OB/GYN Webinar Series 2017-2018

OB/GYN Webinar Series 2017-2018

Special Series: Genetic Testing

Thursday, February 8th, 12pm- 1pm EST

Presented by:

The University of Vermont
LARNER COLLEGE OF MEDICINE

THE University of Vermont MEDICAL CENTER

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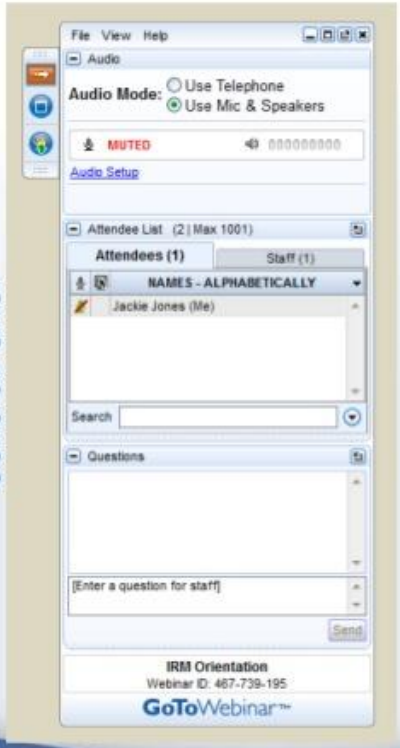

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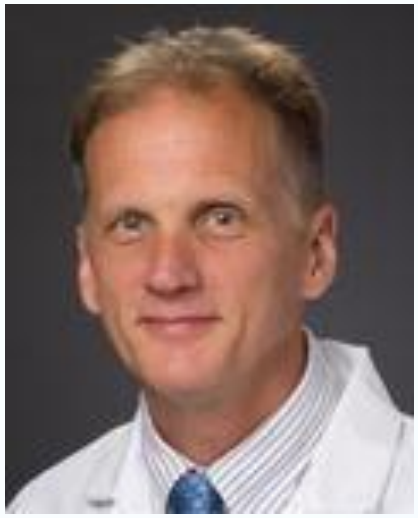
Dr. Stephen Brown, MD



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

Screening for Recessive Genetic Disease

Steve Brown

February 2018

Educational Goals

- Review new ACOG guidelines for carrier screening and expanded carrier screening.
- Review basics of Spinal Muscular Atrophy
- Review rationale behind expanded carrier screening for recessive genetic disease.
- Review technology, feasibility and desirability of “expanded carrier screening”.
- Discuss practical issues related to screening.

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 691 • March 2017

(Replaces Committee Opinion Number 318, October 2005; Committee Opinion Number 432, May 2009; Committee Opinion Number 442, October 2009; Committee Opinion Number 469, October 2010; Committee Opinion Number 486, April 2011)

Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Britton Rink, MD; Stephanie Romero, MD; Joseph R. Biggio Jr, MD; Devereux N. Saller Jr, MD; and Rose Giardine, MS.

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Carrier Screening for Genetic Conditions

The American College of
Obstetricians and Gynecologists
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Carrier Screening in the Age of Genomic Medicine

ABSTRACT: Carrier screening, whether targeted or expanded, allows individuals to consider their range of reproductive options. Ultimately, the goal of genetic screening is to provide individuals with meaningful information that they can use to guide pregnancy planning based on their personal values. Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Because all of these are acceptable strategies, each obstetrician–gynecologist or other health care provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy. Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should be counseled regarding the residual risk with any test result. Screening for any condition is optional and, after counseling, a patient may decline any or all carrier screening. If a patient requests a screening strategy other than the one used by the obstetrician–gynecologist or other health care provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives. Expanded carrier screening does not replace previous risk-based screening recommendations. The determination of the appropriate screening approach for any individual patient should be based on the patient's family history and personal values after counseling. Referral to an obstetrician–gynecologist or other health care provider with genetics expertise should be considered for risk assessment, evaluation, and consideration of diagnostic testing as indicated for any patient with a family history of a genetic condition or concern for a genetic diagnosis.

691: Recommendations?

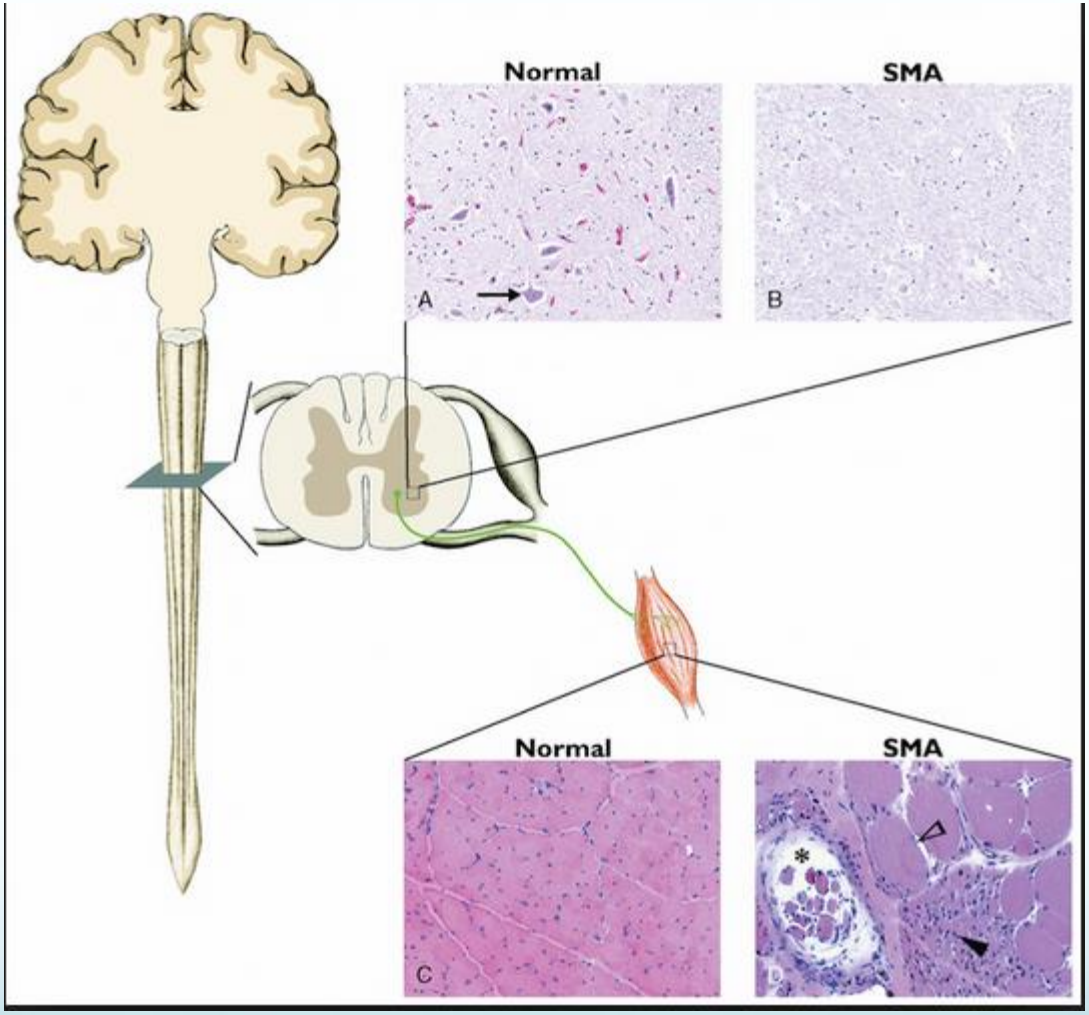
- Information about carrier screening should be provided to all pregnant women.
- Recommendations for CF for all ethnic groups, Ashkenazi Jewish genetic screening, hemoglobinopathy screening and Fragile X all remain unchanged.
- The main new thing is the addition of a recommendation to offer carrier screening for Spinal Muscular Atrophy or “SMA” for all ethnic groups.
- Offers no explanation of why ACOG has changed position on this. In the past, ACOG said that there is not enough published information on best practices, patient attitudes etc…
- ACMGG has recommended offering SMA screening in pregnancy for the past 10 years.

Bottom Line:

- Everyone gets offered SMA carrier screening, regardless of ethnic group.
- Ashkenazi Jewish people get offered “Jewish Panel”.
- People at risk of hemoglobinopathy and sickling disorders get offered appropriate screening.
- CF screening can get offered to everyone, but Caucasians are most relevant and screening Asian people is mostly unhelpful.

What is SMA?

- Recessive condition that affects lifespan of motor neurons in the spinal cord.
- Death of these neurons results in weakness and atrophy of muscles.
- SMA has variable severity. Most severe starts in-utero and is lethal in the neonatal period. Least severe form has onset in early adulthood and has a slowly progressive course. Most common form results in childhood demise due to paralysis.


Normal
SMA
A
B
Normal
SMA
C
D

SMA Facts

- Approximate incidence is 1:5,000.
- Said to be most common genetic cause of neonatal death.
- Corresponds to a carrier frequency of 1:35 (1/35 x 1/35 x ¼ = 1/5,000)
- This means 1 baby in Vermont every year.
- By comparison, Duchenne Muscular Dystrophy and Fragile X Syndrome are almost twice as common.
- If screening costs $200, then cost to identify one affected fetus is $1,000,000.

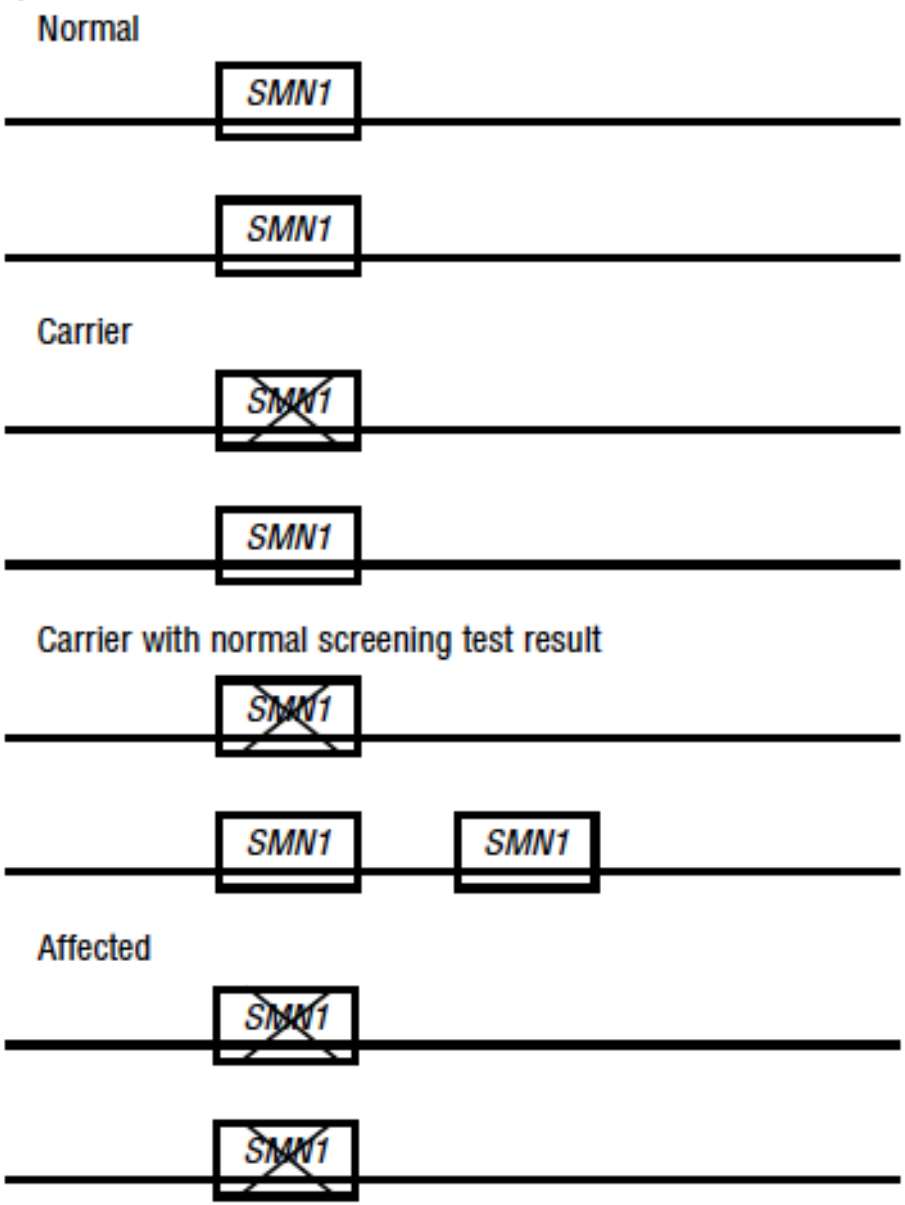
SMA Screening

- SMN locus is complicated because of an evolutionary duplication, resulting in 2 very similar genes, SMN1 and SMN2.
- SMN1 is functional and SMN2, which is almost identical is non-functional.
- Illegitimate recombination can occur, resulting in deletion of SMN1.
- 97-98% of all the SMN1 carriers have a deletion allele.

Carrier Screening

- Aimed at detecting SMA1 (normal exon 7) copy number.
- Technically challenging, but has been solved by several methods.
- Because some people have 2 copies on one chromosome and no copies on the other, normal study can be falsely reassuring in some cases.
- Therefore, results are reported with a Bayesian calculation.

Figure 1. *SMN1* Gene in Normal, Carrier, and Affected States



Residual risks after normal carrier screen

Table 1. Carrier Risk Based on Ethnicity and Residual Risk Assuming Negative Test Results ⇦

Ethnicity	Carrier Detection by Ethnicity (%)	Carrier Risk by Ethnicity	Residual Risk 2 Copies *SMN1*	Residual Risk 3 Copies *SMN1*
Caucasian	95	1:35	1:632	1:3,500
Ashkenazi Jewish	90	1:41	1:350	1:4,000
Asian	93	1:53	1:628	1:5,000
African American	71	1:66	1:121	1:3,000
Hispanic	91	1:117	1:1,061	1:11,000

Adapted with permission from BMJ Publishing Group Limited. Hendrickson BC, Donohoe C, Akmaev VR, Sugarman EA, Labrousse P, Boguslavskiy L, et al. Differences in *SMN1* allele frequencies among ethnic groups within North America. J Med Genet 2009;46:641–4.

Practical Issues

- SMA carrier screen is done by several companies including Mayo.
- Some insurance carriers will cover it, while some will not. Vermont Medicaid will, if sent to a contracted lab.
- For those interested in paying out-of-pocket for testing, the cheapest option is expanded carrier panel through a commercial vendor.

Expanded Carrier Screening

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WOMEN'S HEALTH CARE PHYSICIANS

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Current Commentary

Expanded Carrier Screening in Reproductive Medicine—Points to Consider

A Joint Statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine

Janice G. Edwards, MS, Gerald Feldman, MD, PhD, James Goldberg, MD, Anthony R. Gregg, MD, Mary E. Norton, MD, Nancy C. Rose, MD, Adele Schneider, MD, Katie Stoll, MS, Ronald Wapner, MD, and Michael S. Watson, MD

Green Journal March 2015

Existing Paradigm

- Identify “at risk” individuals by ethnicity.
- Screen for mutations specific to that ethnicity.
- Tay-Sachs in Ashkenazi Jewish people, and so forth….
- Based on core principles that: (1) be of sufficient and uniform clinical severity that most couples would be interested in prenatal diagnosis and potential pregnancy termination if the result is positive; (2) have a set of relatively frequent and well-characterized mutations such that a positive result is predictive of disease and a negative result does not give a false sense of security; and (3) be amenable to testing by a technical platform that is cost-effective, accurate, and comprehensive for the majority of the frequent mutations.

New Paradigm: Pan-ethnic and/or Expanded Carrier Screening

- Change in thinking is driven by technology development. It is now possible to screen for many sequence variants in parallel and at low cost.
- Many companies have ECS products, and you will be confronted with advertisements to use them.
- Patients may ask as well.
- Should understand rationale, problems and professional society recommendations.

Rationale for ECS

- We are all likely to be carriers of something.
- Family history is a very poor tool to identify at risk couples
- Ethnic groups don't work very well either:
  48% of Jewish people marry non-Jews.
  12-20% of infants diagnosed with hemoglobinopathy are not from recognized "at-risk" couples.
- Why not screen for lots of disorders, when it doesn't even cost more?
- Expected (but not proven) to reduce childhood mortality, pediatric hospitalizations and heartache

How much recessive disease is there?

- No perfect way to answer this question.
- Probably >95% of people carry at least one recessive gene mutation.
- About 1% of couples carry mutations in the same gene.
- About 1/400-1/500 babies has a recessive or X-linked genetic condition.
- Responsible for 20% of infant mortality.
- 10-20% of all pediatric hospital admissions.

Expanded Carrier Screening

- Exploit high throughput technologies – Next-Gen sequencing - to detect pathogenic alleles in lots of genes.
- Several companies offer panels that assess 175-400 genes.
- From technical perspective, there is no doubt that this can be done.
- Cost that is similar to or even less than screening for CF mutations.

Counsyl

RESULTS RECIPIENT
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Burlington, VT 05401
Phone: (802) 847-1400
Fax: (802) 847-5528
NPI: 1093729576
Report Date: 01/24/2018

FEMALE
[redacted]
Ethnicity: Northern European
Sample Type: EDTA Blood
Date of Collection: 01/10/2018
Date Received: 01/12/2018
Date Tested: 01/23/2018
Barcode: 11004212172341
Indication: Family history

MALE
N/A

Foresight™ Carrier Screen

POSITIVE: CARRIER

ABOUT THIS TEST

The **Counsyl Foresight Carrier Screen** utilizes sequencing, maximizing coverage across all DNA regions tested, to help you learn about your chance to have a child with a genetic disease.

RESULTS SUMMARY

Risk Details	LYDIA BAKER	Partner
Panel Information	Foresight Carrier Screen Universal Panel with Fragile X Syndrome **(105 conditions tested)**	N/A
POSITIVE: CARRIER Phenylalanine Hydroxylase Deficiency **Reproductive Risk: 1 in 200** **Inheritance: Autosomal Recessive**	**CARRIER*** NM_000277.1(PAH):c.1222C>T (R408W) heterozygote	The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group. Carrier testing should be considered. See "Next Steps".
POSITIVE: CARRIER 21-hydroxylase-deficient Congenital Adrenal Hyperplasia **Reproductive Risk: 1 in 230** **Inheritance: Autosomal Recessive**	**CARRIER*** NM_000500.7(CYP21A2):c.844G>T (V282L, aka V281L) heterozygote	The reproductive risk presented is based on a hypothetical pairing with a partner of the same ethnic group. Carrier testing should be considered. See "Next Steps".
POSITIVE: CARRIER Fragile X Syndrome **Reproductive Risk: Not Calculated** **Inheritance: X-linked Dominant**	**CARRIER*** Intermediate: 30 and 47 repeats	Reproductive risk is predominantly dependent on the female's carrier status.

*Carriers generally do not experience symptoms.

No disease-causing mutations were detected in any other gene tested. A complete list of all conditions tested can be found on page 14.

Original Investigation

FREE

August 16, 2016

Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening

Imran S. Haque, PhD[1]; Gabriel A. Lazarin, MS[1]; H. Peter Kang, MD[1]; et al

» Author Affiliations | Article Information

JAMA. 2016;316(7):734-742. doi:10.1001/jama.2016.11139

Editorial Comment

Design

- Published by Counsyl Corp.
- Used data from 350,000 real screening results to model predicted impact.
- Assumed random mating within ethnic groups to calculate number of affected babies.

JAMA Article

- Out of 100,000 babies born to non-Jewish Caucasian couples, you expect:
  38 with CF
  11-15 with SMA
  28 with Fragile X Syndrome
- If you use their expanded recessive carrier screening panel, you will identify another 47 babies with “severe or profound” genetic illnesses.
- This would be 65% increase in # of detected cases.
- Conclusion: Higher chance to identify positives than DS screening in a low risk population.

Accompanying Editorial

- No data on what would really happen in a real screened population.
- Little discussion on choice of genes in various panels or information on true sensitivity to detect mutations.
- For rare and very rare conditions, phenotype/genotype correlations are generally poor or non-existent. In other words, ability to predict disease severity is poor.

Other arguments against?

- Expensive.
- Poor use of scarce resources – not just money but also provider time.
- Not well understood by patients (or providers).
- High potential to add stress
- False reassurance (screening not 100% sensitive, does not address new mutations in dominant genes, does not address chromosome deletions/duplications)

What does committee opinion 690 actually say?

- Does NOT endorse expanded carrier screening.
- Basic old fashioned approach is fine. Minimal screening should include CF, SMA, hemoglobinopathies and Fragile X in select patients.
- Each practice should have a uniform approach to screening.
- If you are going to bring up expanded screening, be aware of the issues, such as residual risks, high likelihood to need to screen partner and so forth.
- Know about sensitivity and carrier frequency.
- Choose screening panels that are well designed.
- If patient wants expanded screening, respect their wishes.

What About Insurance Coverage?

- Most insurers will cover CF carrier screening.
- Some will cover SMA.
- Few, if any, will cover expanded carrier screening.
- For the time being, if you want to send expanded carrier screening, Counsyl will contact the patient directly and provide an estimate of out-of-pocket cost.
- Maximum is $350 – so, a lot cheaper than sending CF or CF/SMA alone.

So where are we?

- ACOG directive to offer CF and SMA to basically every prenatal patient.
- From a logical perspective, it makes sense to offer expanded carrier screening.
- None of us have time to do this.
- And its frustrating because of insurance coverage and billing.

Summary and Thoughts

- I feel sympathy for the mothers/families being confronted with decisions about genetic testing.
- Psychology is difficult and totally different than it would be if carrier screening occurred prior to pregnancy.
- I can imagine a world where genetic screening is part of general medical care. Couples would know about potential problems long before pregnancy.
- But we are stuck with today's reality.

Summary and Thoughts

- Screening for CF and SMA alone just doesn't seem logical.
- Therefore I feel compelled to discuss expanded screening.
- However, most women/couples aren't that interested. Seems "over the top" and "looking for trouble".
- Even though its not too expensive, its too expensive for most patients.
- However, there are exceptions.

What to do?

- Provide patients with a written brochure that introduces carrier screening and defines the options:
  1. Do no screening
  2. Do ACOG recommended screening
  3. Do expanded screening
- Patients will have to check with insurance carrier.
- VT Medicaid is easy, since Counsyl will accept samples for CF, SMA and Fragile X.

Conclusions

- New guidelines include SMA screening for all ethnic groups.
- New guidelines do NOT endorse expanded carrier screening.
- Discussing carrier screening is difficult and time consuming.
- One approach is to provide patients with written information that asks them to make a specific choice about carrier screening.

Questions?

This webinar was recorded and will be available to view within 5 days at https://vchipwebinars.wordpress.com

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Special Series: Genetic Testing with Dr. Stephen Brown

Thursday, February 15th, 12-1pm EST
Conventional Aneuploidy Screening:
Does it still have a place?

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
Gestational Diabetes

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Thank you!