Exencephaly – Anencephaly
Sequence**

- Exencephaly
 - Defined **acrania**/no calvarium
 - Exposed brain will degenerate due mechanical trauma and injurious environment
 - T1 diagnosis > 11-12 weeks
 - If undetected will be classic "Anencephaly" with "frog eyes"
 -

?

<p>12 weeks</p>	<p>Characteristic Features</p> <ul style="list-style-type: none"> • Monoventricle, absent midline falx • Fusion of the thalami <p>Additional Features</p> <ul style="list-style-type: none"> • Displaced pancake of cortical tissue
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Butterfly Sign : Characteristic absence midline structures

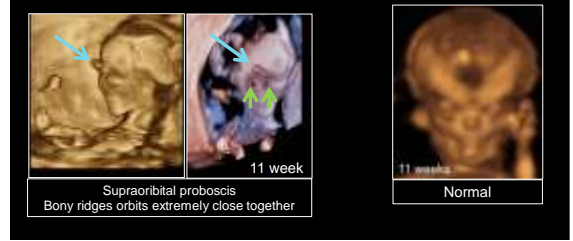
Alobar holoprosencephaly

- Falx visible by 9-10 weeks GA in normal
- Falx absent characterizes disorder
- Prevalence 1/1300

Chromosomes	Recurrence Risk
2/3 aneuploidy	10%
1/3 euploid	1 %
Karyotype for all despite prognosis	



Alobar Holoprosencephaly : Face Predicts Brain



GASTROINTESTINAL ALWAYS DETECT GROUP

Omphalocele & Gastroschisis
&
Bigger Defects

Midgut Physiological Herniation vs Omphalocele

Both Insert in Base UC - membrane covered

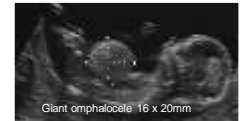
NORMAL

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



OMPHALOCELE

- Persists > 12 weeks
- > 10 mm > 10 wks
- May have liver
- Omphalocele:AC ratio > 0.8



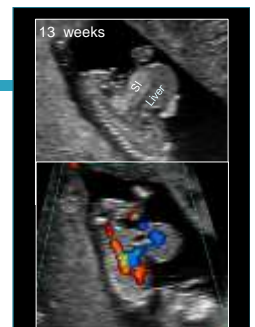
Midgut Physiological Herniation vs Omphalocele

Both Insert in Base UC

Repeat exam after 12 wks if unsure

Omphalocele

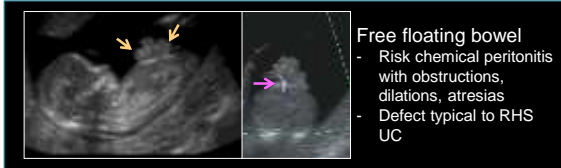
- Liver Out: 10% aneuploidy
- Liver In : 90% aneuploidy
- 70-90% associated anomalies
 - 50% cardiac
- 17% survive till surgery
 - TOP, IUFD, early NND



Pandya 2012

Gastroschisis

- Low aneuploidy (0-3%), low associated anomalies (5-15%)
- Survival 90% but 1/3 gut issues
- Risk IUFD so deliver by 37 wks oligo, FGR, protein loosing



Free floating bowel

- Risk chemical peritonitis with obstructions, dilations, atresias
- Defect typical to RHS UC

Always Detect Group

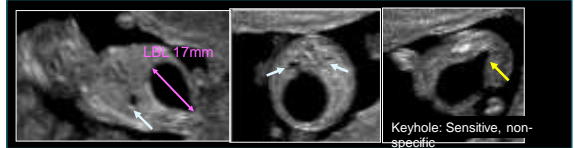
*Limb-body wall,
Pentalogy Cantrell,
Complex OEIS*



ALWAYS DETECT GROUP
MEGACYSTIS

Megacystis @ 11-14 wk Scan

- **LBL 7-15mm 90% resolve if euploid/isolated**
- **LBL > 15mm progressive obstructive uropathy**
- 20-30% aneuploidy (often in < dramatic cases, UCC ? Urethral atresia)



UOG Sebire et al 2006 - UOG 2004, Fontanella et al. Antenatal Workup Early Megacystis Selection Candidates Fetal Therapy. Fetal diagnosis & treatment

EXAMPLES: 13 WEEK SCAN

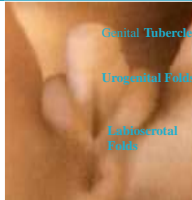


Prenatal Sex Determination & Disclosure



Boys and Girls are Different ?

- First 6 weeks identical bipotential state
- Characteristic external male genitalia complete by 12 weeks, later in female
- Review literature - 16 reports
 - ~ 100% sensitivity & specificity ≥ 8-10 wks cfDNA
 - ~ 100% sensitivity & specificity ≥ 13 wks US



Male genitalia develop 7-14 weeks
Increased incidence hypospadias in severe early onset UPI (19%)

Male or Female Genitalia The Angle of the Dangle

12 wks



Male

Female

Male or Female Genitalia The Angle of the Dangle

12 wks

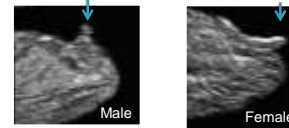


- Measure angle genital tubercle to horizontal line through LS skin surface in midsagittal plane
 - 11-14 wks ~ 100% accurate in male
- Male angle > 30 degrees, anterior directed genital tubercle
- Female angle < 10 degrees, caudally directed genital tubercle
- Indeterminate 10-30 degrees

Ellor et al USG 2009, Chalk et al 2009

Male or Female Genitalia The Angle of the Dangle

9 WEEKS EXTERNAL GENITALIA



Male

Female

Controversy

- World Development Report (WDR) ~ 4 million missing women annually due sex-selective abortion or gendercide
- Historically considered Asian phenomena
- USA: 1.5M:1F if 2 prior female children** (Indian immigrant)
- Canada: Sex ratio for third births (two daughters)
 - Chinese, Korean and Vietnamese immigrants 1.39
 - Indians 1.90 — almost two boys born for every girl*

Almond D, Edlund L. Sex-biased sex ratios in the 2000 United States Census. Proc Natl Acad Sci USA 2008;105:5681-2. ** Working paper prepared for the United States National Bureau of Economic Research. Vogel L. Sex selection migrates to Canada. CMAJ 2012. Puri et al 2011. Fetal sex Selection among Indian immigrants to USA.

Guidelines Disclosure

- SRU & AIUM 2010
 - Recommend assess fetal genitalia only medically indicated and ALL multiple gestations
 - Only 55% twins discordant for sex
- SOGC 2007
 - Attempt in routine but not prolong/repeat for sex determination
 - Does not explicitly address disclosure
 - Supreme Court 1992 female legal autonomy PHI
- Danish 2015
 - Disclose if requested, not recommend prior 14 wks without indication

Just one other thing! Pre-Eclampsia Screening

- Etiology multifactorial but appears defective placentation with trophoblast invasion limited to inner third myometrium
- **Fetal Side:** Incomplete remodeling with persistent high resistive circuit lead to relative ischemia, FGR...PTB
- **Maternal Side:** Results in release into maternal circulation anti-angiogenic factors result in clinical symptoms pre-eclampsia

Tan Myet et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. UOG 2018 Jun;51(6):743-50.

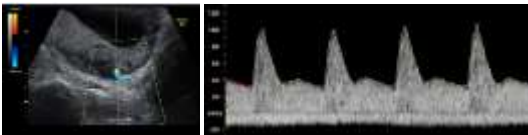
Pre-eclampsia

- PE complicate 2-3% pregnancies
 - ▣ Major morbidity/mortality both fetal/maternal
 - ▣ Costs ~ 2.2 billion/1st 12 months primarily due PTB< 32wk (US)
- Recent evidence reports aspirin (≥ 100 mg) during latency phase disease (<16 wk) will reduce risk preterm PE by 67%
- SPREE study (screening program pre-eclampsia) reports if combine maternal factors with PIGF (placental growth factor), PAPP-A and **uterine artery PI** (pulsatility index) can **double DR same FPR**

Tan Myet et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. UOG 2018 Jun;51(6):743-50. Reddy, Maya, et al. "How to perform first trimester combined screening for pre-eclampsia." Australasian JUM (2018). Sotiriadis A, ... Glanc P. ISUOG Practice Guidelines: role of ultrasound in screening pre-eclampsia. UOG 2018 Oct 15.

Recommendation: Uterine artery PI measured at NT

- Measure UTA PI where it runs along cervix at level internal os
- Measure TAS or TVS level internal cervical os (slightly > values TVS)



Sotiriadis A, ... Glanc P. ISUOG Practice Guidelines: role of ultrasound in screening for and follow-up of pre-eclampsia. UOG 2018 Oct 15.

Take Home Points: First Trimester

- Detailed first trimester anatomy is coming
 - Here for high-risk and ? Intermediate – risk
 - Important emerging role in obese gravida
 - Need standardized detailed anatomical protocol & learning curve
- Early sex determination is achievable but controversial
- Uterine artery PI has become part of the first trimester screen pre-eclampsia



THANK YOU

Handouts @ www.phyllisglanc.com next week