



## Prenatal Genetic Screening


**Pooja Mittal Green, MD**  
IHA Maternal-Fetal  
Medicine

Women's Health Symposium 

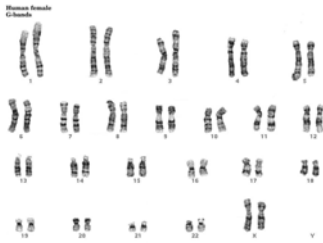
## History of screening

- 1860s: British physician John Langdon Down describes syndrome
- 1900s: association between Down and age
- 1959: Down syndrome identified as a trisomy of 21
- 1970s: amniocentesis
- 1980s-1990s: maternal serum screening
- 2000s: first trimester screening AND ultrasound
- 2010s: Non-invasive prenatal screening with cell-free fetal DNA




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## Most common chromosome abnormalities




- 1/160 live births
  - 13, 18, 21 and sex chromosomes
- Live births
  - Trisomy 21 (Down syndrome): 1/800
  - Trisomy 18 (Edwards syndrome): 1/6000
  - Trisomy 13 (Patau syndrome): 1/10,000

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### Maternal Age Related Risk for Chromosome Abnormalities

Maternal Age	Down Syndrome	Edwards Syndrome	Patau Syndrome
15	1 in 1552	1 in 1741	1 in 1477
16	1 in 1125	1 in 1384	1 in 1363
17	1 in 810	1 in 1048	1 in 1449
18	1 in 600	1 in 817	1 in 1411
19	1 in 504	1 in 620	1 in 1362
20	1 in 452	1 in 505	1 in 1240
21	1 in 409	1 in 409	1 in 1127
22	1 in 378	1 in 327	1 in 976
23	1 in 350	1 in 267	1 in 823
24	1 in 326	1 in 221	1 in 707
25	1 in 306	1 in 183	1 in 615
26	1 in 289	1 in 151	1 in 536
27	1 in 274	1 in 123	1 in 468
28	1 in 261	1 in 100	1 in 410
29	1 in 250	1 in 82	1 in 360
30	1 in 241	1 in 68	1 in 323
31	1 in 234	1 in 57	1 in 293
32	1 in 228	1 in 48	1 in 268
33	1 in 224	1 in 40	1 in 244
34	1 in 221	1 in 33	1 in 224
35	1 in 219	1 in 27	1 in 207
36	1 in 218	1 in 22	1 in 194
37	1 in 218	1 in 18	1 in 183
38	1 in 218	1 in 15	1 in 174
39	1 in 218	1 in 12	1 in 167
40	1 in 218	1 in 10	1 in 161
41	1 in 218	1 in 8	1 in 156
42	1 in 218	1 in 7	1 in 151
43	1 in 218	1 in 6	1 in 147
44	1 in 218	1 in 5	1 in 143
45	1 in 218	1 in 4	1 in 140
46	1 in 218	1 in 4	1 in 137
47	1 in 218	1 in 3	1 in 134
48	1 in 218	1 in 3	1 in 131
49	1 in 218	1 in 3	1 in 128
50	1 in 218	1 in 2	1 in 125
51	1 in 218	1 in 2	1 in 122
52	1 in 218	1 in 2	1 in 119
53	1 in 218	1 in 2	1 in 116
54	1 in 218	1 in 2	1 in 113
55	1 in 218	1 in 2	1 in 110
56	1 in 218	1 in 2	1 in 107
57	1 in 218	1 in 2	1 in 104
58	1 in 218	1 in 2	1 in 101
59	1 in 218	1 in 2	1 in 98
60	1 in 218	1 in 2	1 in 95

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## Outline

- Screening
  - Serum
  - Genetic sonogram
- Diagnosis
  - CVS
  - Amniocentesis
- Free fetal DNA
  - MaterniT21 Plus

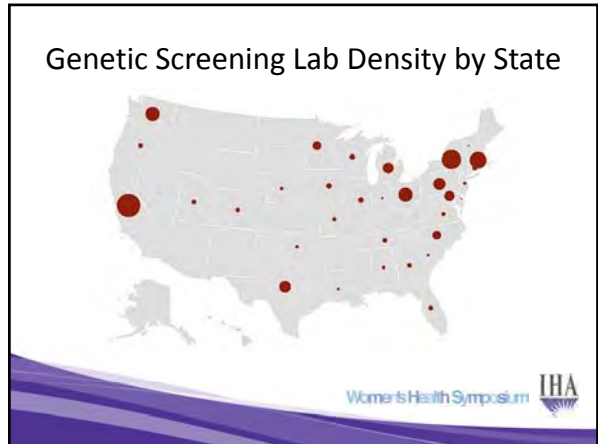
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# SCREENING

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- ## Available "blood tests"
- First trimester screen
  - Sequential screen
  - Quad screen
- } Requires performance of ultrasound at 11-13 weeks of pregnancy
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- ## First Trimester Screen
- Two steps
    1. 11-13 weeks: nuchal translucency measurement +/- nasal bone assessment
    2. 11-13 6/7 weeks: PAPP-A and hCG
  - Turnaround time is 2-3 business days (from blood draw)
  - Detects 85% of babies affected by Down Syndrome
    - False positive rate of 5%
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- ## Sequential Screen
- Three steps
    1. 11-13 weeks: nuchal translucency measurement +/- nasal bone
    2. 11-13 6/7 weeks: PAPP-A
    3. 15-22 6/7: AFP, uE3, hCG, inhA
  - Turnaround time is 2-3 business days (from 2<sup>nd</sup> draw)
  - Detects 88% of babies with Down Syndrome
    - False-positive rate of 1%
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- ## QUAD Screen
- One step @ 15 1/7 to 22 6/7 weeks
    - AFP, uE3, hCG, inhA
  - Detection 80% of babies with Down Syndrome
    - False positive screen of 5%
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# GENETIC ULTRASOUNDS

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## FIRST TRIMESTER GENETIC ULTRASOUND (NT ULTRASOUND)

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### Nuchal Translucency



- Most reliable and widely used
- Measured in first trimester (11-13wks)
- Increased measurement:
  - Down, Turner syndromes
  - Heart defects
  - Genetic syndromes
  - Adverse outcome

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## SECOND TRIMESTER GENETIC ULTRASOUND (18-20 WEEKS)

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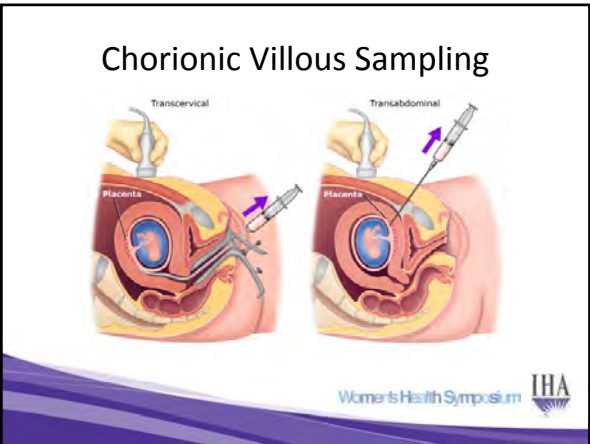
### “Soft” Markers

- Ultrasound findings of uncertain significance
- Most often:
  - are normal variants (found in 11 to 17% of normal fetuses)
  - have no long-term problems
  - are usually resolved by the time of delivery
- May carry increased risk for aneuploidy
- Detection and reporting is **CONTROVERSIAL**

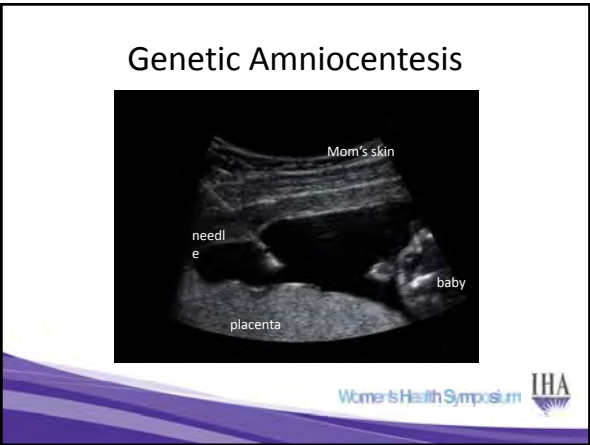
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# DIAGNOSTIC TESTS

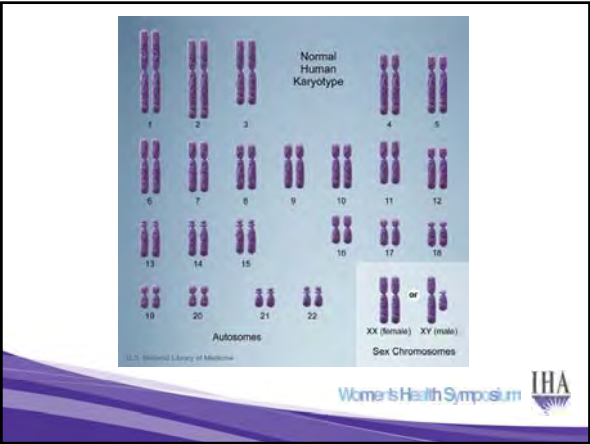
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- ## Chorionic Villous Sampling (CVS)
- Performed from 10-13 weeks
  - Loss rates similar to amniocentesis loss rates
    - Background pregnancy loss rates high in the first trimester
    - Background loss rates increase with maternal age
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- ## Genetic Amniocentesis
- Performed from 15+ weeks
  - Loss rates debated
    - 1980s - 1/100
    - FASTER trial 1/1600
    - ACOG: " <1-300-500"
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The "blood test for Down Syndrome"

# FREE FETAL DNA

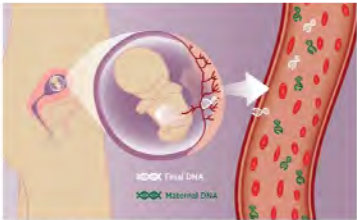


## Non-Invasive Prenatal Test (NIPT)


- Rapidly evolving and exciting area
- Four companies in US offer NIPT
  - First offered in the US in October of 2011
- All companies engaged in litigation
  - Complex intellectual property rights

## Cell-free fetal DNA (cffDNA)




- Cell-free (cffDNA) are short DNA fragments  
 - cffDNA in maternal blood comes from both mother and fetus.  
 - In February 21 the amount of cffDNA for chromosome 21 is higher than in normal pregnancies




## Cell-free fetal DNA

- Plentiful in maternal serum
- Unique to current pregnancy
  - Unlike intact fetal cells
- Apoptotic syncytiotrophoblast and ? fetal erythroblasts
- Present by 5<sup>th</sup> week gestation
- 3-6% of total DNA in maternal circulation
  - Rises with gestational age




## Cell-free fetal DNA

- Most useful for Down Syndrome
- Results:
  - Percent of babies without Down who have a negative test → 99.7%
  - Percent of babies with Down who have a positive test → 99.1%
- Diagnostic confirmation of positive results is recommended





## Cell-free fetal DNA Indications for testing

- Maternal age 35 years or older at delivery
- Suspicious ultrasound findings
- Prior pregnancy with a testable genetic syndrome
- Increased risk for genetic syndrome on other screening test or family history




## Why is the test not recommended for all women?




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**NIPT Performance:  
Down syndrome, 20-year-old**




**NIPT Performance:  
Down syndrome, 40-year-old**




Positive Predictive Value: % of positive tests that are actually positive

Much higher FALSE positive rate has led to more amniocentesis in low-risk patients

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## Summary... PRENATAL SCREENING ALGORITHM

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ALL WOMEN SHOULD BE OFFERED SCREENING OR DIAGNOSTIC TESTS

Do not want further testing


Want further information but do not want risk of invasive tests

Women who want to know as much as possible

Detailed ultrasound is still recommended for all women regardless of testing decisions. Nuchal translucency provides information beyond genetic risk


SCREENING		
Nuchal Translucency	NIPT	
11-13 wks and/or 18-22 wks	10-14 wks	11-14 wks
97%	99.9%	99.9%
13-22 wks	10-14 wks	11-14 wks
97%	99.9%	99.9%

Amniocentesis or CVS

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## Fertility Facts: What you should know before trying to conceive

**Christine Pipitone, MD**  
IHA Canton OB/GYN

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## Planning to become pregnant?

- Congratulations!
- What next?
  - Take steps to maximize your chances of a healthy pregnancy
  - Your doctor can help you with this
    - Make an appointment for preconception counseling!



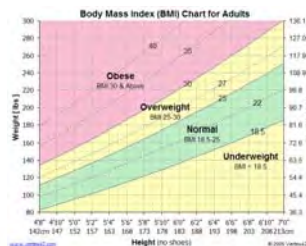
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## Your preconception visit

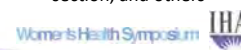
- Can be a quick discussion during your annual exam or a separate visit for in-depth discussion, depending on your risks and needs
- What will be discussed?
  - Your medical history and prior surgeries
  - Infection history and vaccines
  - Family history and risk of genetic problems
  - Previous pregnancy history
  - Medications you are taking
  - Smoking and use of alcohol or drugs
  - Exposure to harmful substances



## The importance of a healthy weight



- Try to obtain a normal (or as close to normal as possible) BMI prior to pregnancy
- Women who weigh too much or too little have increased risks of complications during pregnancy: miscarriage, diabetes, high blood pressure, cesarean section, and others



## Healthy Lifestyle

- Exercise
  - 30 minutes of moderate intensity exercise 5 days per week is recommended before and during pregnancy
- Diet
  - Eat a wide variety of healthy foods
- PRENATAL VITAMINS!
  - Start now, don't wait until you are already pregnant

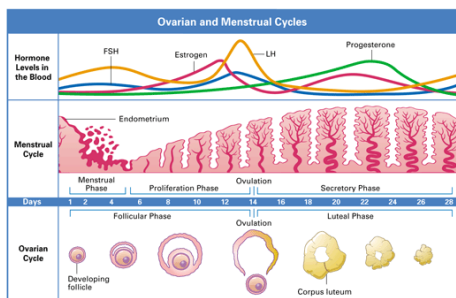


## So you're ready... what now?

- Timed intercourse
  - Coitus at least every other day during your fertile window
  - Your fertile window consists of the days around ovulation
    - For women with an average 28-day cycle, days 12-18

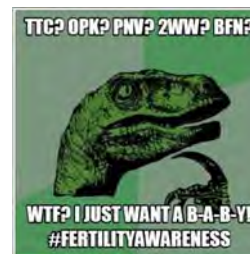




## Menstrual cycle 101



## Fertility Awareness

- Ways to determine whether and when you are ovulating:
  - Home ovulation predictor kits
  - Basal body temperature tracking
  - Tracking of other fertility indicators
  - With your doctor:
    - Ultrasound in the middle of your cycle
    - Blood tests to check progesterone



- Many smart phone apps are available to help you track your periods and fertility indicators

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Or...



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### How do I know if there is a problem?

- It can take normal couples with no issues up to a year to become pregnant
  - Give it some time
- See your doctor if
  - You have been having unprotected intercourse for a year without becoming pregnant
  - You have had more than two miscarriages in a row (often you will be checking in with your doctor anyway if a miscarriage takes place)
- If you are over age 35, are not having regular periods every 21-35 days, or have other factors that make you worry about infertility, see your doctor sooner
  - After 6 months of trying without success to achieve pregnancy

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### INFERTILITY



How my friends with kids see it

How society sees it

How my partner sees it


How I see it

How it really is

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### What can I expect if I need a workup for infertility?

- Questions about your medical history, general health and that of your partner
- Your doctor may suggest testing to evaluate
  - Your partner's semen and sperm
  - Whether your fallopian tubes are open
  - Your uterine cavity
  - Your hormone levels and ovulatory function



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### At the end of the day...



- The goal is a healthy you and a healthy baby
- Your doctor is here to help you achieve this goal!
- As soon as you have a positive pregnancy test, call your doctor to ask when your first appointment should be

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## Take home points



- Start prenatal vitamins early!
- Live a healthy lifestyle!
  - Healthy weight, healthy diet, adequate exercise
- Track your periods and know your body!
- If questions or concerns arise, ask your doctor– we are here to help!

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## QUESTIONS?

*Thank you for coming!*

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