43rd Annual
Vail Obstetrics and Gynecology
FEBRUARY 19th-24th, 2017

CONFERENCE
Vail Marriott Mountain Resort & Spa - Vail, Colorado

Thursday
February 23rd, 2017

Presented by:
Department of Obstetrics and Gynecology
University of Colorado School of Medicine

Sponsored by:
University of Colorado School of Medicine
Office of Continuing Medical Education
CONFERENCE SCHEDULE

THURSDAY, FEBRUARY 23RD, 2017

6:45 a.m.  Breakfast with the Professors
           Patrick Kneeland, MD and Jane Limmer, MD

7:15 a.m.  Recreational and Medicinal Use of Marijuana during Pregnancy
           Jane Limmer, MD
7:45 a.m.  Q&A
7:55 a.m.  Quality of Care and Peer Review
           Patrick Kneeland, MD
8:25 a.m.  Q&A
8:35 a.m.  Using Motivational Interviewing Techniques in Your Practice
           Paul Cook, PhD
9:05 a.m.  Q&A

9:15 a.m.– 3:30 p.m.  MID-DAY BREAK

4:00 p.m.  Dealing with Substance Abuse in Gyn Practice
           Kaylin Klie, MD
4:40 p.m.  Q&A

4:50 p.m.–5:00 p.m.  BREAK

Breakout Sessions

5:00 PM  Break-Out Session A: The Evolving Approaches of Detecting Aneuploidy
         Teresa Harper, MD
5:45 PM  Break-Out Session B: Case Studies in Contraception and Sterilization
         Stephanie Teal, MD

Adjourn for the day

Visit CUVAILOBGYN.COM
Marijuana Use in Pregnancy: Sorting Through the Weeds

Jane S Limmer, MD
Vail Obstetrics & Gynecology Conference 2017
Disclosures

- None
Learning Objectives

- Summarize national prevalence and current legal status of marijuana use.
- Identify the biology of cannabis and its relationship to fetal development.
- Analyze the potential short and long-term risks of marijuana use in pregnancy and lactation.
- Implement screening for Ob patients on marijuana use.
Marijuana Use in the U.S.

- Increase from 2007-2012
  - 14.8 -> 19.8 million current users
  - 41% - 42.8% lifetime prevalence
Reported Prevalence Rates in Pregnancy

- Most common illicit drug used in pregnancy

- *Self-reported* prevalence rates
  - 2-5% in most studies
  - 11-28% in high-risk women
Legalization of Marijuana

Colorado Laws

- 2000  Medical Marijuana Registry created
- 2008  First dispensaries opened
- 2012  Personal use of cannabis legalized
- 2016  “Social use” in Denver legalized
MARIJUANA PREGNANCY AND BREASTFEEDING GUIDANCE
FOR COLORADO HEALTH CARE PROVIDERS

March 18, 2015

TALKING TO YOUR PATIENTS: LAWS

If pregnant women report their substance use to their prenatal health care provider and/or have a positive drug test during a prenatal care visit, Colorado law prevents that information from being used in criminal prosecution. (C.R.S. § 13-25-136)

Tetrahydrocannabinol (THC), both recreational and medical, is considered a Schedule 1 drug under federal and Colorado law. (C.R.S. § 18-18-203)

Current Colorado law defines a baby testing positive at birth for a Schedule I substance (including recreational or medical THC or other drugs) as an instance of child neglect, which requires a report to social services. (C.R.S. § 19-3-102)

Please inform your patient: Marijuana is now legal for adults over 21. But this doesn’t mean it is safe for pregnant moms or babies. Some hospitals test babies after birth for drugs. If your baby tests positive for THC at birth, Colorado law says child protective services must be notified.

In the News

How Marijuana Legalization Leaves Mothers and Pregnant Women Behind

May 12, 2014, 10:07am  Kristen Gwynne

The legislative push to punish women for marijuana use during pregnancy is based not on science suggesting harm from which to protect children, but the notion of fetal rights.

https://rewire.news/article/2014/05/12/marijuana-legalization-leaves-mothers-pregnant-women-behind/
What is Cannabis?

- Genus of flowering plant
- Medicinal and psychoactive effects (THC)
- THC=delta-9-tetrahydrocannabinol

- Half-life in adipose = 8 days
- Small, lipophilic molecule that easily crosses the blood-brain and placental barriers
- Cannabinoid receptors largely in the CNS, retina, and immune cells
- THC potency in marijuana has increased in recent years
Cannabinoids and Fetal Development

- **Cannabinoids in adults**
  - THC interferes with synaptic neurotransmitter release
  - THC alters regulation of motor control and memory, among other brain functions

- **Cannabinoid receptors in fetal neurodevelopment**
  - Neuronal proliferation, migration, and synaptogenesis
  - Regulation of neural progenitor cell commitment and survival
  - Possible disruption of dopamine synthesis and expression of opioid and serotonin receptors
Why Studying THC Use in Pregnancy is Hard

- Subjective report vs. biologic testing
- Biologic testing will be positive depending on timing and chronicity of THC use
- Impossible to quantify which type and what amount of marijuana is being used and amount of THC consumed
- Ethical issues of reporting maternal substance use in pregnancy
- Concurrent substance use, especially tobacco, and socioeconomic factors confound results
- Difficulty of long-term follow-up for potentially affected children
Benefits to Marijuana Use?

- Potential treatment for nausea & vomiting

- “Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai’i.”
  - Roberson et al, 2014
  - Severe nausea more prevalent in women using marijuana (3.7% vs. 2.3%)

- “Survey of medicinal cannabis use among childbearing women.”
  - Westfall et al, 2006
  - 51% of those studied used marijuana for nausea/vomiting
  - 92% found this to be effective
What are the Potential Risks?

- Growth Restriction
- Fetal Malformations
- Stillbirth
- Preterm birth
- Neonatal Withdrawal
- Abnormal Neurodevelopment
Marijuana and Neonatal Morbidity

Maternal marijuana use and neonatal morbidity

Shayna N. Conner, MD, MSCI; Ebony B. Carter, MD, MPH; Methodius G. Tuuli, MD, MPH; George A. Macones, MD, MSCE; Alison G. Cahill, MD, MSCI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marijuana (n = 680)</th>
<th>No marijuana (n = 7458)</th>
<th>RR (95% CI)</th>
<th>aOR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight &lt;2500 g (n = 437)</td>
<td>8.5%</td>
<td>5.1%</td>
<td>1.7 (1.3–2.2)</td>
<td>1.3 (0.91–1.8)</td>
<td>.09</td>
</tr>
<tr>
<td>NICU admission (n = 58)</td>
<td>1.3%</td>
<td>0.7%</td>
<td>2.0 (1.0–4.1)</td>
<td>1.6 (0.7–3.5)</td>
<td>.25</td>
</tr>
<tr>
<td>Five minute Apgar &lt;7 (n = 117)</td>
<td>1.9%</td>
<td>1.4%</td>
<td>1.4 (0.8–2.4)</td>
<td>1.2 (0.7–2.3)</td>
<td>.51</td>
</tr>
<tr>
<td>Umbilical artery pH &lt;7.10 (n = 150)</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.9 (0.5–1.6)</td>
<td>0.9 (0.5–1.7)</td>
<td>.76</td>
</tr>
<tr>
<td>Composite (n = 674)</td>
<td>11.6%</td>
<td>8.0%</td>
<td>1.5 (1.2–1.8)</td>
<td>1.3 (0.96–1.6)</td>
<td>.10</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; RR, relative risk.
* Adjusted for smoking, drug use, and African American race.

Marijuana and Fetal Growth

Maternal cannabis use and birth weight: a meta-analysis

D. R. ENGLISH, G. K. HULSE, E. MILNE, C. D. J. HOLMAN & C. I. BOWER

Department of Public Health, University of Western Australia, Australia

- 10 studies included
- Adjustments made for tobacco exposure
- Most studies used self-report not biologic testing
- Pooled OR 1.09 (0.94-1.27)
- Heavy marijuana use (4x/wk) associated with average decreased fetal growth of 131g
Marijuana and Fetal Growth

Intrauterine Cannabis Exposure Affects Fetal Growth Trajectories: The Generation R Study

Hanan El Marroun, M.Sc., Henning Tiemeier, Ph.D., Eric A.P. Steegers, Ph.D., M.D., Vincent W.V. Jaddoe, Ph.D., M.D., Albert Hofman, Ph.D., M.D., Frank C. Verhulst, Ph.D., M.D., Wim van den Brink, Ph.D., M.D., Anja C. Huizink, Ph.D.

- Prospective growth ultrasounds
- Self-reported marijuana use

- Growth decreased by 11.2g/wk among fetuses with early exposure compared to fetuses with no exposure (n=214)
Marijuana and Fetal Growth

Prenatal marijuana use and neonatal outcome

- Prospective study
- N=319
- Birth-weight *increased* among fetuses with significant marijuana exposure (>1/day) in the third trimester:
  - 3357g vs. 3215g, *P = 0.4*
Marijuana and Fetal Malformations

- Association with gastroschisis, anencephaly, VSD
- No proven association

- 2 prospective studies (n=1,638)
- Multiple retrospective cohort studies (n=2,912)

- Limitations:
  - Recall bias
  - Trimester of exposure not determined
  - Limited quantification of exposure
  - Inadequate adjustment for confounders
Marijuana and Stillbirth

- Case-control study from 3/2006-9/2008
- Biologic testing using umbilical cord blood
- Increased risk in women using marijuana: OR 2.34 (1.13-4.81)
- Effect was partially confounded by tobacco use
Marijuana and Preterm Birth

- Conflicting results & most show no increased risk
- At least 7 prospective cohort studies

- 2 retrospective, population-based studies did demonstrate an increased risk.
  - OR 1.5 (1.1 – 1.9)
  - 18.8% vs. 5.8% (p < .001)

- Varying methodology
  - Limited documentation of the indication for preterm delivery
  - Limited quantification of marijuana use
Marijuana Use and Neonatal Withdrawal

- No significant withdrawal syndrome has been reported.

- No report of pharmacological treatment for cannabis withdrawal.

- Potential neurobehavioral disturbances:
  - Sustained startle reflexes
  - High-pitched cries
  - Sleep cycle disturbances
Marijuana and Long-Term Neurodevelopment

- **Animal Models**
  - Altered dopaminergic pathways
  - Increased hyperactivity
  - Decreased memory functions
Impact on Long-Term Neurodevelopment

**Ottawa Prenatal Prospective Study (n=180)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Observed Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4years</td>
<td>No differences in behavior, intellect, visual perception, language, attention and memory tasks</td>
</tr>
<tr>
<td>&gt;4years</td>
<td>Increased behavioral problems, memory difficulties, weaker performance on tasks involving visual perception and language</td>
</tr>
<tr>
<td>9-12years</td>
<td>No difference in global IQ scores or visual task performance; Impaired impulse control and executive functioning</td>
</tr>
</tbody>
</table>
## Impact on Long-Term Neurodevelopment

### Maternal Health Practices and Child Development Project

<table>
<thead>
<tr>
<th>Age</th>
<th>Observed Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 years (n=655)</td>
<td>No differences</td>
</tr>
<tr>
<td>3-6 years</td>
<td>Decreased verbal reasoning; impaired short-term memory</td>
</tr>
<tr>
<td>10 years (n=636)</td>
<td>Decreased attention, increased hyperactivity and impulsivity, Poorer reading and spelling performance</td>
</tr>
<tr>
<td>14 years (n=524)</td>
<td>Lower reading, math, spelling scores; Earlier age of onset of substance use</td>
</tr>
</tbody>
</table>
Marijuana Use During Lactation

- Newborn exposed to an estimated 0.8% of mother’s drug exposure.

- Difficult to separate effect of use in pregnancy from use during lactation.

- Currently AAP says breastfeeding is contraindicated.
How to Screen and Test

- **ACOG:**
  - Screen all patients
  - Encourage cessation and refer to treatment programs prn
  - Do not prescribe or recommend medicinal THC use in pregnancy or lactation

- Preferred testing method: maternal urine

- No accurate way to quantify amount of THC ingested in the clinical setting
How to Screen: CO Dept of Public Health

- **Prenatal and Postpartum Visits**
  - “Have you used marijuana in the last year?
  - “How often do you use and how much? What form?”
  - “How has your use changed since finding out you are pregnant?”
  - “Does anyone use marijuana in your home?”
  - “Can you tell me about why you are using?”
  - “How does marijuana help you?”
  - “Do you want to stop? Do you think you can stop? If you need help, assistance is available.”
<table>
<thead>
<tr>
<th>Biological sample</th>
<th>Duration of positive result</th>
<th>Test limitations</th>
</tr>
</thead>
</table>
| Maternal urine    | 2–3 days in occasional users
                    | Several weeks in chronic users |
| Maternal serum    | 2–3 days in occasional users
                    | Several weeks in chronic users |
| Maternal hair     | Several weeks |
| Meconium          | Positive result indicates second- and third-trimester exposure
                    | Small amount of detectable THC in the samples
                    | High false-positive rate (up to 43%) |
| Neonatal hair     | Positive result indicates third-trimester exposure |

THC, delta-9-tetrahydrocannabinol.

How Good Are We At Screening?

Obstetric Health Care Providers’ Counseling Responses to Pregnant Patient Disclosures of Marijuana Use

- Green Journal, April 2016
- N=468

- 19% of patients endorsed marijuana use.
- In 48% of visits, Ob/Gyn providers offered no counseling in response.
Why Is Screening Controversial?

- Goal should be to help women obtain treatment, not institute punishment.
- Do not want to deter women from seeking prenatal care or disclosing behaviors to providers.

October 2015 Gray Journal Letter to the Editor: “Screening women for marijuana use does more harm than good.”
  - Sexist: exposes women to legal consequences in many states
  - Racist: black people are 4 times more likely than white people to be arrested for marijuana possession
Conclusions

- Marijuana use is becoming more prevalent and more available across the country.
- There are many potential risks to a developing fetus, but proof of harm is admittedly limited.
- Screening for all substance use in pregnancy is important, and patients should receive appropriate counseling.
- Keep reading – we need more data!


Fried, PA. The Ottawa Prenatal Prospective Study (OPPS): Methodological Issues and Findings – It’s Easy To Throw the Baby Out with the Bath Water. Life Sci 1995;56:2159-68.


References

Practicing “Just Culture” and Organizational Fairness

Patrick Kneeland MD
Medical Director for Patient ad Provider Experience | University of Colorado
Director of Quality and Innovation | Division of Hospital Medicine
3 Key Practices to Drive Patient Safety

• Leader Rounding – Visibility and understanding fundamental knowledge (how the work gets done)

• Data Transparency

• Reinforce Psychological Safety: Freedom to speak up across a power gradient
Healthcare Value

\{ 
\begin{align*} 
\text{Quality Improvement} & \quad \text{Patient Safety} \\
(\text{evidence based care}) & \quad (\text{safety culture} \\
& \quad \text{and never} \\
& \quad \text{events}) \\
& \quad \text{Patient} \\
& \quad \text{Experience} \\
& \quad (\text{HCAHPS, user} \\
& \quad \text{experience}) \\
\end{align*} \\
\text{Cost} & \quad \text{(waste)} 
\end{align*} \}
44K-98K deaths every year due to error
Patients

$17 Billion

Providers
Hospital professionals are highly proficient:
Function at 99% proficiency level
Hospital professionals are highly proficient:

- Function at 99% proficiency level
- 16K lost pieces of mail each hour
- 32K check deductions from the wrong bank account each hour
- 2 unsafe plane landings at DIA every day
Have you ever been hesitant to report (or didn’t report at all), an error that you participated in or observed?
Have you ever been hesitant to report (or didn’t report at all), an error that you participated in or observed?

Why?
“The single greatest impediment to error prevention in the medical industry is that we punish people for making mistakes.”

Lucian Leape
To err is human
To drift is human

from David Marx
“How could this happen?”
“How could this happen?”

“Who messed up?”
“How could this happen?”

“Who messed up?”

“What will we do to prevent the next patient from being harmed?”
Balancing “No Blame” with Accountability in Patient Safety

Robert M. Wachter, M.D., and Peter J. Pronovost, M.D., Ph.D.
<table>
<thead>
<tr>
<th>Human Error</th>
<th>At-risk Behavior</th>
<th>Reckless Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadvertent action, slip, lapse, mistake</td>
<td>A choice. Risk not recognized or believed to be justified. Drift.</td>
<td>Conscious disregard of unreasonable risk.</td>
</tr>
</tbody>
</table>

**Improve through:**
- Processes
- Procedures
- Design
- Environment
- Training

**At-risk Behavior**
- Removing incentives for at-risk behavior
- Creating incentives for healthy behaviors
- Build systems that support ideal behavior

**Reckless Behavior**
- Remedial action
- Punitive action

---

**Console**

**Coach**

**Remediation**

Adapted from James Reason, David Marx, Michael Leonard, Allen Franke
Case 34-2010: A 65-Year-Old Woman with an Incorrect Operation on the Left Hand

David C. Ring, M.D., Ph.D., James H. Herndon, M.D., M.B.A., and Gregg S. Meyer, M.D.
65 year old-woman admitted to day-surgery unit for release of a trigger finger of the L ring finger

Seen in ortho clinic 3 months earlier with complaints of pain and stiffness in the ring finger of the L hand, with finger intermittently getting stuck in flexion

The patient elected a trial of dexamethasone, which was injected locally. At follow-up 8 weeks later, she reported no improvement in the joint symptoms. The examination was unchanged. The risks, benefits, limitations, and alternatives of operative and non-operative treatment were discussed. The patient decided to proceed with surgery.
Ten days later, the patient was admitted to the day-surgery unit, and carpal-tunnel-release surgery was performed without complications.

Immediately after completing the procedure, the surgeon realized that he had performed the incorrect operation.

Referred to event review.
What is the purpose of event review?
What is the purpose of event review?

Credentialing?

Improvement?

Risk mitigation?
“How could this happen?”
What will we do to prevent the next patient from being harmed?

**Step 1. Systems contributors.**

In evaluating the case, what system breakdowns contributed to the adverse event?
What will we do to prevent the next patient from being harmed?

Step 1. Systems contributors.
In evaluating the case, what system breakdowns contributed to the adverse event?

Patient Factors
- First case of the day complicated by anxious patient
- After delay asked to console patient from earlier case

Communication Factors
- Spanish speaking only
- No interpreter available

Equipment Factors
- No tourniquet in room, forcing circulator to leave during usual timeout period

Personnel Factors
- Personnel turned over - including RN who had assisted in pre-op
- Change in nursing team mid-procedure
- Case moved to another OR

Technology Factors
- Last patient of day, local anesthesia after 3 larger, general cases

Environmental Factors
- Several surgeons behind schedule - case delayed

Wrong Site Surgery
Seek simplicity, but never trust it.
What will we do to prevent the next patient from being harmed?

Step 2. Provider/staff actions.
In evaluating the case, were there provider/staff actions that contributed to the outcome?
Step 2. Provider actions.
In evaluating the case, were there provider/staff actions that contributed to the outcome?

What will we do to prevent the next patient from being harmed?

- Mindset: “I have 3 big procedures that I have specifically planned and prepared for, and ‘a few carpal tunnels’ to perform today”
- Did not perform a time-out
- Planned incision site not marked (the correct arm was marked on the wrist)

- Mindset going into OR “I will perform the best carpal tunnel I have ever performed”
- During OR delay, went inpatient to perform a consult

Wrong Site Surgery
Step 2.1 Provider actions.

Do these actions best fit into category of . . .

• Human error (slip or lapse)

• At-risk behavior (a short cut, “drift,” or inexperience)

• Reckless behavior (willfully ignoring safety steps that are workable within the system, clearly spelled out, and routinely used)
Step 2.2 Provider actions. Substitution test.

- When evaluating provider/staff actions, could three other reasonable provider/staff with similar skills and training do the same action under similar circumstances?

What will we do to prevent the next patient from being harmed?
No Harm

Harm

Use of the equipment resulted in no harmful outcome.

Use of the equipment resulted in a harmful outcome.

Staff | Executives | Physicians | Managers
---|---|---|---
19% | 11% | 0% | 0%
29% | 14% | 45% | 50%
Step 3. Event response.

3.1 What steps can be taken to improve faulty systems that contributed to this event? How would these steps be implemented practically?

3.2 What steps can be taken to provide direct and timely feedback to the involved provider(s)/staff?

3.3 How will we support the involved provider(s)?

3.4 Disclosure to the patient
Take Homes

- There’s a lot at stake for patients, providers, and our communities

- Getting this right requires both a cultural shift and deliberate process design

- The “Just Culture” philosophy offers a framework to create proactive review processes that are:
  (a) Fair
  (b) Transparent
  (c) Consistent
  (d) Drive organizational learning and improvement
Bibliography


Using Motivational Interviewing in Your Practice

Paul F. Cook, PhD
University of Colorado College of Nursing
MY GOALS FOR YOU

1. Identify key motivational interviewing principles: listen carefully, understand, resist the urge to “fix,” and empower the patient

2. Recognize MI “micro-skills” like reflection, open-ended questions, and the elicit-provide-elicit method of patient education

3. Summarize the research basis for motivational interviewing as an emerging best practice, and some potential applications to prenatal and postnatal care
Getting Stuck

• Arguing
  – challenging, discounting, hostility
  – nonverbals: crossed arms, shaking head

• Interrupting
  – talking over, cutting off, sighing

• Denying
  – blaming, disagreeing, excusing, minimizing
  – claiming impunity
  – pessimism, reluctance, unwillingness to change

• Ignoring
  – inattention, non-answer, no response, sidetrack
Patients Don’t Cooperate!

- People behave in ways counter to their own interests
- Labels (like “noncompliant”) increase resistance
- Confronting denial increases resistance
- Appeals to fear increase resistance
- External incentives can decrease motivation
- Increased knowledge ≠ behavior change

12 Roadblocks

- Ordering
- Threatening
- Persuading
- Lecturing
- Moralizing
- Criticizing
- Shaming
- Psychoanalyzing
- Sympathizing
- Praising
- Questioning
- Changing the Subject

Try It!

Gordon, 1970
Help, I really want to change!
AMBITIOUS
WELL YES
AND NO
Motivational Interviewing “SPIRIT”

• MI is not primarily a set of techniques; it is an attitude or a different way of being with people

• MI is at the same time …
  – Empathic (caring) and
  – Guiding (directive)

• Some characteristics of MI (ACCE):
  – Accepting
  – Collaborative / Person-Centered
  – Compassionate
  – Evoking and Strengthening Motivation to Change

Miller et al., 2013, Motivational Interviewing, 3rd Ed.
A Way Through Resistance

- Listen carefully
- Understand people’s motivations
- Resist the urge to “fix it”
- Empower the client

Lucy Bradley-Springer, CU School of Medicine
(adapted from Rollnick et al., 2011)
One Way of Looking at It

When we catch fish, we bait the hook with what the fish like, not what the fisherman likes.

(Gregory and Chapman, 2003)
Motivational Interviewing

- Developed for substance abuse
- Intended to motivate “resistant” clients
- Based on social psychology principles
  - Social influence/persuasion
  - People resist efforts to change them
  - Person-centered counseling
- “A method for exploring and resolving ambivalence”
  - NOT: teaching, changing, controlling
- “MI is like dancing”

*Try It!*

The Evidence for MI

• Review of 119 studies with almost 9,000 participants, most with 3-12 month follow-up data

• Total amount of MI provided: 30 min to 4 hrs

• Moderate changes in alcohol use, drug use, diet & exercise, emotional distress, treatment adherence

• Smaller but still significant changes for smoking (about half as strong), based on 16 studies

• Smaller numbers of studies on safe sex show weaker effects; strongest effects are for gambling

• No difference by provider discipline or training

MI “Micro-Skills”: OARS

- **Open-Ended Questions**
  - Problem recognition
  - Concern about the problem / pros and cons
  - Optimism about change
  - Intention to change

- **Affirm**

- **Restate**  Reflect 2x for each question!
  - Reflect content
  - Reflect emotion (worry, concern, upset)
  - Reflect intention
  - Reflect meaning (go one step further)

- **Summarize** (“what else?”)
Elicit-Provide-Elicit

- Elicit what the client already knows
  - What concerns you about your smoking?
- Provide new information
  - Yes, it’s a cause of cancer, and did you know it also weakens your immune system?
- Elicit the client’s response
  - How do you think that will affect your tobacco use?
Recognizing Readiness

Sustain Talk
• Seeing benefits of current behavior
• Seeing costs of new behavior

**Strategy:** back off, build motivation  
*(the “strong principle of change”: increase benefits)*

Change Talk
• Seeing benefits of new behavior
• Seeing costs of current behavior

**Strategy:** support efforts for change  
*(the “weak principle of change”: decrease barriers)*

Prochaska et al. (1995). *Changing for Good*
Red Light / Green Light

**SUSTAIN TALK**
- LURE: listen, understand, resist the urge to “fix it,” empathize

**AMBIVALENCE**
- OARS: open-ended questions, affirm, reflect, summarize
- Use elicit-provide-elicit to educate

**CHANGE TALK**
- EARS: explore, affirm, reflect, summarize
- Challenge the change

Dart, M.A. (2011). *Motivational Interviewing in Nursing Practice*
How MI Works

Smoking example:

https://www.youtube.com/watch?v=URiKA7CKtfc
Learn More about MI

• Rollnick, Miller, & Butler (2007). *Motivational Interviewing in Health Care*
• Rollnick, et al. (1999). *Health Behavior Change*
• MI home page: [www.motivationalinterview.org](http://www.motivationalinterview.org)
• Rosengren (2009). *Building Motivational Interviewing Skills: A Practitioner Workbook*
• Seminars: [professional.development@ucdenver.edu](mailto:professional.development@ucdenver.edu)
• Online MI courses: [www.regonline.com/cumotivate](http://www.regonline.com/cumotivate)
Substance Use Disorders in Gynecology

Kaylin A Klie, MD, MA
Addiction Medicine
Denver Health and Hospital/UC Health
Departments of Family Medicine and Psychiatry
University of Colorado School of Medicine
Learning Objectives

At the conclusion of this presentation, the participant should be able to:

1. Summarize epidemiology of substance use disorder (SUD)
2. Identify diagnostic criteria for SUD
3. Understand the nuances of SUD in setting of chronic pain
4. Improve recognition of SUD and referral for treatment
5. Implement pre-conception counseling for women with SUD and/or receiving chronic opioid therapy
Disclosures

No financial, professional, or personal conflicts of interest.
Epidemiology

• **2015**
  - 66.7 million reported binge drinking
  - 27.1 million illicit or misused prescription medication

• Almost **8 percent** of the population met diagnostic criteria for a substance use disorder for alcohol or illicit drugs

• Another **1 percent** met diagnostic criteria for both an alcohol and illicit drug use disorder.

• Although 20.8 million people (9 % of the population) met the diagnostic criteria for a substance use disorder in 2015, only 2.2 million individuals (**10.4 percent**) received any type of treatment.
“The clear implications of these data are that a comprehensive approach to reducing the misuse of alcohol and drugs—one that includes the implementation of effective prevention programs and policy strategies as well as high-quality treatment services—is needed to reduce the problems and costs of substance misuse in the United States. In fact, greater impact is likely to be achieved by reducing substance misuse in the general population—that is, among people who are not addicted—than among those with severe substance use problems. Of course, efforts to reduce general population rates of substance use and misuse are also likely to reduce rates of substance use disorders, because substance use disorders typically develop over time following repeated episodes of misuse (often at escalating rates) that result in the progressive changes to brain circuitry that underlie addiction.”
Women

- Women were more likely than men to report use of any prescription opioid (29.8% females vs. 21.1% males, p<0.001) (Green, 2009)

- Women more likely to be given opioids for pain and at higher doses (Cicero, 2009)

- Non-medical use of prescription pain medications increasing most rapidly in ages 18-25

- More women started using prescription pain meds than marijuana or cocaine (NDSUH, 2006)

- Average age 25
Overdose

**48,000**
Nearly 48,000 women died of prescription painkiller overdoses between 1999 and 2010.

**400%**
Deaths from prescription painkiller overdoses among women have increased more than 400% since 1999, compared to 265% among men.

**30**
For every woman who dies of a prescription painkiller overdose, 30 go to the emergency department for painkiller misuse or abuse.
Chronic Pain: Dependence or Addiction?

- Gray zone
- Physical dependence and tolerance are expected outcomes of repeated exposure to opiates
- Loss of Control
- Expanding pts world, or contracting it
  - Use opioids to engage in the world, or to escape it
How Do I Know?

- Trust your intuition, to a point
  - Not all patients prescribed opiates have an opiate use disorder
  - Tolerance and dependence ≠ addiction
  - Not all patients with pain without a use disorder will easily reduce or stop opiate therapy
  - Pay attention to the other properties of opiates: antidepressant, anxiolytic, sleep, energizing, more social, decreased inhibition
Substance Use Disorder

The five Cs:
- Craving
- Compulsive use
- Continued use despite harm (consequences)
- Impaired control over drug use
- Chronicity

- Inability to fulfill work and social obligations
- Use in dangerous situations
- Legal problems
- Interpersonal problems

Mild (1-3), Moderate (4-5), Severe (6+)
SBI...

- Many medical practices have implemented basic screening
  - Paper forms (AUDIT, DAST, ORT)
  - Conversation:
    - Parents?
    - Partner? Peers?
    - Past?
    - Present?

- Brief conversations with health care providers, even if provider has no special training, shown to reduce risky substance use
The referral to treatment is often the hard part:
- Create relationships with addiction providers
- www.signalbhn.org
- www.linkincare.org
- SAMHSA.org
- www.mothersconnection.com
- www.drugabuse.gov
Harm Reduction is Good Medicine

- Can’t stop all concerning use or behavior easily
- Help reduce the harms to our patients while continuing supportive motivational enhancement
  - Not prescribing opiates in combination with benzodiazepines
  - Not prescribing opiates to women with risky alcohol use
  - Prescribing naloxone
- Contraception: discuss with any women of reproductive age receiving opiates
- OIC treatment, syringe exchange, etc
References

- Substance Abuse Treatment: Addressing the Specific Needs of Women. A Treatment Improvement Protocol TIP 51. Substance Abuse and Mental Health Services Administration. 2015
- National Institute on Drug Abuse. www.drugabuse.gov
Non invasive prenatal testing

Terry Harper, MD
Division Chief
Maternal Fetal Medicine
No Disclosures

University of Colorado Hospital
Children’s Hospital Colorado
University of Colorado School of Medicine
Objectives

- Through case study format, we will
  - Review indications for NIPT
  - Caveots to NIPT
  - Specific properties of each technology
Properties of Non Invasive Prenatal Testing (NIPT)

• Able to access the fetal DNA information through a maternal blood draw
• Cell Free Fetal DNA has a short life span in plasma of about 16 minutes after delivery
• Its origin is most likely the placenta
• Currently focused on chromosomes 13, 18, 21, X and Y
• Some microdeletions offered
• Clinically available since October 2011
• Offered after 10 weeks gestation
What does your patient want to know?

- Nothing?
- Lethal abnormalities only?
- Any abnormality?
What does ACOG say?

- **ACOG Committee Opinion – 2012**
  - Patients at increased risk for aneuploidy
    - AMA
    - Family history
    - Abnormal serum testing
    - Abnormal ultrasound

- **ACOG Committee Opinion – 2015**
  - All patients should have a discussion of screening and diagnostic tests
  - Conventional screening methods are first-line for general population
  - Do not do parallel testing with multiple technologies
  - Routine screen for microdeletions should not be performed
CASE STUDIES
• 35 y/o G1P0 at 12 weeks
• Offered sequential, NIPT, CVS or amniocentesis
• Accepts NIPT- returns normal and declines invasive testing
PQ

- 20 y/o G1P0 at 13 weeks
- Discussed sequential, NIPT, CVS or amniocentesis
- Accepts NIPT
• NIPT positive “Extra chromosome 21 material”
• Level II anatomy unremarkable at 17 weeks
• Amniocentesis negative
LOW RISK POPULATION

- NEJM Feb 27, 2014 CARE study
  - 1914 women from 21 centers
  - Compared standard screening to NIPT
  - Mean Maternal age 29.6 years
  - Mean Gestational age 20.3 weeks

- AJOG Aug 2014 SNP (Low/High Risk)
  - Clinical retrospective data on all comers
  - Mean Maternal age 33 years
  - Mean gestational age 14 weeks
### Table 3. Test Performance.*

<table>
<thead>
<tr>
<th>Trisomy</th>
<th>No. of Cases</th>
<th>cfDNA Testing</th>
<th>Standard Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
<td>100 (47.8–100)</td>
<td>100 (29.2–100)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td>99.7 (99.3–99.9)</td>
<td>96.4 (95.4–97.2)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>45.5 (16.7–76.6)</td>
<td>4.2 (0.9–11.7)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td></td>
<td>100 (99.8–100)</td>
<td>100 (99.8–100)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td></td>
<td>100 (99.8–100)</td>
<td>100 (99.8–100)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>2</td>
<td>100 (15.8–100)</td>
<td>100 (2.5–100)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td>99.8 (99.6–100)</td>
<td>99.4 (99.0–99.7)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>40.0 (5.3–85.3)</td>
<td>8.3 (0.2–38.5)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td></td>
<td>100 (99.8–100)</td>
<td>100 (99.8–100)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td></td>
<td>100 (99.8–100)</td>
<td>100 (99.8–100)</td>
</tr>
</tbody>
</table>

* Included in the test performance analysis for standard screening were 1912 patients who were tested for trisomy 21 (1909 unaffected patients plus 3 with true positivity) and 1906 patients who were tested for trisomy 18 (1905 unaffected patients plus 1 with true positivity). For the cfDNA test performance, results from standard screening were not required. Test analysis for cfDNA included 1952 patients who were tested for trisomy 21 (1947 unaffected patients plus 5 with true positivity) and 1952 patients who were tested for trisomy 18 (1950 unaffected patients plus 2 with true positivity).


Eliminates 89% of invasive tests over traditional screens
Individual Predictive Values
www.perinatalquality.org

NIPT/Cell Free DNA Screening
Predictive Value Calculator

Overview | PPV Calculator | NPV Calculator | Definitions | FAQs | Resources | References

The prevalence of Trisomy 21 at 16 weeks gestation for a woman who is 20 at EDD is 1 in 1,777.

The probability that result is a true positive (the fetus is affected) PPV: 48%

Probability that it is a false positive (the fetus is not affected): 52%

PPV = (sensitivity x prevalence) / ((sensitivity x prevalence) + (1 - specificity)(1 - prevalence))

Please note, the post-test probability for an individual patient may differ based on other factors that influence her unique prior risk to have an affected pregnancy, such as gestational age of the patient, ultrasound findings, and biochemical screening.
• 39 y/o G1P0 declines all serum screening until...
• 19 week ultrasound with LVEIF
• Opt for NIPT
What happened?

- Extra chromosome 21 material found
- Patient opts to continue the pregnancy, declines amniocentesis confirmation but proceeds with fetal echo which reveals cardiac defect and enables optimal delivery planning in a tertiary care center
- Trisomy 21 confirmed at delivery
MK

- 36 y/o G2P1 at 19 3/7
- NIPT: “additional 13 material”
- Ultrasound:
  - Cerebellar hypoplasia
  - Omphalocele
  - Single umbilical artery
  - LV echogenic focus
  - Polydactyl
  - AGA
What happened?

- Amniocentesis: Trisomy 13
- Opted for TOP
# Rates of DS detection at specified screen positive rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Second Trimester (14–22 wk)</th>
<th>First Trimester (10–13 wk)</th>
<th>First and Second Trimesters</th>
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<tbody>
<tr>
<td></td>
<td>Double Test†</td>
<td>Triple Test‡</td>
<td>Quadruple Test§</td>
</tr>
<tr>
<td>False positive rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>35</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>3%</td>
<td>50</td>
<td>62</td>
<td>69</td>
</tr>
<tr>
<td>5%</td>
<td>59</td>
<td>69</td>
<td>76</td>
</tr>
<tr>
<td>7%</td>
<td>65</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Detection rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>5.4</td>
<td>2.7</td>
<td>1.6</td>
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<tr>
<td>70%</td>
<td>9.4</td>
<td>5.2</td>
<td>3.2</td>
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<tr>
<td>80%</td>
<td>16.5</td>
<td>10.2</td>
<td>6.6</td>
</tr>
<tr>
<td>90%</td>
<td>30.5</td>
<td>21.5</td>
<td>15.2</td>
</tr>
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</table>

### Statistical Yield for 13, 18, 21

#### MaterniT21

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>FP</th>
</tr>
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<tbody>
<tr>
<td>T21</td>
<td>99.1</td>
<td>0.2</td>
</tr>
<tr>
<td>T18</td>
<td>&gt;99.9</td>
<td>0.3</td>
</tr>
<tr>
<td>T13</td>
<td>91.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

#### Progenity/Verifi

<table>
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<tr>
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<th>Sens</th>
<th>FP</th>
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</thead>
<tbody>
<tr>
<td>T21</td>
<td>&gt;99.9</td>
<td>0.2</td>
</tr>
<tr>
<td>T18</td>
<td>97.3</td>
<td>0.4</td>
</tr>
<tr>
<td>T13</td>
<td>87.5</td>
<td>0.1</td>
</tr>
</tbody>
</table>

#### Panorama

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>FP</th>
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<tbody>
<tr>
<td>T21</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>T18</td>
<td>&gt;99</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>T13</td>
<td>&gt;99</td>
<td>0</td>
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</table>

#### Harmony

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>FP</th>
</tr>
</thead>
<tbody>
<tr>
<td>T21</td>
<td>&gt;99</td>
<td>0.1</td>
</tr>
<tr>
<td>T18</td>
<td>98</td>
<td>0.1</td>
</tr>
<tr>
<td>T13</td>
<td>80</td>
<td>0.05</td>
</tr>
</tbody>
</table>
• 41 y/o G8P3042
• Anhydramnios at 15 weeks
• Offered placental biopsy but opted for NIPT by MPSS technology
• NIPT : Reassuring
• Ultrasound
  – Anhydramnios
  – Large placental
  – IUGR
  – Pyelectasis
What happened?

- Offered termination, declined
- IUFD at 25 weeks
- Karyotype: Triploidy
- Why did NIPT not pick this up?
How is NIPT performed?

3 ways to sequence using cfDNA

- Massively Parallel Sequencing
  - MaterniT21, Progenity/Verify
- SNP
  - Panorama
- Targeted Sequencing
  - Harmony
Massively Parallel Sequencing Approach

Sequencing tells you which chromosome the ccf fragment comes from.

- TCCGCCCAGCCATAGGGACCTGGAATGGCTGAT chr21
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- GACACGGTGAGCTCCGACACCCAGGGAGCTGG chr14
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- ACAGTGGTGGGCCCAGGCCATCCCTGGGTAGGAAGCTCAGTT chr21
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- TCCGCCCAGCCATAGGGACCTGGAATGGCTGAT chr21
- GACACGGTGAGCTCCGACACCCAGGGAGCTGG chr14
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- ACAGTGGTGGGCCCAGGCCATCCCTGGGTAGGAAGCTCAGTT chr21
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
- GACACGGTGAGCTCCGACACCCAGGGAGCTGG chr14
- GGCCTGGGGACAGTCTCCAATCCACTGAGTCATCT chr10
DNA MPS* does not differentiate which fragments come from the mother and which from the fetus.

The quantitative over-representation of Trisomy 21 fragments in an affected pregnancy is significant and can be measured with high precision.

* MPS - Massively Parallel Sequencing
Targeted Sequencing Concept

**cfDNA in blood**
- Chr 21, 18, 13, X, Y
- cfDNA
- Other Chr cfDNA
- Unmapped cfDNA

Massively Parallel Shotgun Sequencing (MPSS)

Directed analysis (DANSR)
Our Technology

Proprietary SNP analysis distinguishes between maternal & fetal DNA
• 37 y/o G3P1 at 17 weeks
• Sequential 1:4 for T21, 1:38 for T18
• NIPT: reassuring
• Ultrasound Findings
  – Borderline NT 2.6 mm in first trimester
  – Single umbilical artery
  – Cerebellar hypoplasia
  – Pericardial effusion
  – IUGR
What happened?

- Amniocentesis: Mosaic Trisomy 22
- Counseling: Spectrum of phenotypes with range from normal to severe neurodevelopmental abnormalities, cardiac anomalies, IUGR, facial abnormalities
- Opted for TOP
- Why did NIPT not pick this up?
Prenatal Prevalence of Chromosomal Abnormalities
Remember what and why you are testing!

Percent of Reported Chromosome Abnormalities

- T21: 53%
- T18: 16%
- T13: 8%
- 45,X: 5%
- Sex trisomy: 13%
- Other rare: 5%

MISSING 16% OF ABNORMALITIES

Data adapted from Wellesley, D, et al., Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. *Eur J of Hum Gen*, 11 January 2012.
FULL GENOME SEQUENCING

- Ultrasound Ob/Gyn March 2014
  - Full genome sequencing of 1982 women
  - 100% sens/spec of common aneuploidies
  - Adding all other chromosomes increases the screen positive rate by 1%
  - Detect next most often sex chromosome abnormalities
  - Cases of CPM also detected (IUGR risk)

- AJOG 2016
  - Clinical Validation of NIPT for Genome-Wide Detection of Fetal CNV
  - Sensitivity of >99.9% for T21,18,13, SCA
  - Sensitivity of 97.7% for CNVs (not 21,18,13)
  - Specificity 99.9%
Full Genome Sequencing

- Massively parallel sequencing
- Genome wide screening, 23 chromosomes
- Analyzes events >= 7 Mb, select microdeletions
- Review of first 5000 results: Indications below
Results: 5.8% positive
32% would not have been detected by NIPT

Positivity by Indication
• 35 yo G2P1 at 13 weeks
• NIPT returns aneuploidy suspected (T18)
• 14 week ultrasound
  – Appropriate growth
  – Early anatomy all reassuring including 4 chamber views
What happened?

• Amnio: Normal karyotype
• Explanation: Likely confined placental mosaicism
• Follow up: serial growth for IUGR
HG

- 34 yo G1P0 at 13 weeks
- NIPT positive for Monosomy X
- Opts for CVS
• CVS + monosomy X
• Reviewed risk for false positive
• Declined amnio
• Neonate normal karyotype
What happened?

- Likely confined placental mosaicism
What test do we recommend to confirm NIPT results?

- Grati et al 2015 Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Risk for CPM</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
<th>Monosomy X</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2%</td>
<td>4%</td>
<td>22%</td>
<td>59%</td>
</tr>
<tr>
<td>Likelihood for TP by amnio</td>
<td>44%</td>
<td>14%</td>
<td>4%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Thank you!!!
Optional Reference Slides
What should we do now?

- **AMA**
  - Offer serum screen, NIPT, CVS, Amniocentesis
  - Consider 11-13 week ultrasound for early anatomy/dating/nuchal evaluation

- **Not AMA**
  - Offer serum screen (quad or first/sequential) ?and NIPT
  - NIPT can be offered
  - Consider 11-13 week ultrasound for early anatomy/dating/nuchal evaluation
Special Cases: Cautions!

• Multiple Gestations-ACOG says no
• Vanishing twin
• Donor Egg
• Structural anomalies
• Positive test should always prompt discussion about CVS/Amniocentesis
## Comparison of Tests

<table>
<thead>
<tr>
<th></th>
<th>MaterniT21</th>
<th>Verifi</th>
<th>Panorama</th>
<th>Harmony</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results Report</td>
<td>Positive/Negative</td>
<td>Borderline (0.5%)</td>
<td>Risk Scoring Cell Free Fraction</td>
<td>High/Low Risk Cell Free Fraction</td>
</tr>
<tr>
<td>Redraw Rate</td>
<td>0.9%</td>
<td>0.07%</td>
<td>4%</td>
<td>1-3%</td>
</tr>
<tr>
<td>Egg donor</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Microdeletions</td>
<td>Optional</td>
<td>Optional</td>
<td>Optional</td>
<td>No</td>
</tr>
<tr>
<td>Time to Result</td>
<td>5 calendar days</td>
<td>5-7 business days</td>
<td>5-7 calendar days</td>
<td>7 business days</td>
</tr>
<tr>
<td>Triploidy/Vanishing Twin</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>
### Microdeletion Panels

<table>
<thead>
<tr>
<th>Sequenom</th>
<th>Verifi product</th>
<th>Panorama</th>
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</thead>
<tbody>
<tr>
<td>DiGeorge</td>
<td>DiGeorge</td>
<td>Di George</td>
</tr>
<tr>
<td>Cri du Chat</td>
<td>Cri du Chat</td>
<td>Cri du Chat</td>
</tr>
<tr>
<td>PraderWilli</td>
<td>Prader Willi</td>
<td>Prader Willi</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>Trisomy 16</td>
<td>1p36 deletion</td>
</tr>
<tr>
<td>Trisomy 22</td>
<td>Trisomy 9</td>
<td></td>
</tr>
<tr>
<td>1p36 deletion</td>
<td>Wolf-Hirshhorn</td>
<td></td>
</tr>
<tr>
<td>11q (Jacobsen)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8q (Langer-Giedion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4p (Wolf-Hirshhorn)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sens 91.6 (60-100%), Specificity 99.8%
Microdeletion Panels

• Initial disorders chosen by incidence, severity
• Reported sensitivity 94%, specificity 99% but..
  – Depends on size of deletion eg 3 MB (DiGeorge) will have a 60-85% sensitivity as opposed to 11 MB Cri-du-chat (85-90%)
• Touted as helping families avoid the “Diagnostic Odessy”
• How to Counsel?? “It is clear that in the case of a microarray test, this traditional interpretation of informed consent is untenable. It is impossible to extensively inform parents of all possible findings, including their clinical consequences. To do so would probably result in such an overload of information, that the parents will in fact be incapacitated to give their informed consent.”
  » De Jong Hum Genet 2013
What do we do with ultrasound after a normal NIPT result?

• NT still provides useful information
  – Confirms dates
  – Assess for increased NT/hygroma
  – First trimester anomalies
• Genetic Markers not useful
  – Low yield/high false positive rate of EIF, CPC, etc
• Confirm gender phenotype
References

- Ehrich et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. AJOG 2011; 204:31-11.
- Dan S et al Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. Prenatal Diagnosis. 32, 1225-1232.
- ACOG Committee Opinion Sept 2015
Importance of Prevalence of Disease

![Graph showing the relationship between prevalence of disease and predictive value. The graph indicates the predictive value for both positive and negative tests as the prevalence of disease varies.](attachment:image.png)
Principles of Fetal Trisomy 21 Testing From Maternal Blood Sample Using DNA Sequencing

- ~10% of the DNA fragments in a pregnant woman’s blood are from the fetus (Orange)
- ~90% are from the mother (Blue)

Schematic of DNA Fragments Isolated From Maternal Plasma Containing Maternal DNA and Euploid Fetal DNA

Schematic of DNA Fragments Isolated From Maternal Plasma Containing Maternal DNA, Fetal DNA and Extra Fragments of Chromosome 21 Contributed by a Fetal Trisomy 21

Euploid Fetus

Fetus with Trisomy 21
Targeted Sequencing with SNPs

Genotyopic Data from Mom +/- Dad

Multiple hypotheses for each chromosome

Data from Human Genome Project (HapMap)

Sub-hypotheses with different crossover points
• Baby Deafness And Homeopathy by *********
• A young mum came into my clinic with her 3 month baby. The problem, she said, was that the baby had just been diagnosed as deaf!! He was placid and did not respond to any sounds as normal babies do.
• I took a detailed case history of her pregnancy, which was uneventful. She said she had not had any falls, did not have any emotional trauma. On further enquiry, she did say that she had had eight ultrasound scans as the doctors were worried that the baby was too small!! This sent alarm bells ringing and I prescribed homeopathic Ultrasound 30 as a remedy (obtainable from homeopathic pharmacies). I gave her two pills to be taken one at night, and the other the next morning. As she was breastfeeding the baby, he would have received the remedy via his feed.
• A month later, she returned. I did not have to ask her how things were, as this little chap was looking around inquisitively at everything. She said that she noticed a change in him within a week and his hearing was fully restored.
• I now prescribe Ultrasound 30, one pill to be taken after any ultrasound scan, to counteract any possible negative effects.
Future Directions for NIPT

- Expanding patient eligibility:
  - Multiple gestations
  - General population testing
- Expanding menu content:
  - Other whole chromosome aneuploidy (eg T9,16,22)
  - Mosaic conditions (fetus, placenta, patient)
  - Sub-chromosomal copy number variations
  - Single gene disorders
  - Cellular DNA diagnostics
### Hallmark Studies by Each Company

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Palomaki et al. Mat 21</th>
<th>Bianchi et al. Verifi</th>
<th>Norton et al. Harmony</th>
<th>Nicolaides Panorama</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk undergoing invasive prenatal procedure (9-22 wks)</td>
<td>High Risk undergoing invasive prenatal procedure (8-22 wks), including ART</td>
<td>Undergoing invasive prenatal procedure (10-22 wks)</td>
<td>High risk undergoing CVS</td>
<td></td>
</tr>
<tr>
<td><strong>Total Cohort</strong></td>
<td>4,664</td>
<td>2,882</td>
<td>4,003</td>
<td>242</td>
</tr>
<tr>
<td><strong>Selected Cohort</strong></td>
<td>1,988</td>
<td>534</td>
<td>3,228</td>
<td>229</td>
</tr>
<tr>
<td><strong>T21 Analysis</strong></td>
<td>212 (non-mosaic)</td>
<td>90 + 3 mosaic</td>
<td>84</td>
<td>25</td>
</tr>
<tr>
<td><strong>T18 Analysis</strong></td>
<td>62 (non-mosaic)</td>
<td>38 + 1 mosaic</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td><strong>T13 Analysis</strong></td>
<td>12 (non-mosaic)</td>
<td>16</td>
<td>N/A</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other Abnormal</strong></td>
<td>none</td>
<td>73 abnormal karyotypes, analyzed across all chromosomes</td>
<td>81 abnormal karyotypes collected</td>
<td>4</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>Euploid</td>
<td>Euploid + all abnormal karyotypes</td>
<td>Euploid</td>
<td>Euploid</td>
</tr>
</tbody>
</table>
43rd Annual
Vail Obstetrics and Gynecology
FEBRUARY 19th-24th, 2017

CONFERENCE
Vail Marriott Mountain Resort & Spa - Vail, Colorado

Lecture Slides not available at time of printing

They will be available on the website.

Presented by:
Department of Obstetrics and Gynecology
University of Colorado School of Medicine

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