OB/GYN Webinar Series 2017-2018

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Special Series: Genetic Testing

Thursday, February 15th, 12pm- 1pm EST

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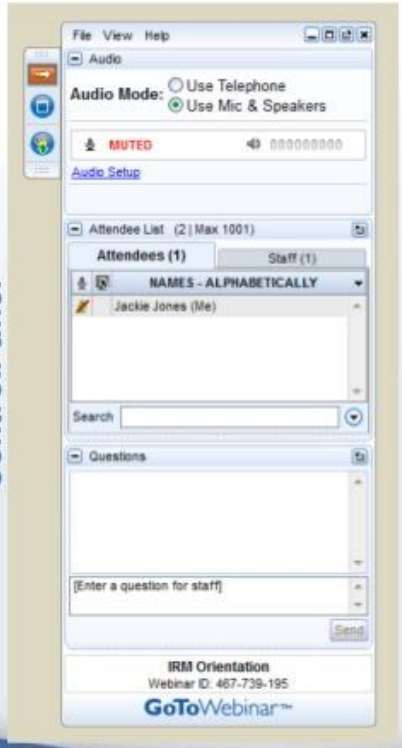

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Question Pane

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Dr. Stephen Brown, MD

Obstetrics & Gynecology, University of Vermont Medical Center
Associate Professor, University of Vermont Larner College of Medicine

Areas of Expertise:

- Clinical Genetics and Molecular Genetics
- Reproductive Genetics
- Prenatal Diagnoses

Webinar 3 Conventional Aneuploidy Screening: Does it still have a place?

STEVE BROWN, FEBRUARY 2018

Educational Goals

- Discuss whether NIPT should replace conventional aneuploidy screening in low-risk women, either medically or economically.
- Discuss the role of routine ultrasound at 12-13 weeks.

Why discuss this question?

- It's a practical problem. Many patients want NIPT and are willing to pay for it. Should we encourage or discourage them?
- For many years, most women have had a "NT" ultrasound scan at 12-13 weeks. What do we do in women who have had NIPT?
- Major changes in how we do things should be made carefully and thoughtfully.

Advantages of NIPT

- High sensitivity
- Low false positive rate (< 1:1000)
- No NT scan required
- Identifies fetal sex
- Providers love it, for all these reasons.
- Patients love it – reassurance and a major reduction in number of invasive tests.

So why not NIPT for everyone?

- Insurers have resisted coverage, citing lack of validation studies in low risk population.
- As it stands, most insurers will not cover low-risk women, although some will.
- Thought leaders have argued that conventional screening with NT, PAPP-A and HCG has value beyond detection of common trisomy and therefore should not be replaced by NIPT.

Lack of validation studies in low risk women?

- Many existing studies were performed on HR women.
- Sensitivity does not change with the prevalence of the condition being tested for.
- Positive predictive value (PPV) will change.
- Clearly, a positive NIPT result in a 40 year old has a higher chance to be a true positive than it does in a 20 year old.
- Expect that sensitivity will remain 99% and that PPV will go down as prior risk (maternal age) goes down.

Low Risk Validation

ULTRASOUND
in Obstetrics & Gynecology

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Original Paper

Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146 958 pregnancies

H. Zhang, Y. Gao, F. Jiang, M. Fu, Y. Yuan, Y. Guo, Z. Zhu, M. Lin, Q. Liu, Z. Tian, H. Zhang, F. Chen, T. K. Lau, L. Zhao, X. Yi, Y. Yin, W. Wang ✉

First published: 8 April 2015 Full publication history

NIPT performance	High-risk group (*n* = 72 382)	Low-risk group (*n* = 40 287)	*P* *
True positive	624	96	NA
False positive	39	22	NA
False negative	5	1	NA
Sensitivity	99.21 (98.51–99.90)	98.97 (94.39–99.97)	0.82
Specificity	99.95 (99.93–99.96)	99.95 (99.92–99.97)	0.98
Positive predictive value	94.12 (92.33–95.91)	81.36 (74.33–88.38)	< 0.00001
Negative predictive value	99.99 (99.99–100)	100 (99.99–100)	0.30

Data are given as *n* or % (95% CI).

* Statistical analysis by Fisher's exact test. NA, not applicable.

How much validation is needed?

- The idea that validation in a low-risk population is lacking is innaccurate.
- NIPT has been validated in low-risk pregnancies, and it works exactly as expected.

What about cost?

- Several different cost assessment studies – all confusing.
- Is cost of NT ultrasound included in conventional screening?
- Is cost of false positives correctly accounted for?
- Human cost of false positives is very significant.
- Is cost to health care system of undetected trisomy accounted for?
- Meta-analysis of studies concluded that, at least for low-risk women, conventional screening with NIPT for screen positive women is more cost effective.

What do they do in UK, Netherlands and Denmark?

- UK has adopted a “contingent” policy for all women under 38.
- Netherlands: News report in 2017 said that NIPT was available to all pregnant women.
- Denmark seems to have adopted “contingent” model for low-risk women.

Does conventional screening have value beyond identification of common aneuploidy?

- Enlarged NT can be used to screen for other things than T21.
- Associated with CHD, Noonan Syndrome, other syndromes and atypical chromosome abnormalities.
- PAPP-A and HCG abnormalities are associated with poor pregnancy outcome.

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Original Paper

Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first-trimester screening

O. B. Petersen ✉, I. Vogel, C. Ekelund, J. Hyett, A. Tabor,

the Danish Fetal Medicine Study Group, the Danish Clinical Genetics Study Group

First published: 25 February 2014 Full publication history

DOI: 10.1002/uog.13270 View/save citation

Cited by: 24 articles Citation tools

Study Design

- All women who had NT scan and/or biochemistry in Denmark from 2008-2011.
- Study population is almost 200,000 women!!
- All women with DS risk > 1:300 for T21 were offered CVS/amnio.
- Cases where chromosome abnormalities were discovered later in pregnancy or post natal were included.
- Cytogenetics was mostly routine but array results were included if array was performed.
- All chromosome results were classified as normal or into one of 3 abnormal groups: 1) detectable by NIPT; 2) atypical and clinically relevant but not detectable by NIPT; 3) Balanced translocation.

Results

- 193,638 women completed screened with NT, PAPP-A and HCG.
- 5.3% or 10,205 had karyotype – 9461 by CVS/amnio, 580 after pregnancy termination and 217 from postnatal samples.
- Of these, 1122 were abnormal of which 262 (or 24%) would have been missed altogether by NIPT.
- So far, this result is in keeping with what we talked about the other day, in the 1st webinar.

Table 1 Tests performed and karyotype results in singleton pregnancies booked for combined first-trimester screening during a 4-year period (2008–2011)

					Abnormal karyotype				
					Group 1 (detectable by NIPT)			Not detectable by NIPT	
Risk group	*Total*	*Karyotyping performed*	*Analytic failure*	*Abnormal*	*Trisomy 21**	*Trisomy 13 or 18**	*Sex chromosome aneuploidy**	*Group 2 (atypical)**	*Group 3†*
Singleton pregnancy booked for NT scan	219 324	12 278	31	1337	570	236	156	314	61
CRL 45–84 mm + NT	215 223	11 864	30	1278	557	222	144	298	57
CRL 45–84 mm + NT + PAPP-A + free β-hCG	194 443	10 263	26	1133	502	190	129	265	47
Trisomy 21 risk calculation performed	193 638	10 205	26	1122	500	189	126	262	45

Data given as *n*. *Likely to be of phenotypic importance. †Unlikely to be of phenotypic importance. Group 2, atypical abnormal karyotype (not trisomy or sex-chromosome anomalies) likely to be of phenotypic importance, undetectable by NIPT, including unbalanced karyotypes, marker chromosomes and triploidies. Group 3, balanced translocation. β-hCG, β-human chorionic gonadotropin; CRL, crown–rump length; NIPT, non-invasive prenatal testing; NT, nuchal translucency measurement; PAPP-A, pregnancy-associated plasma protein-A.

What about conventional screening for atypical chromosome abnormalities?

- Authors go through a series of simulations to ask which screening strategy yields the highest proportion of both common and atypical chromosome abnormalities.
- NT > 99th % strongly enriches for chromosome abnormalities, but majority of atypical had NT in the normal range.
- PAPP-A < 1st % enriches for atypical chromosome abnormality but most had PAPP-A closer to normal range.
- Same for HCG.
- So, no perfect way to detect atypical chromosome abnormalities.

Performance of different screening cut offs

Risk group	*Total pregnancies**	*Atypical abnormal karyotype§*
cFTS trisomy 21 risk		
> 1:300	8018 (4.1)	84 (32.4)
> 1:10	734 (0.4)	13 (3.4)
1:10 to 1:19	448 (0.2)	7 (8.9)
1:20 to 1:49	1240 (0.6)	22 (19.3)
1:50 to 1:99	1580 (0.8)	22 (22.9)
1:100 to 1:199	2169 (1.1)	13 (20.0)
1:200 to 1:299	1847 (1.0)	7 (18.4)
1:300 to 1:999	11 135 (5.8)	26 (34.7)
≤ 1:1000	174 485 (90.1)	152 (54.9)
Total	193 638 (100.0)	262 (23.4)

Authors Conclude??

- Relying on NIPT results in 100% of atypical chromosome abnormalities being missed.
- But…. 100% of T21 and T18 get detected.
- A contingent strategy that offers women with risk > 1:300 CVS, will pick up 25% of atypical chromosome abnormalities and 90% of T21.
- Cut offs for contingent screening could be adjusted to meet the needs of different groups.
- They favor a strategy that offers combined first trimester (conventional) screening to everyone, with CVS for women with risk > 1:300 and NIPT for risk < 1:300 but > 1:1000.

Maybe in Denmark…

- Here in Vermont, most patients do not want CVS/Amnio, even when risk is much higher than 1:100.
- When I speak with patients who have a positive conventional screening result, most want to do NIPT, even when I explain that a substantial proportion of all chromosome abnormalities will be missed.
- The idea that we are going to add a lot of value by continuing with conventional screening does not seem valid.
- Maybe its better to just do NIPT to begin with, as long as cost is not a concern.

So what about the "NT Ultrasound" at 12-13 weeks?

- Probably cannot justify it on the basis of the NT itself.
- Its true that big NT is associated with atypical chromosome abnormalities, but >90% had NT < 95th %.
- When NT is >99th %, about 10% will have Noonan Syndrome gene mutation.
- When NT is > 99th % about 3-4% will have a microdeletion such as 22q deletion.
- Yield is reasonable, but should you do 100 NT scans to find one with a 15% risk of genetic abnormality?

Are there other benefits to first trimester scan?

- Almost all of our patients have an early first trimester scan for dating and viability.
- If a patient presents for care “late”, then clearly they need a scan.
- What about women who have had an early scan and NIPT, do they need an 11-13 week scan?
- This has been debated at meetings and in published literature.

Swedish Study of Utility of Ultrasound

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

Detection of fetal structural abnormalities by an 11–14-week ultrasound dating scan in an unselected Swedish population

Marie Cedergren ✉, Anders Selbing

First published: August 2006 Full publication history
DOI: 10.1080/00016340500448438
Citing literature

Volume 85, Issue 8
August 2006
Pages 912–915

Methods

- 2708 consecutive scans.
- Scans performed by experienced midwives.
- Abnormal cases sent for same day re-scan by fetal medicine specialist.
- Final outcomes determined with comprehensive national database (94% of cases with neonatal data)

Results

- 104/2708 (4%) non-viable/missed abortion
- 33 twins (~1.2%)
- 1.2% (32/2708) of fetuses with structural abnormality (final outcome data).
- Of these, 13 (41%) were detected by scan.
- That translates into roughly 1 major anomaly per 200 scans and maybe 1 or two non viable pregnancies.

Anomaly	Gestational age when detected (weeks)	Outcome	Comments
Anencephaly	12 + 2	TOP	Malformation confirmed
Anencephaly	12 + 5	TOP	Malformation confirmed
Anencephaly and spina bifida	12 + 5	TOP	Malformation confirmed
Hydranencephaly	13 + 0	TOP	
Hydrocephalus, Dandy-Walker	14 + 0	TOP	Malformation confirmed
Gastroschisis	12 + 6	Live birth, week 37	Neonatal surgery
Gastroschisis	13 + 1	Live birth, week 36	Neonatal surgery
Hydronephrosis	13 + 1	Live birth at term	Decreased during pregnanc normal at birth
Hydrops	12 + 4	TOP	Malformation confirmed
Multiple malformations	11 + 6	TOP	Malformation confirmed
Cystic hygroma	11 + 6	TOP	Karyotype: 46,X
Cystic hygroma	11 + 6	TOP	Declined karyotype
Cystic hygroma	13 + 2	Live birth at term	Karyotype: normal

Another Swedish Study

BJOG An International Journal of Obstetrics and Gynaecology

Detection of malformations in chromosomally normal fetuses by routine ultrasound at 12 or 18 weeks of gestation—a randomised controlled trial in 39 572 pregnancies

S Saltvedt ✉, H Almström, M Kublickas, L Valentin, C Grunewald

Volume 113, Issue 6
June 2006
Pages 664–674

Study Design and Goals

- Swedish health care system provides ultrasound at 18 weeks gestation.
- Goal of study was to see if ultrasound could be performed earlier and still detect major cardiac anomalies.
- Randomized nearly 40,000 women to 12 vs 18 week scan.
- 12 week scan performed poorly for detection of cardiac anomalies.
- However, the MAJORITY (80%) of anomalies that led to a decision to terminate pregnancies were detected at a 12 week scan.

Ultrasound Obstet Gynecol 2012; 39: 157–163
Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.10070

First-trimester detection of structural abnormalities and the role of aneuploidy markers

M. GRANDE, M. ARIGITA, V. BOROBIO, J. M. JIMENEZ, S. FERNANDEZ and A. BORRELL

Department of Maternal-Fetal Medicine, Institute of Gynecology, Obstetrics and Neonatology, Hospital Clínic Barcelona, Barcelona, Catalonia, Spain

Summary

- Retrospective review of ~13,000 scans.
- Excluded all cases with chromosome abnormality
- Comprehensive follow up.
- Considered “major” vs “minor” structural defects.
- Overall, ~50% of major anomalies were detected in the first trimester. Best detection was for CNS (except for spina bifida).

Value of 12-13 week scan

- Other studies have also reported > 50% of major anomalies can be detected by a 12-13 week scan.
- Such anomalies are identified in 1-2% of scans.
- This corresponds to our own experience.
- We have now seen situations where the patient did not have a 12-13 week scan because NIPT was normal and then went on to have a 20 week scan with catastrophic anomalies and late termination.
- Is this is sufficient reason to perform such scans routinely?
- I would say; “yes”

Overall Summary

- Replacing first trimester conventional DS screening with NIPT will dramatically reduce false positives and will marginally increase detection of T21.
- Although there is compelling data that support the idea that conventional screening will identify a substantial proportion of cases with atypical chromosome anomalies, probably not in Vermont.
- I don't see any reason not to replace conventional screening with NIPT.
- There is still value in 12-13 week ultrasound evaluation, even in women with normal NIPT.
- But you do not need evaluation of NT.

OB/GYN Webinar Series 2017-2018

Tuesday, March 13th, 12-1pm EST

Topics: Low Dose Aspirin
Domestic Violence

Tuesday, May 8th, 12-1pm EST

Topics: Tranexamic Acid for Postpartum Hemorrhage
Preconception Health and Well Women Care
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