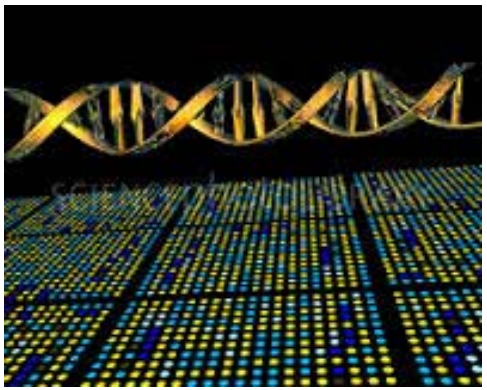
OBSTETRICAL UPDATES
OUTREACH 2016

Regional Perinatal Program of CNY

SUNY Upstate and Crouse Hospital

No Financial Disclosures



UPDATES IN GENETICS

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

Society for Maternal-Fetal Medicine

(Published Electronically Ahead of Print on March 1, 2016)

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 163, MAY 2016

(Replaces Practice Bulletin Number 77, January 2007)
(See also Practice Bulletin Number 162, *Prenatal Diagnostic Testing for Genetic Disorders*)

Screening for Fetal Aneuploidy

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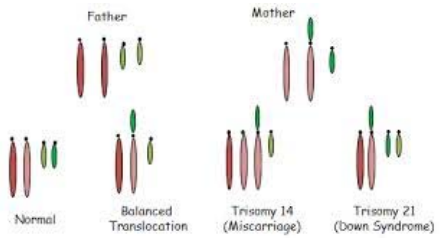
(Replaces Practice Bulletin Number 88, December 2007)
(See also Practice Bulletin Number 163, *Screening for Fetal Aneuploidy*)

Prenatal Diagnostic Testing for Genetic Disorders

Chromosomal Aberrations

- Aneuploidy >> unbalanced translocations, del/dup
- 66% chemical pregnancies
- 50% clinical first trimester losses
- 5% fetal demises
- 5-7% infant and childhood deaths



Cell-free DNA Screening (aka NIPT)

- Fragments of fetal DNA in maternal circulation
  - Harmony, MateriniT21, Consyl
- Trisomy 21: 98% sensitivity, 0.5% FPR
- Less for trisomy 18, 13 and XY anomalies
- PPV: T21-93%, T18-64%, T13-44%, XY-39%
  - Wang *Genet Med* 2015
- Around 5% of samples are indeterminate/"no call"
  - Early EGA, high BMI
  - Higher risk for aneuploidy: 22% were aneuploid (out of 8% of total cases that were "no call")
- Can be offered to low risk women with further increase in FPR
- Not recommended for multiples
- **NOT A SUBSTITUTE** for invasive testing

Table 2. Characteristics, Advantages, and Disadvantages of Common Screening Tests for Aneuploidy

Screening Test	Gestational Age Range for Screening (Weeks)	Detection Rate for Down Syndrome (%)	Screen Positive Rate* (%)	Advantages	Disadvantages	Method
First trimester†	11–14‖	82–87	5	1. Early screening 2. Single test 3. Analyte assessment of other adverse outcome	Lower DR than combined tests NT required	NT+PAPP-A and hCG
Triple screen	15–22	69	5	1. Single test 2. No specialized US required 3. Also screens for open fetal defects 4. Analyte assessment for other adverse outcomes	Lower DR than with first-trimester or quad screening Lowest accuracy of the single lab tests	hCG, AFP, uE3
Quad screen†	15–22	81	5	1. Single test 2. No specialized US required 3. Also screens for open fetal defects 4. Analyte assessment for other adverse outcomes	Lower DR than combined tests	hCG, AFP, uE3, DIA
Integrated†	11–14, then 15–22	96	5	Highest DR of combined tests Also screens for open fetal defects	Two samples needed before results are known	NT+PAPP-A, then quad screen
Sequential‡ Stepwise	11–14, then 15–22	95	5	First-trimester results provided; Comparable performance to integrated, but FTS results provided; also screens for open fetal defects; analyte assessment for other adverse outcomes.	Two samples needed	NT+hCG+ PAPP-A then quad screen
Contingent screening‡		88–94	5	First-trimester test result: Positive: diagnostic test offered Negative: no further testing Intermediate: second-trimester test offered Final: risk assessment incorporates first- and second-trimester results	Possibly two samples needed	NT+hCG+ PAPP-A, then quad screen
Serum Integrated†	11–14; then 15–22	88	5	1. DR compares favorably with other tests. 2. No need for NT	Two samples needed; no first-trimester results	PAPP-A+quad
Cell-free DNA§	10 - term	99 (in patients who receive a result)	0.5	1. Highest DR for Down syndrome 2. Can be performed at any gestational age after 10 weeks 3. Low false-positive rate in high-risk women (or women at high risk of Down syndrome)	1. NPV and PPV not clearly reported 2. Higher false-positive rate in women at low risk of Down syndrome 3. Limited information about three trisomies and fetal sex 4. Results do not always represent a fetal DNA result	Three roughly equivalent molecular methods
Nuchal Translucency†	11–14‖	64–70	5	Allows individual fetus assessment in multifetal gestations Provides additional screening for fetal anomalies and possibly for twin–twin transfusion syndrome	1. Poor screen in isolation 2. Ultrasound certification necessary	US only

New ACOG Procedure-Related Risk Estimates

- Amniocentesis 0.11% (1 in 900)
- CVS 0.22% (1 in 422)

Total procedure-related miscarriage risk

0.1 to 0.3%

Twins 1%

Microarray Analysis

- Genome-wide technique detecting gain/loss
  - Better detection of microdeletion/duplications
  - Misses balanced translocations, triploidy, low mosaicism
- First line for fetal death
  - Direct prep more successful than cell culture
- First line for structural anomalies
  - 6% clinically significant microarray findings in patients with normal karyotype
    - Wapner NEJM 2012
- **Can be offered to ALL undergoing testing**

Use of Ultrasound Only

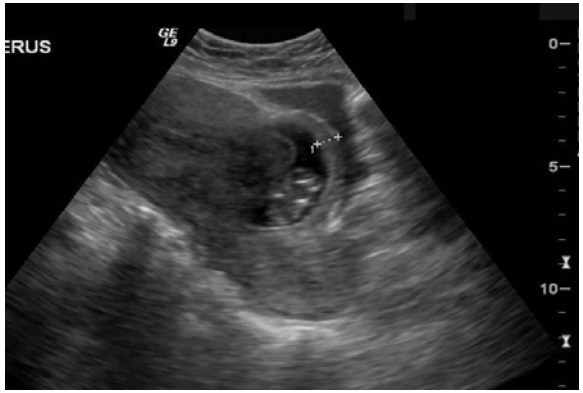
- Trisomy 21
  - Normal ultrasound reduces age-related risk 80%
  - Detection rate only 50-60%
- Enlarged NT with normal karyotype should be followed with ultrasound and fetal echocardiogram
- Soft marker evaluation
  - Third trimester f/u for echogenic bowel, renal pelvis dilation, short humerus/femurs

Table 3. Management of Ultrasonographic Markers for Aneuploidy

Soft Marker	Imaging Criteria	Aneuploidy Association	Management
First trimester: enlarged nuchal translucency	Certified ultrasonography measurement ≥ 3.0 mm or above the 99th percentile for the CRL	Aneuploidy risk increases with size of NT Also associated with Noonan syndrome, multiple pterygium syndrome, skeletal dysplasias, congenital heart disease, and other anomalies	1. Genetic counseling 2. Offer cfDNA or CVS 3. Second-trimester detailed anatomic survey and fetal cardiac ultrasonography
First trimester: cystic hygroma	Large single or multilocular fluid-filled cavities, in the nuchal region and can extend the length of the fetus	If septate, approximately 50% are aneuploid	1. Genetic counseling 2. Offer CVS 3. Second-trimester detailed fetal anatomic survey and fetal cardiac ultrasonography
Second trimester: echogenic intracardiac foci	Echogenic tissue in one or both ventricles of the heart seen on standard four-chamber view	LR 1.4–1.8 for Down syndrome Seen in 15–30% of Down syndrome and 4–7% euploid fetuses	1. If isolated finding, aneuploidy screening should be offered if not done previously 2. If aneuploidy screen result is negative, no further evaluation is required.
Second trimester: pyelectasis	Renal pelvis measuring ≥ 4 mm in anteroposterior diameter up to 20 weeks of gestation	LR 1.5–1.6 for Down syndrome	1. If isolated finding, aneuploidy screening should be offered if not performed previously 2. Repeat ultrasonography in third trimester for potential urinary tract obstruction
Second trimester: echogenic bowel	Fetal small bowel as echogenic as bone	LR 5.5–6.7 for Down syndrome Associated with aneuploidy, intra-amniotic bleeding, cystic fibrosis, CMV	1. Further counseling 2. Offer CMV, CF, and aneuploidy screening or diagnostic testing
Second trimester: thickened nuchal fold	≥ 6 mm from outer edge of the occipital bone to outer skin in the midline	LR 11–18.6 with 40–50% sensitivity and > 99% specificity for Down syndrome Most powerful second-trimester marker	1. Detailed anatomic survey 2. Further detailed genetic counseling and aneuploidy screening or diagnostic testing
Second trimester: mild ventriculomegaly	Lateral ventricular atrial measurement between 10–15 mm	Associated with aneuploidy LR 25 for Down syndrome	1. Genetic counseling 2. Second-trimester detailed anatomic ultrasound evaluation 3. Consider diagnostic testing for aneuploidy and CMV 4. Repeat ultrasound in third trimester
Second trimester: choroid plexus cysts	Discrete cyst(s) in one or both choroid plexus(es)	In isolation, no aneuploidy association	1. Second-trimester detailed anatomic survey and fetal cardiac ultrasound 2. No further follow-up if isolated 3. Consider aneuploidy screening or diagnostic testing if other markers are present
Second trimester: short femur length	Measurement < 2.5 percentile for gestational age	LR 1.2–2.2 for Down syndrome. Can be associated with aneuploidy, IUGR, short limb dysplasia	1. Second-trimester detailed fetal anatomic evaluation for short limb dysplasia 2. Further detailed counseling 3. Consider repeat ultrasonography in third trimester for fetal growth

Screening Advice

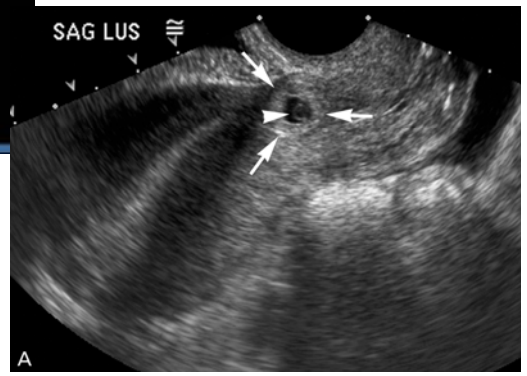
- Decide on options for your practice and know their pros/cons/limitations
  - staff education
- Discuss options including diagnostic testing at first visit for *all* women
- Alert patient to numerical risk assessment
  - comparing to age-related can be helpful
- cfDNA or first trimester screening requires MSAFP *or* ultrasound *or* both for ONTD screen



UPDATES IN ABNORMAL PLACENTATION

Cesarean Scar Pregnancy

Incidence: 1 in 1800-2500 pregnancies after cesarean



Cesarean Scar Pregnancy Criteria

1. Positive bHCG
2. Endometrial and cervical cavities devoid of pregnancy
3. Placenta or gestational sac embedded in the hysterotomy scar
4. Triangular sac that fills the scar niche in early gestation
5. Fetal/embryonic pole or yolk sac +/- cardiac activity
6. Thin (1-3mm) or absent myometrial layer between sac and bladder
7. Prominent vascularity at scar
   - Timor-Tritsch *J Ultrasound Med* 2015

Don't Mistake for Aborting IUP

CSP Outcomes

- Risk of hemorrhage and uterine rupture prior to viability requiring hysterectomy
  - Multiple case reports, incidence difficult to ascertain
  - Higher risk with extruding sac
- High risk for morbidly adherent placenta
  - 50-100% risk of c-hysterectomy based on two series (20 pts) who chose expectant mgmt
- Recurrence risk is 1%
- Risk for concurrent AVM (6 reported cases)

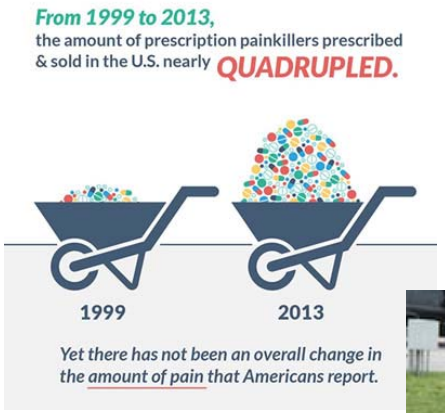
Options Counseling: Termination

- D&C: most complicated when used alone
- Surgical excision
  - Laparoscopy: 30% complications
  - Lapx and hystx: 7% complications
  - Transvaginal excision: 7% complications
  - Laparotomy with excision
  - Hysterectomy
- Uterine artery embolization: 47% complications
  - Less when combined with other methods, D&C, foley
- Methotrexate/Potassium chloride (heterotopics)
  - Systemic: 60% complications
  - Intragestation: 5-10% complications, *6-8 weeks best choice

Options Counseling: Expectant

- Early referral for MFM Consult
- Precautions for vaginal bleeding or signs/sx of hemoperitoneum
- Serial ultrasound +/- MRI
- Planned delivery with likely hysterectomy

UPDATES ON OPIOID DEPENDENCE



www.cdc.gov

2009:
Death from overdose >
Death from motor vehicle collisions

CDC: National Statistics

- 28,000 deaths per year
  - (up 400% for women since 1999)
- Most common substances in overdose deaths
  - Hydrocodone (Vicodin)
  - Oxycodone (OxyContin)
  - Oxymorphone (Opana)
  - Methadone

5 things to prevent opioid abuse
AMA Statement 2015

1. Register and use your state prescription drug monitoring program to check your patient's prescription history.
2. Educate yourself on managing pain and promoting safe, responsible opioid prescribing.
3. Support overdose prevention measures, such as increased access to naloxone.
4. Reduce the stigma of substance use disorder and enhance access to treatment.
5. Ensure patients in pain aren't stigmatized and can receive comprehensive treatment.

SAMHSA - 2013

The number of persons who had heroin dependence or abuse in 2013 (**517,000**), higher than the numbers in 2002 to 2008 (ranging from 189,000 to 324,000).

In 2013, **22.7 million** persons aged 12 or older needed treatment for an illicit drug or alcohol use problem (8.6 percent of persons aged 12 or older). Of these, **2.5 million** (0.9 percent of persons aged 12 or older and 10.9 percent of those who needed treatment) received treatment at a specialty facility.

Signs of Opioid Withdrawal
(6-48 hours of abstinence)

- Yawning
- Muscle aches
- Anxiety/agitation
- Runny nose
- Tachycardia/Hypertension
- Sweating
- Piloerection

OPIOID MAINTENANCE TREATMENT IN PREGNANCY

BENEFITS

- **Substitution therapy minimizes illicit drug use**
- **Stabilizes addiction and leads to sustainable recovery**
- **Solidifies engagement with antenatal care provider with improved maternal/fetal health care**
- **Shown to be cost effective**

Methadone vs Buprenorphine

	Methadone	Buprenorphine
Experience	Decades	10-12 yrs
Risk Category	B	C
Approved for pregnancy	Yes	With informed consent
Medical complications	cardiac	Liver?
Overdoses	Yes	Less, has a ceiling
NAS	Yes	Less incidence?
Newborn Hospitalization	Yes	Less time
Child Development	Good	So far so good

Adding Naloxone?

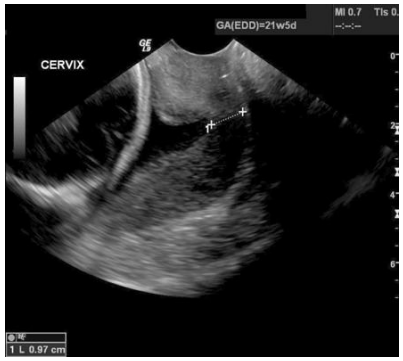
- Buprenorphine only vs with naloxone
  - Subutex vs Suboxone
- Designed to deter abuse or diversion
- Suboxone may have greater availability
- Available evidence
  - 87 women no difference in outcomes
  - No evidence of congenital anomalies
    - Weigand S *AJOG* 2014

Availability of Treatment in CNY

- 55+ registered providers for buprenorphine
- 2 methadone centers
  - Syracuse, Binghamton
- www.samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator

Detoxification in Pregnancy: What is the Evidence?

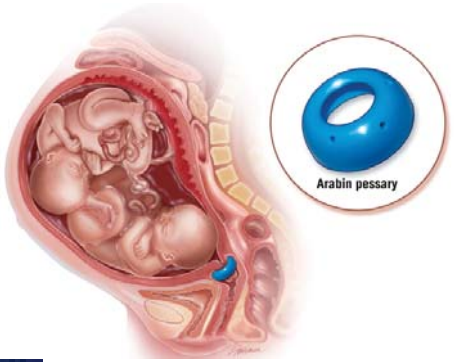
- 95 women electing inpatient detoxification
  - 53% successful (no illicit drugs at delivery)
  - Median 25 days maternal inpatient
  - Lower rates of neonatal NAS, LOS (3 vs 22d), withdrawal (10 vs 80%)
  - No factors predicted success, but were more likely to have stayed to complete the program
    - Stewart RD *AJOG* 2013
- Historical cohort study in Norway: perinatal outcomes
  - Improvement in delivery GA and birth weight, no NAS
  - No differences in loss rate or maternal morbidities
    - Haabrekke *J Addict Dis* 2014



UPDATES ON PRETERM BIRTH

Multiples: RCTs of Pessary Use

- Unselected twins: 1180 women
  - Post hoc analysis of 213 women with CL<2.5 cm
    - PTB <34 no sig difference 31% pessary vs 26% control
      - Nicolaides K *AJOG* 2016
- PECEP twins: 137 women with CL<2.5 cm
  - PTB <34 weeks 16% pessary vs 39% controls
    - relative risk 0.41 (95% CI, 0.22-0.76)
    - Goya M *AJOG* 2016



American College of Obstetricians and Gynecologists (ACOG)/Society for Maternal-Fetal Medicine (SMFM) Obstetric Care Consensus

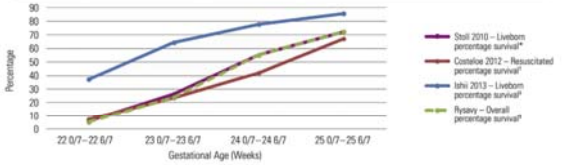
#3: Periviable birth

All applicable Practice Bulletins updated to reflect changes in published outcomes for periviability:

CONSIDER

betamethasone series at 23w0d

FIGURE 1
Percentage of survival by gestational age



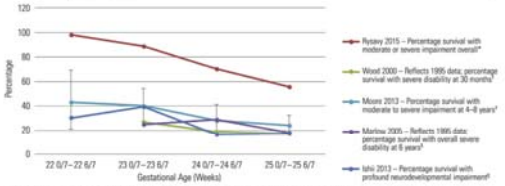
*Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Pediatrics 2010;126:443–56.

†Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;345:e7976.

‡Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Outcomes of infants born at 22 and 23 weeks' gestation. Neonatal Research Network, Japan. Pediatrics 2013;132:62–71.

§Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 2015;372:1801–11.

FIGURE 2
Percentage with severe or moderate disability by gestational age among surviving newborns



*Rysavy MA, Li L, Bell EF, Das A, Hintz SR, Stoll BJ, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 2015;372:1801–11.

†Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med 2000;343:378–84.

‡Moore GP, Lemyre B, Barrowman N, Daboval T. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis. JAMA Pediatr 2013;167:967–74.

§Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. EPICure Study Group. N Engl J Med 2005;352:9–19.

¶Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Outcomes of infants born at 22 and 23 weeks' gestation. Neonatal Research Network, Japan. Pediatrics 2013;132:62–71.

ACOG. Periviable birth. Am J Obstet Gynecol 2015.

TABLE 3
General guidance regarding obstetric interventions for threatened and imminent periviable birth by best estimate of gestational age[a]

	20 0/7 weeks to 21 6/7 weeks	22 0/7 weeks to 22 6/7 weeks	23 0/7 weeks to 23 6/7 weeks	24 0/7 weeks to 24 6/7 weeks	25 0/7 weeks to 25 6/7 weeks
Neonatal assessment for resuscitation[b]	Not recommended 1A	Consider 2B	Consider 2B	Recommended 1B	Recommended 1B
Antenatal corticosteroids	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Tocolysis for preterm labor to allow for antenatal corticosteroid administration	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Magnesium sulfate for neuroprotection	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Antibiotics to prolong latency during expectant management of preterm PROM if delivery is not considered imminent	Consider 2C	Consider 2C	Consider 2B	Recommended 1B	Recommended 1B
Intrapartum antibiotics for group B streptococci prophylaxis[c]	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Cesarean delivery for fetal indication[c]	Not recommended 1A	Not recommended 1A	Consider 2B	Consider 1B	Recommended 1B

PROM, premature rupture of membranes.

[a] Survival of infants born in the periviable period is dependent on resuscitation and support. Between 22 weeks and 25 weeks of gestation, there may be factors in addition to gestational age that will affect the potential for survival and the determination of viability. Importantly, some families, concordant with their values and preferences, may choose to forgo such resuscitation and support. Many of the other decisions on this table will be linked to decisions regarding resuscitation and support and should be considered in that context; [b] Group B streptococci carrier, or carrier status unknown; [c] For example, persistently abnormal fetal heart rate patterns or biophysical testing, malpresentation.

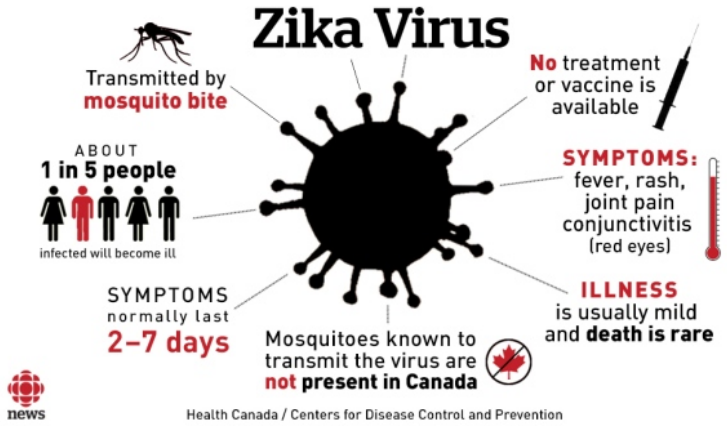
ACOG. Periviable birth. Am J Obstet Gynecol 2015.

Counseling with neonatal outcomes **INDIVIDUALIZED** to clinical scenario (use calculator and RPP data) **AND** maternal outcomes (classical incision)

OUTCOMES CALCULATOR

www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo_case.aspx?start¼13:15:46)

UPDATES ON ZIKA VIRUS



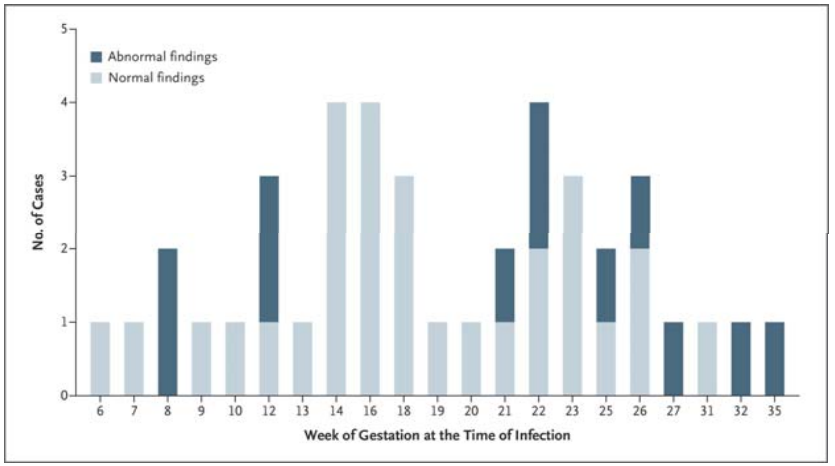
www.cdc.gov/zika/pregnancy/

www.health.ny.gov/diseases/zika_virus/

WHO/PAHO

Zika Virus: Vertical Transmission

- Viral neurotropism on autopsy findings
- Microcephaly and other CNS anomalies
  - (Ca^{2+}, agyria/arrest of cortical development)
    - Mlakar *NEJM* 2016
- Rate and timing importance uncertain
    - Brasil *NEJM* 2016



Brasil P et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1602412

CDC 2/26 - MMWR

- 9 pregnant US women with confirmed travel exposure
  - 6 first trimester
    - 2 early losses – PCR proven Zika
    - 2 elective terminations – one with usg CNS anomalies
    - 1 live born infant with microcephaly
    - 1 continuing
  - 2 second trimester – no evidence of disease
  - 1 third trimester – healthy live born

Prevention of Zika Infection

- Covering exposed skin
- Mosquito nets
- DEET, permethrin-infused clothing
- Abstain from intercourse or use condoms with exposed males
  - NYS case

ACOG and SMFM – Feb/Mar 2016

- Antibody testing to be ordered for all pregnant patients who traveled to or live in affected areas or with exposed partner **even without history of clinical illness**
  - With clinical s/sx within 2 weeks (viral PCR and IgM)
  - 2-12 weeks after exposure (IgM)
- Discuss Zika risks with reproductive age women in context of travel plans
- Counsel that history of Zika infection does not appear to pose risk for future pregnancy

Fetal Evaluation and Surveillance

- Focus on microcephaly and CNS calcifications
- Ultrasound q 3-4 weeks in positive or indeterminate cases
- Zika can be tested by amniocentesis via PCR
  - Uncertainty re timing, correlation with outcomes
- Send placentas or products of conception
- Breastfeeding not contraindicated