Overview of Prenatal Testing

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Overview

1. Why do we do prenatal screening?
2. Who do we offer prenatal screening?
3. What types of screening are available?
4. How do the screening tests compare?
5. What is included in the California Prenatal Screening Program?
6. What do we offer at our continuity clinics?

Prenatal Screening: Why do we do it?

- Prenatal screening (PNS) is performed to identify pregnant women at high risk of carrying a fetus with certain chromosomal disorders in order to help patients decide how to plan for/proceed with pregnancy and prepare them and their newborns for what to expect after delivery
- Conditions screened:
  - Trisomy 21 (Down syndrome)
  - Trisomy 18 (Edward syndrome)
  - Trisomy 13 (Patau syndrome)
  - Neural Tube Defects
  - Abdominal Wall Defects
  - Smith-Lemli-Opitz syndrome (SLOS)

Brief Genetics Review

- Normal human cell contains 46 chromosomes
- Chromosomal abnormalities include:
  - Aneuploidy (Absence or Addition of *entire* chromosome)
  - Microdeletions
  - Duplications
  - Translocations
- Standard Prenatal SCREENING looks for risk of aneuploidy
- Chromosomal microarray analysis (CMA) can be used on DNA from chorionic villus sampling (CVS, as early as 10 weeks) or amniocentesis (between 15-20 weeks) = DIAGNOSTIC

Question: How often do chromosomal abnormalities occur?

A. 1 in 50 live births
B. 1 in 150 live births
C. 1 in 300 live births
D. 1 in 1000 live births

Answer:

A. 1 in 50 live births
B. 1 in 150 live births
C. 1 in 300 live births
D. 1 in 1000 live births

How Common are Chromosomal Abnormalities?

- Prevalence is greater earlier in gestation
- Aneuploidy accounts for large proportion of early pregnancy loss
- Incidence of fetal chromosomal abnormalities increases with patient’s age but can affect patients at any age
- Incidence of fetal chromosomal abnormalities is not related to race or ethnicity

Examples of Aneuploidy and Their Prevalence

- Trisomy 21 (Down syndrome) = approximately 1 in 700 live births
- Trisomy 18 (Edward syndrome) = approximately 1 in 3,000 live births
- Trisomy 13 (Patau syndrome) = approximately 1 in 6,000 live births
- 47, XXY (Klinefelter syndrome) = approximately 1 in 500 males
- 45 X (Turner syndrome) = approximately 1 in 2,500 and is unrelated to maternal age

Risk Factors for Chromosomal Abnormalities

- Increasing maternal age
- Parental translocation or other chromosomal abnormality
- Previous pregnancy with a chromosomal abnormality
- Prenatal US abnormalities
- Screen positive test result

Chromosomal Abnormalities in 2nd Trimester Pregnancies Based on Maternal Age at Term

	Trisomy 21	Trisomy 18	Trisomy 13	Sex Chromosome Aneuploidy	Microarray or Rare Chromosomal Abnormality	All Chromosomal Abnormalities
Age 20	1 in 1,250	1 in 5,000	1 in 10,000	1 in 294	1 in 270	1 in 122
Age 25	1 in 1,000	1 in 5,000	1 in 10,000	1 in 294	1 in 270	1 in 119
Age 30	1 in 714	1 in 2,500	1 in 5,000	1 in 294	1 in 270	1 in 110
Age 35	1 in 294	1 in 1,111	1 in 2,500	1 in 285	1 in 270	1 in 84
Age 40	1 in 86	1 in 333	1 in 714	1 in 196	1 in 270	1 in 40

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

Prenatal Screening: Who do we offer it to?

- ALL PREGNANT PATIENTS!
- Prenatal Screening is OPTIONAL
- In CA, 3 out of 4 pregnant women elect to have PNS.

Prenatal Screening: What types are available?

- *Cell-free DNA (cfDNA) AKA Noninvasive Prenatal Testing (NIPT)
- *First trimester screen
- *Quad screen (Second trimester screen)
- *(Sequential) Integrated screen
- *Serum integrated screen
- Sequential stepwise screen
- Contingent screen
- *Nuchal translucency (NT) alone

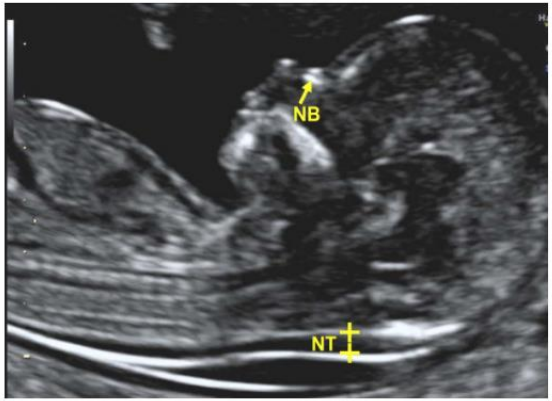
Serum Markers Used for Prenatal Screening

	Where does it come from?	High Levels May Be Associated With…	Low Levels May Be Associated With…
Alpha-Fetoprotein (AFP)	Fetal liver	Spina Bifida Anencephaly Abdominal Wall Defect	Trisomy 21 Trisomy 18 SLOS
Human Chorionic Gonadotropin (hCG)	Placenta	Trisomy 21	Trisomy 18 SLOS
Inhibin (Dimeric Inhibin-A, DIA, INH)	Ovaries Placenta	Trisomy 21	
Pregnancy-Associated Plasma Protein A (PAPP-A)	Embryo Placenta	LGA	Trisomy 13 Trisomy 18 Trisomy 21 SGA Prematurity Preeclampsia Stillbirth
Unconjugated Estriol (uE3)	Fetal Adrenal Glands Fetal Liver Placenta		Trisomy 21 Trisomy 18 SLOS

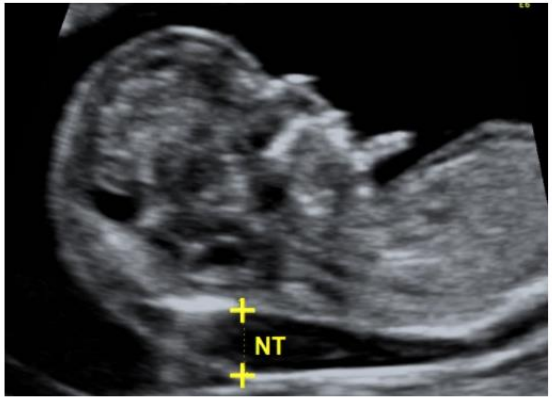
Significance of the Nuchal Translucency (NT)

- NT = fluid-filled space on the dorsal aspect of the fetal neck
- Enlarged NT (generally ≥ 3.0 mm or ≥ 99th percentile for crown-rump length) is independently associated with fetal aneuploidy and structural malformations including cardiac anomalies, abdominal wall defects, and diaphragmatic hernia *even with normal chromosomes on diagnostic testing*
- Risk of adverse fetal outcome is proportional to the degree of NT enlargement
- ***NT measurement alone does not add benefit in detecting aneuploidy when cfDNA screening has been performed in a singleton gestation***
- Must be performed by credentialed MD

Normal nuchal translucency



High nuchal translucency



Prenatal Screening: How do the available options compare?

- Each has its relative advantages and limitations
- Discussion should be held between physician and patient during each pregnancy re: available tests, pt's risks, implications of testing, **PPV**, pt's values/goals, **risk of false negatives/false positives**
- Blood tests take into account factors such as patient's age, weight, race and presence of pregestational diabetes
- Screen Negative = low risk, no follow up testing offered
- Screen Positive = high risk, follow up testing offered

The Effect of Maternal Age on the PPV of cfDNA Screening for Trisomy 21

Maternal Age	Age Related Risk per 10,000 pregnancies at 10 wks GA	Positive Predictive Value
20	1 in 804	38-80%
35	1 in 187	73-95%
40	1 in 51	91-99%

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

cfDNA/NIPT

- Looks at the fetal component (fetal fraction) of cfDNA in maternal circulation that is derived from placental trophoblasts undergoing apoptosis
- Normal fetal fraction in maternal blood approximately 3-13% (increases with GA)
- Quantity of fetal fraction is affected by factors including
  - GA
  - maternal BMI
  - maternal race
  - aneuploidy status if present
  - fetal or maternal mosaicism
  - singleton vs multiple gestation
- **Can identify fetal sex and sex chromosome aneuploidies**

cfDNA: How good is it?

- **>99% detection rate for fetal trisomy 21**
- **98% detection rate for fetal trisomy 18**
- **99% detection rate for fetal trisomy 13**
- **Combined false-positive rate of 0.13%**
- ***Uninterpretable results are associated with an increased risk of aneuploidy***

- **Some labs also screen for trisomy 16 and 22 (associated with non-viable gestation) and microdeletions but detection rate and false-positive rate is not established**

- ***Although it is the most sensitive and specific screening test for the common fetal aneuploidies, it is NOT equivalent to diagnostic testing***

**Data from Gil MM, Accurti V, Santacruz B, Plana MN, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017;50:302-14. (Systematic Review and Meta-Analysis)*

cfDNA/NIPT

Approximate GA Range for Screening	9-10* wks through term
Detection Rate (DR) for Trisomy 21	99%
Screen Positive Rate	2-4%
Advantages	1. Highest Detection Rate (DR) 2. Can be performed at any gestational age after 9-10 wks 3. Lowest false-positive rate
Disadvantages	1. Results may reflect underlying maternal aneuploidy or maternal disease 2. Generally limited to singleton pregnancies
Method	Several molecular methods

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

First-Trimester Combined Screen (Serum + NT US)

Approximate GA Range for Screening	10-13 6/7 wks
Detection Rate (DR) for Trisomy 21	82-87%
Screen Positive Rate	5%
Advantages	1. Early Screening 2. Single time point test
Disadvantages	1. Lower DR than 1st trimester and second trimester combined tests 2. NT required
Method	NT +PAPP-A, free beta hCG, +/- AFP

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

Quad Screen (2nd trimester draw)

Approximate GA Range for Screening	15-22 wks
Detection Rate (DR) for Trisomy 21	81%
Screen Positive Rate	5%
Advantages	1. Single time point test 2. No specialized US required
Disadvantages	Lower DR than 1st trimester and first and second trimester combined tests
Method	hCG, AFP, uE3, DIA

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

(Sequential) Integrated Screen (Blood tests + NT)

Approximate GA Range for Screening	10-13 6/7 wks then 15-22 wks
Detection Rate (DR) for Trisomy 21	96%
Screen Positive Rate	5%
Advantages	1. High DR
Disadvantages	1. 2 samples needed 2. No 1st trimester results 3. NT required
Method	NT +PAPP-A, then quad screen

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

Serum Integrated Screen (Blood only)

Approximate GA Range for Screening	10-13 6/7 wks then 15-22 wks
Detection Rate (DR) for Trisomy 21	88%
Screen Positive Rate	5%
Advantages	1. DR comparable to 1st trimester screening 2. No NT US required
Disadvantages	1. 2 samples needed 2. No 1st trimester results
Method	PAPP-A + quad screen

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

Nuchal Translucency US Alone

Approximate GA Range for Screening	10-13 6/7 (or 14 2/7) wks
Detection Rate (DR) for Trisomy 21	70%
Screen Positive Rate	5%
Advantages	1. Allows individual fetus assessment in multifetal gestations 2. Provides additional screening for fetal anomalies
Disadvantages	Poor sensitivity and specificity in isolation
Method	US only

Based on Table from ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

The California Prenatal Screening Program: GOAL

- To identify pregnant women at high risk of carrying a fetus with certain genetic conditions/birth defects.
- To reduce the emotional and financial burden of disability and death.

CA Prenatal Screening Program: SERVICES PROVIDED

- Prenatal screening
- Patient and provider education to promote informed decision-making
- Access to follow-up diagnostic services when indicated, at state-approved Prenatal Diagnosis Centers, at no extra charge
- Genetic counseling and additional follow up testing including:
  - Ultrasound
  - cell free DNA (cfDNA) AKA NIPT
  - diagnostic testing (CVS and amniocentesis)

Prenatal Screening: WHAT DOES IT COST?

- The California Prenatal Screening Program costs $221.60
- Program does NOT cover NT US
- Most health insurances (including Medi-cal) cover most of or all of this fee

What’s available at our clinics?

UFHC

- Based on insurance and risk factors
- High risk pts (and pts who desire) cfDNA + NT + Quad screen
- NIPT and NT likely has copay if <35yo
- Workflow different based on insurance - ask me if you have a question!

MV:

- ALL patients currently offered cfDNA after 11 weeks ONLY
- No NT US
- No 2nd trimester screen

Prenatal Screening: Updates

- ***CA PNS Program will likely cover cfDNA for ALL pregnant patients in addition to 2nd trimester maternal serum alpha-fetoprotein (MSAFP) for neural tube defects starting SPRING 2022***
- **Currently CA PNS Program only covers cfDNA as a follow up for a screen positive result**
- They will continue to fund genetic counseling and f/u dx services at state-approved centers after positive screen results up to 24 wks GA
- They will not will not include screening for sex chromosome abnormalities or microdeletions (can be added for additional costs)
- Rationale:
  - cfDNA will be available earlier than standard 1st trimester screen (between 10 weeks 0 days and 21 weeks 0 days of pregnancy)
  - cfDNA provides higher sensitivity and lower false-positive rates, resulting in fewer screen-positive cases referred for follow-up diagnostic services.

Prenatal Screening: Helpful Tools

- Prenatal Screening Calculator: https://www.cdph.ca.gov/Programs/CFH/DGDS/Pages/pns/Prenatal-Screening-Test-Calculator.aspx
- Online calculators to help determine the chance that a positive cfDNA result will be confirmed (assess PPV)

  https://www.med.unc.edu/mfm/nips-calc/

  https://www.perinatalquality.org/vendors/nsgc/nipt/

References

ACOG Practice Bulletin No. 226: Screening for Fetal Chromosomal Abnormalities. October 2020.

ACOG Committee Opinion No. 693: Counseling About Genetic Testing and Communication of Genetic Testing Results. April 2017.

ACOG Practice Bulletin No. 162: Prenatal Diagnostic Testing for Genetic Disorders. May 2016.

The California Prenatal Screening Program. California Department of Public Health. https://www.cdph.ca.gov/Programs/CFH/DGDS/Pages/pns/default.aspx

Questions?