2016 MDF
ANNUAL CONFERENCE

September 15-17 2016, Washington DC

MYOTONIC DYSTROPHY FOUNDATION

Care and a Cure

FAMILY PLANNING 2016 ANNUAL MYOTONIC DYSTROPHY CONFERENCE SEPTEMBER17, 2016

Alice Schindler, MS, CGC; Julie Cohen, MS, CGC; Karin Blackmore, MD

Presentation Overview

- Genetics of DM
  - Alice B. Schindler, MS, CGC
    - NGB/NINDS/NIH
- Pre-conception and prenatal genetic testing
  - Julie Cohen, MS, CGC
    - Kennedy Krieger Institute
- Pregnancy with DM
  - Karin Blackmore, MD
    - Director, Prenatal Genetics, Prenatal Diagnostic Center, Professor of Gynecology and Obstetrics Johns Hopkins School of Medicine

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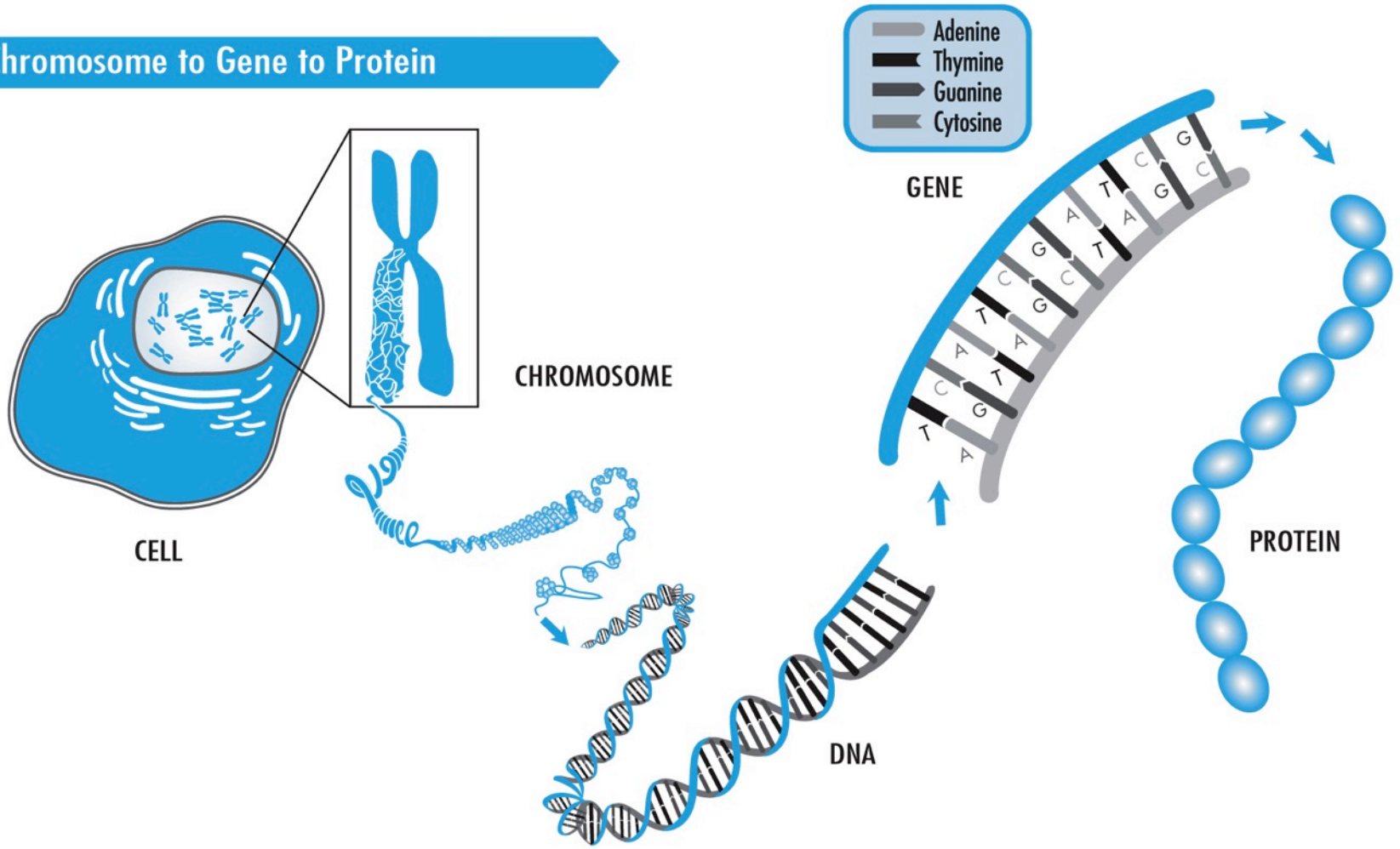
GENETICS OF MYOTONIC DYSTROPHY

Myotonic Dystrophy 1 (DM)

- Prevalence 1:20,000 - 3 classifications
  - Mild DM: Onset 20-70 years
    - Cataracts, mild myotonia, diabetes
    - Diagnosis usually after an affected family member
  - Classical DM: Onset 10-30 years
    - Distal muscle weakness, facial weakness, muscle myotonia

      ophthalmoplegia, nasal speech, cardiac, cataracts, frontal balding, endocrinopathies, GI abnormalities, psychological involvement
  - Congenital DM
    - Prenatal – polyhydramnios, reduced fetal movement
    - Neonatal period
      - Hypotonia, generalized weakness, including facial muscles, clubfoot
      - Respiratory insufficiency or failure – mortality - 25% within first 18 months
    - After neonatal period
      - Able to walk but delayed, intellectual disability possible due to early respiratory failure

Chromosome to Gene to Protein



Greenwood Genetic Center

DM1 genetics

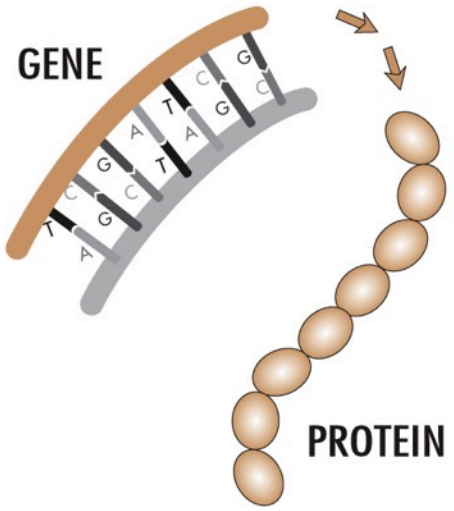
- CTG repeats in 3' UTR of DMPK gene located on 19q13
- Autosomal Dominant: mRNA gain of function (abnormal RNA transcript processing)
  - Premutation: 35 to 49
  - Mild: 50 to ~150
  - Classic: ~100 to ~ 1000
  - Congenital: >2000
- Anticipation typically occurs from maternal allele
  - Maternal CTG repeat <300, risk for child who inherited expanded allele to have congenital DM is 10%. Maternal CTG repeat >300,

    risk for child who inherited expanded allele to have congenital DM is 59% (Cobo et al. 2002).
- Paternal transmission with anticipation including congenital DM has been reported, but is rare.
- Meiotic and mitotic instable.
- Phase 1: Multiple Doses of ISIS-DMPKRx (antisense drug) in Adults With Myotonic Dystrophy Type 1

DM 2

- **Phenotype:** Similarities to adult-onset DM1: progressive weakness, myotonia, cardiac arrhythmias, cataracts, male hypogonadism, and diabetes.
- Differences from DM1: no congenital form; no intellectual disability in juvenile cases; less weakness in distal, facial, and bulbar; less pronounced muscle atrophy. DM2 patients first seek medical attention for muscle pain, stiffness, fatigue, proximal lower extremity weakness
- **Molecular genetics:** AD, 3q21, ZNF9 (zinc finger protein 9) gene – CCTG repeat expansion in intron 1
  - Normal allele is $\leq$176bp
  - Borderline allele is between 177-372bp
  - Abnormal allele is >372 bp, but are usually much larger, approx 20,000bp
    - Frequently, repeats can be shorter in offspring after both maternal and paternal transmission

Trinucleotide Repeat Disorders



A **trinucleotide** is a group of 3 chemical bases within a gene. Trinucleotides code for **amino acids**. Amino acids are the building blocks of **proteins.**

TRINUCLEOTIDE C G G

Normal number of repeated trinucleotide segments within a gene = **Normal Protein Function.**

CGG CGG CGG CGG

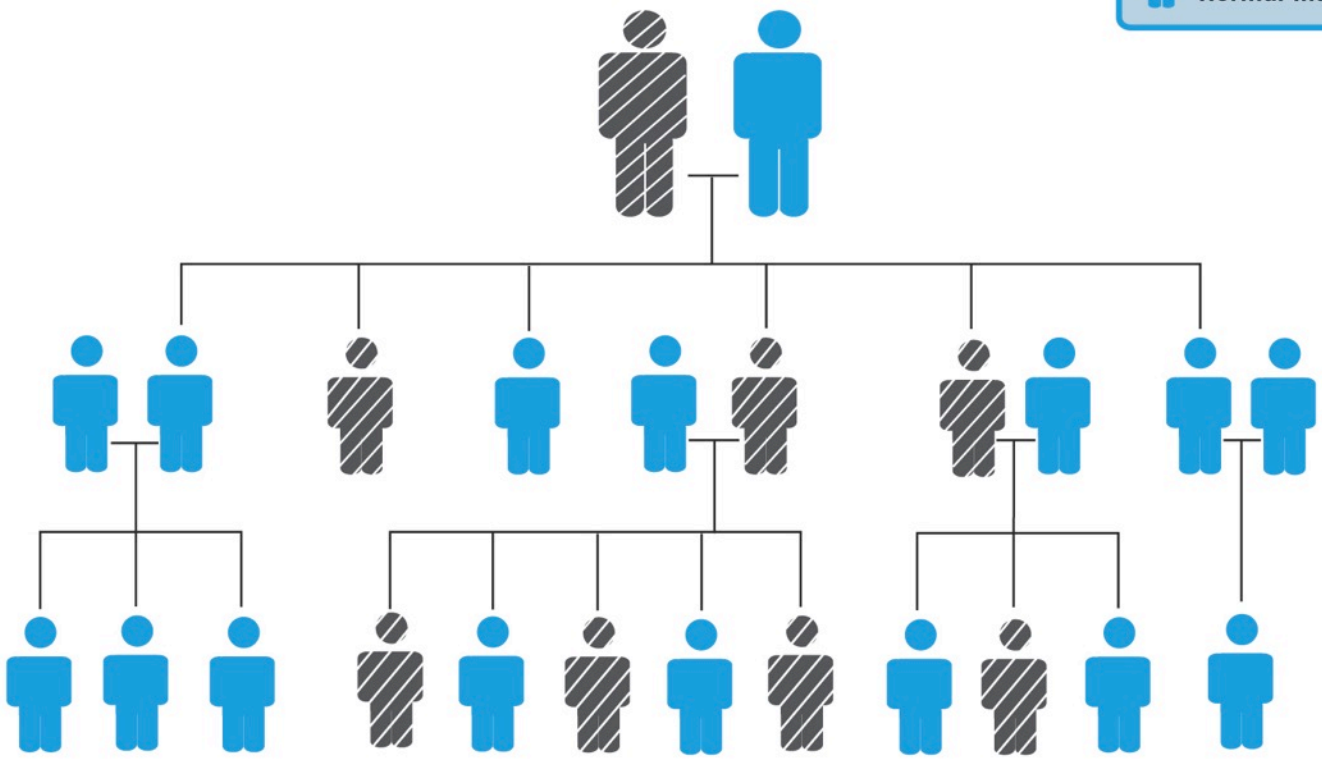
Mildly expanded number of repeated trinucleotide segments = **Normal Protein Function.**

CGG CGG CGG CGG CGG CGG CGG

Fully expanded number of repeated trinucleotide segments = **Abnormal or Absent Protein.**

CGG CGG CGG CGG CGG CGG CGG CGG CGG CGG CGG

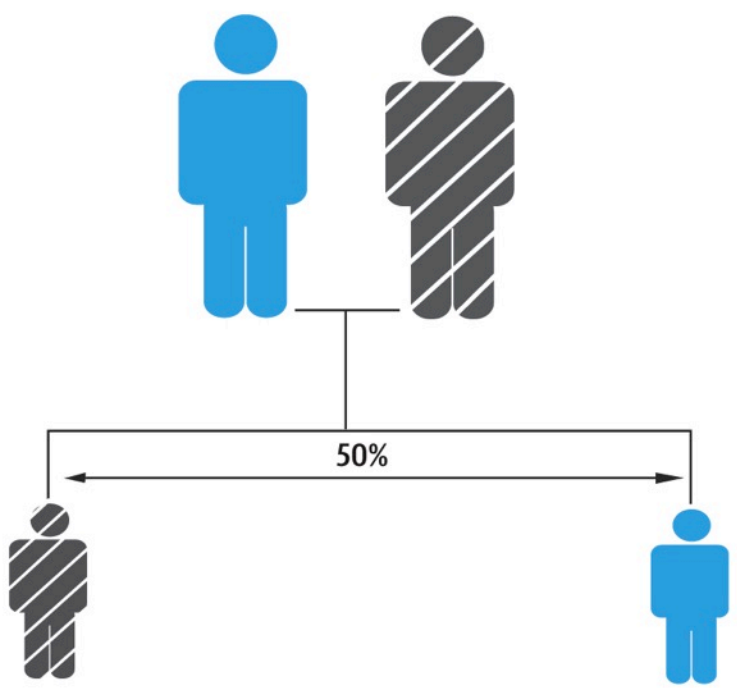
Autosomal Dominant Inheritance



Characteristics of Autosomal Dominant Inheritance

- Multiple generations affected
- Males and females are equally likely to be affected
- Male to male transmission occurs
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected

Autosomal Dominant Segregation, One Parent Affected



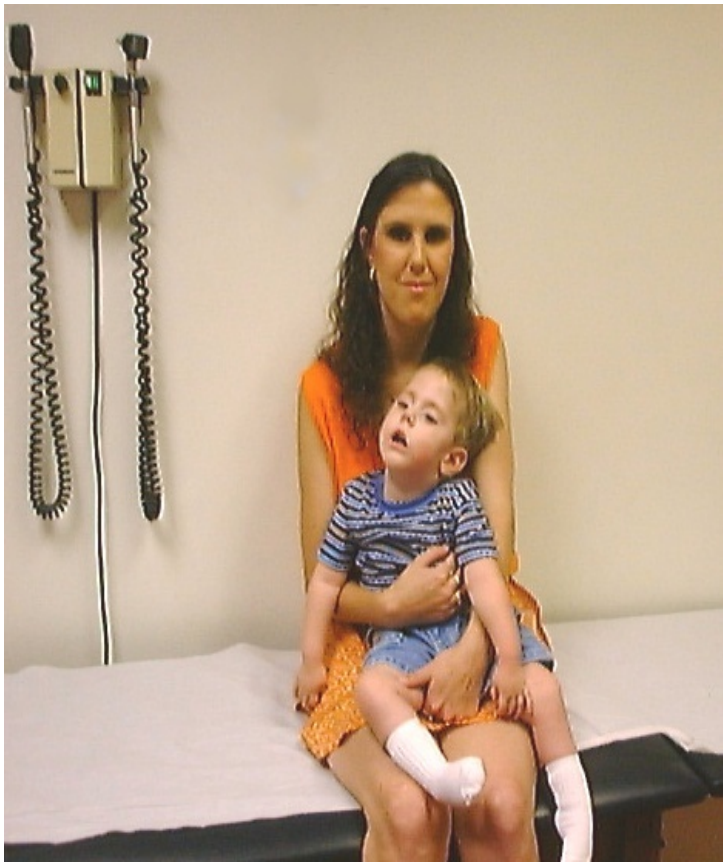
1 in 2 chance (50%) that the child will be affected

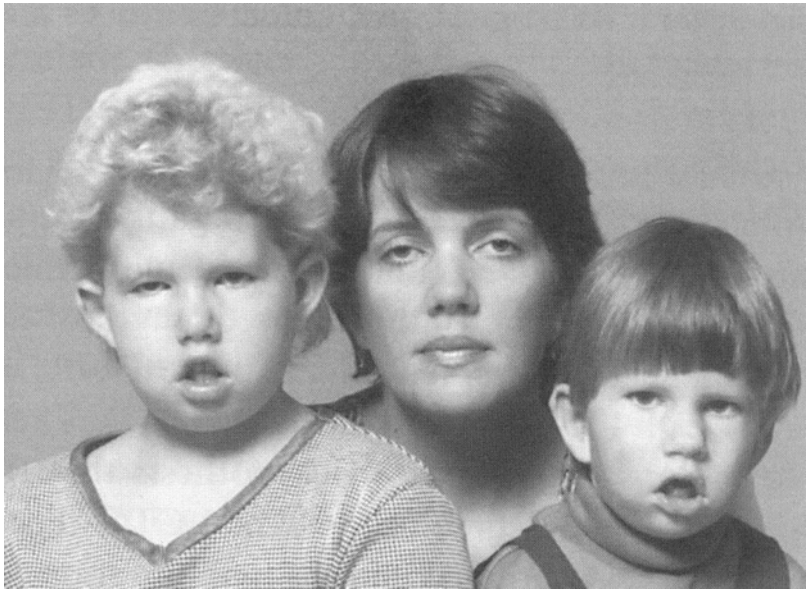
1 in 2 chance (50%) that the child will not be affected

Genetic Testing

- Genetic Dx required for family planning
- Clinically available through several labs in US and worldwide
- PCR-based, 2-4 weeks
- Test cost $290-700 (lab, self- insurance- institutional billing)
- Insurance coverage:
  - **CPT codes: 81401x1**
  - **ICD10 codes: G71.11**

Myotonic Dystrophy (DM)





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FAMILY-BUILDING OPTIONS FOR MYOTONIC DYSTROPHY

Family-Building Options

Family-Building Options

IVF + PGD

Donor Eggs/ Sperm

Prenatal Testing

Adoption

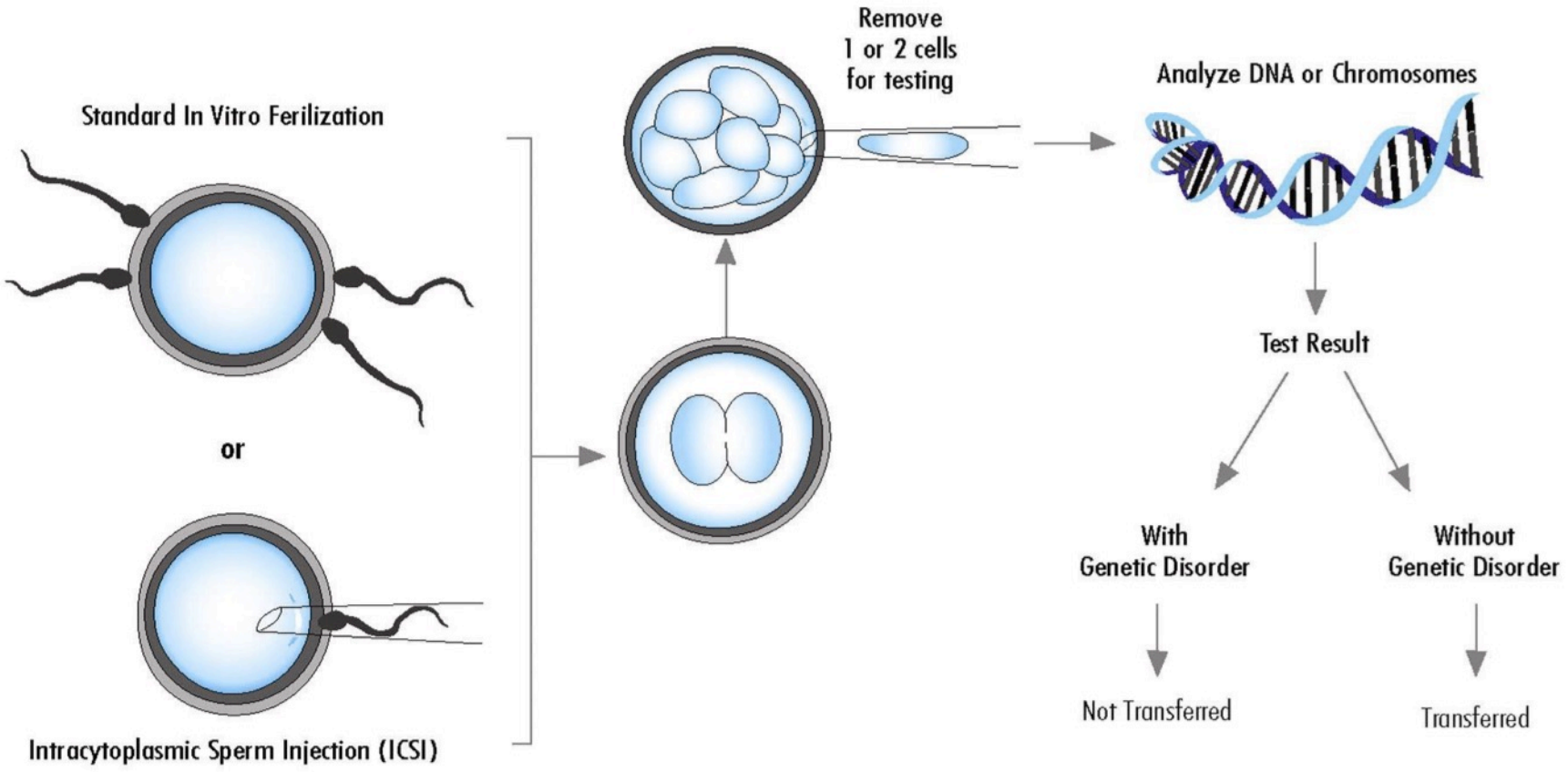
IVF + PGD

- **IVF: In Vitro Fertilization**
  - Combine eggs & sperm in lab to create embryos
- **PGD: Preimplantation Genetic Diagnosis**
  - Genetic testing of embryos created by IVF
  - Only “unaffected” embryos (without DM) transferred to woman’s womb to start pregnancy

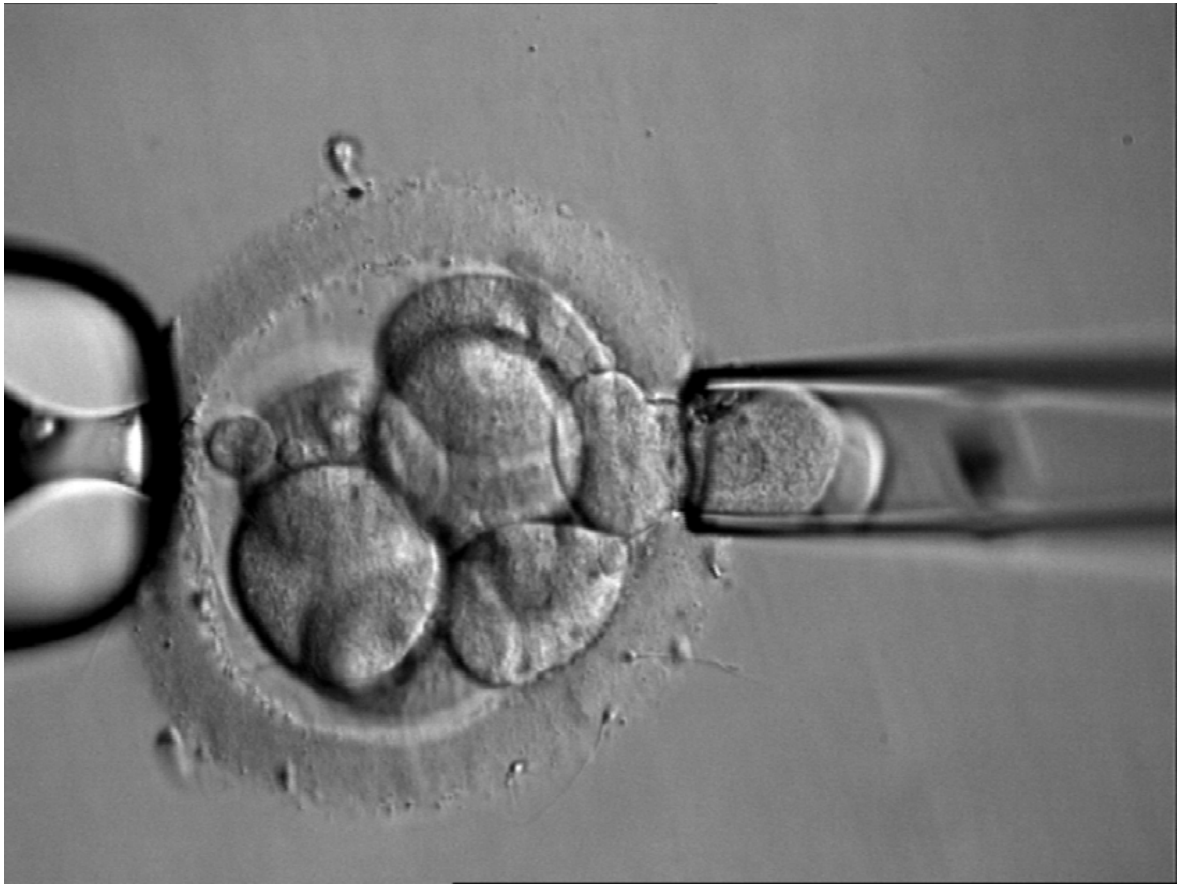
IVF + PGD

- Woman takes medications (oral and injections) to regulate cycle and stimulate ovaries to produce multiple eggs, monitored by frequent ultrasounds and blood tests
- Eggs retrieved (minor surgery), male partner provides semen sample
- Eggs fertilized by intracytoplasmic sperm injection (ICSI)
- Early embryos grow in lab for several days
- **PGD:** Embryo biopsy 3-6 days after fertilization, perform genetic testing on single cells (results may take several days or longer so often embryos will be frozen and transferred in a subsequent cycle)
- Transfer of one or more embryos to womb

IVF + PGD


Standard In Vitro Ferilization
or
Intracytoplasmic Sperm Injection (ICSI)
Remove
1 or 2 cells
for testing
Analyze DNA or Chromosomes
Test Result
With
Genetic Disorder
Not Transferred
Without
Genetic Disorder
Transferred

IVF + PGD



IVF + PGD: Pros & Cons

ADVANTAGES

- Increases likelihood of birth of unaffected child without need for termination of an ongoing pregnancy
- Highly accurate

DISADVANTAGES

- You don't get to conceive the "fun" way!
- IVF not always successful, may need multiple cycles
- Costly, may not be covered by insurance

IVF + PGD: Financial Considerations

	Approximate Cost
Fresh IVF Cycle	$12,400*
ICSI	~ $1,500
Medications	~ $3,000-5,000
PGD	~ $5,000
TOTAL	**~ $20,000 - $25,000**

- Costs and insurance coverage varies widely
- Don't assume it's not covered! Schedule consultation with IVF/ PGD clinic to find out actual costs, your specific insurance coverage, and financial options

**U.S. average [source: www.asrm.org]*

IVF + PGD: Financial Considerations

- Many resources available:
  - Refund programs through IVF clinics
  - Discounts for military/veterans
  - Financing and loans
  - Grants
  - Crowdfunding

www.resolve.org

Prenatal Testing

- Get pregnant "naturally"
- Genetic testing during pregnancy
- Option to end pregnancy if baby has DM

- Two procedures
  - **Chorionic villus sampling (CVS)**: performed 11-13 weeks
  - **Amniocentesis**: performed at 15-20 weeks

- Highly accurate, small risk of miscarriage

Prenatal Testing

- Two procedures
  - **Chorionic villus sampling (CVS)**

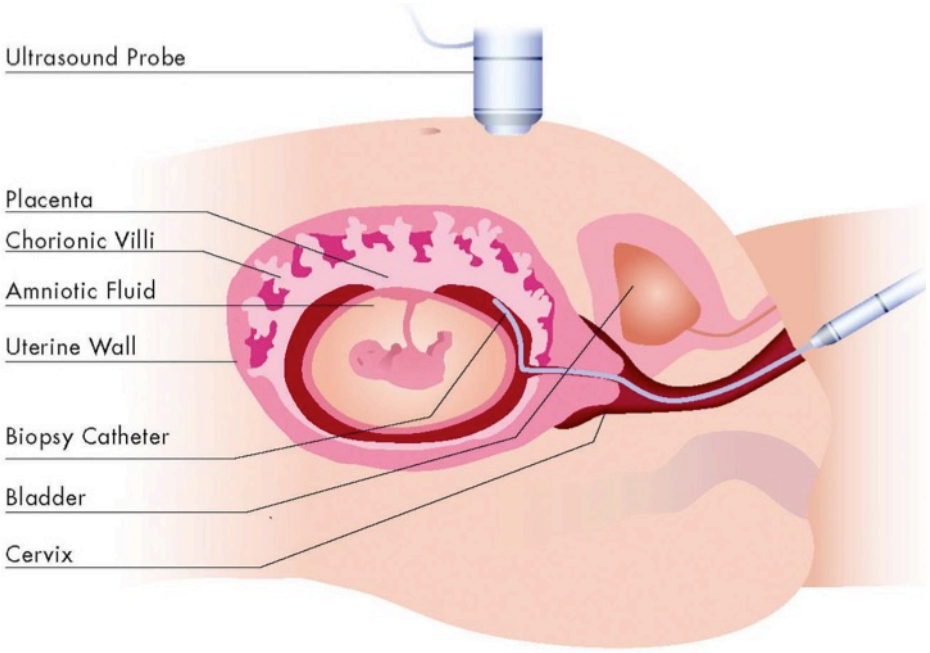
    Performed at 11-13 weeks (~3 months)

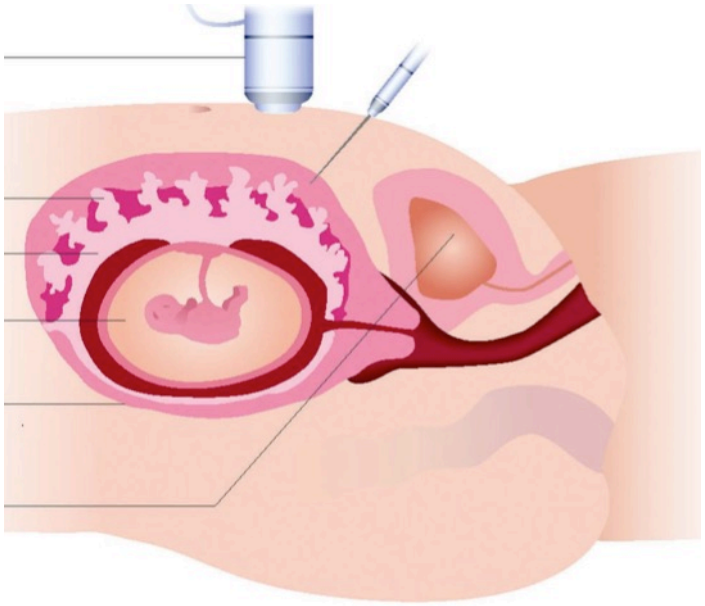
  - **Amniocentesis (Amnio)**

    Performed at 15-20 weeks (~4-5 months)

Prenatal Testing: CVS

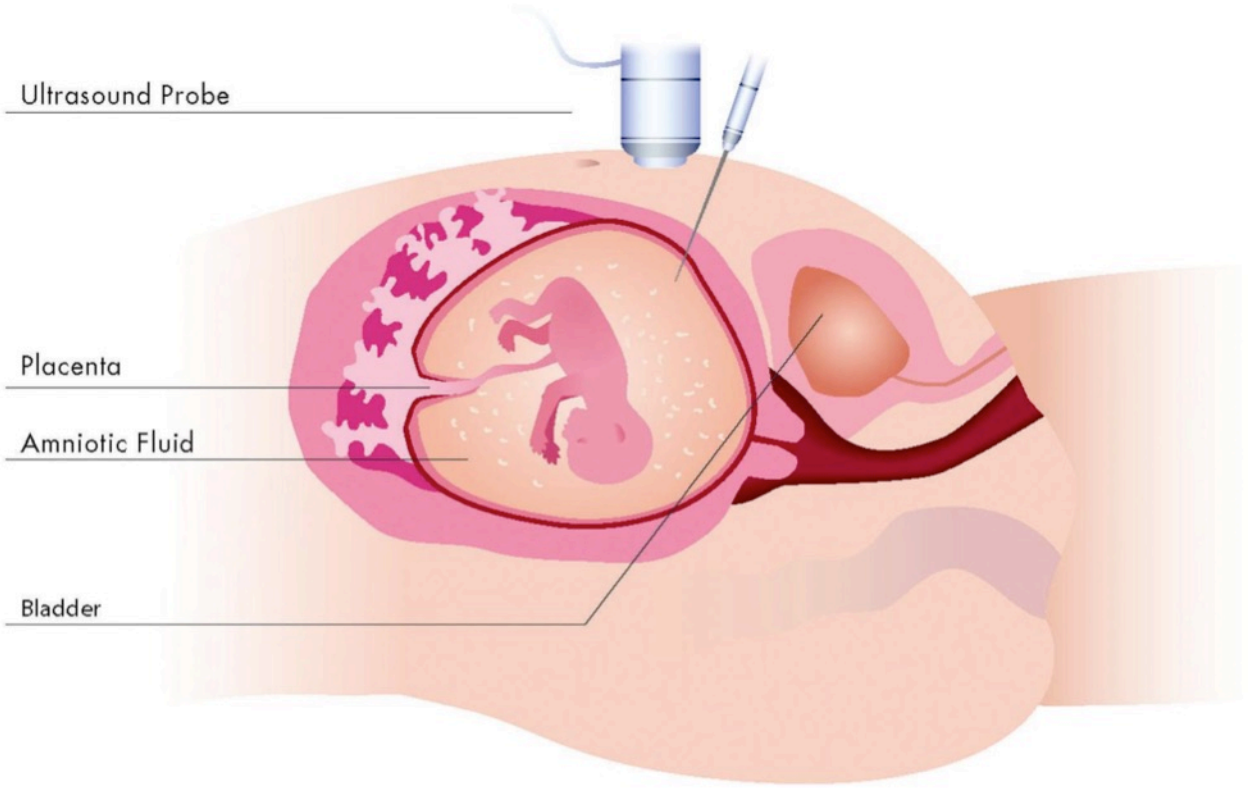
- Needle through abdomen or catheter through cervix to obtain chorionic villi (part of placenta)
- Risk of miscarriage = 1/200 (0.5%)





Prenatal Testing: Amnio

- Needle through abdomen to remove small amount of amniotic fluid that contains cells from baby
- Risk of miscarriage = 1/300 (0.3%) or less



Prenatal Testing: Pros & Cons

ADVANTAGES

- Highly accurate (>99%)
- Likely covered by insurance

DISADVANTAGES

- Cannot "fix" abnormal gene, option is to end pregnancy (abortion)
- Small risk of miscarriage

Donor Eggs/Sperm

- Use eggs or sperm from donor who does not have myotonic dystrophy
- Available from storage banks
- Donor sperm can be inseminated directly into the woman's womb or used in IVF procedures
- Donor eggs can be used in IVF procedures

Donor Eggs/Sperm: Pros & Cons

ADVANTAGES

- Guaranteed child without DM, no need for genetic testing of embryo or fetus
- Child is genetically related to one parent
- Woman can carry pregnancy

DISADVANTAGES

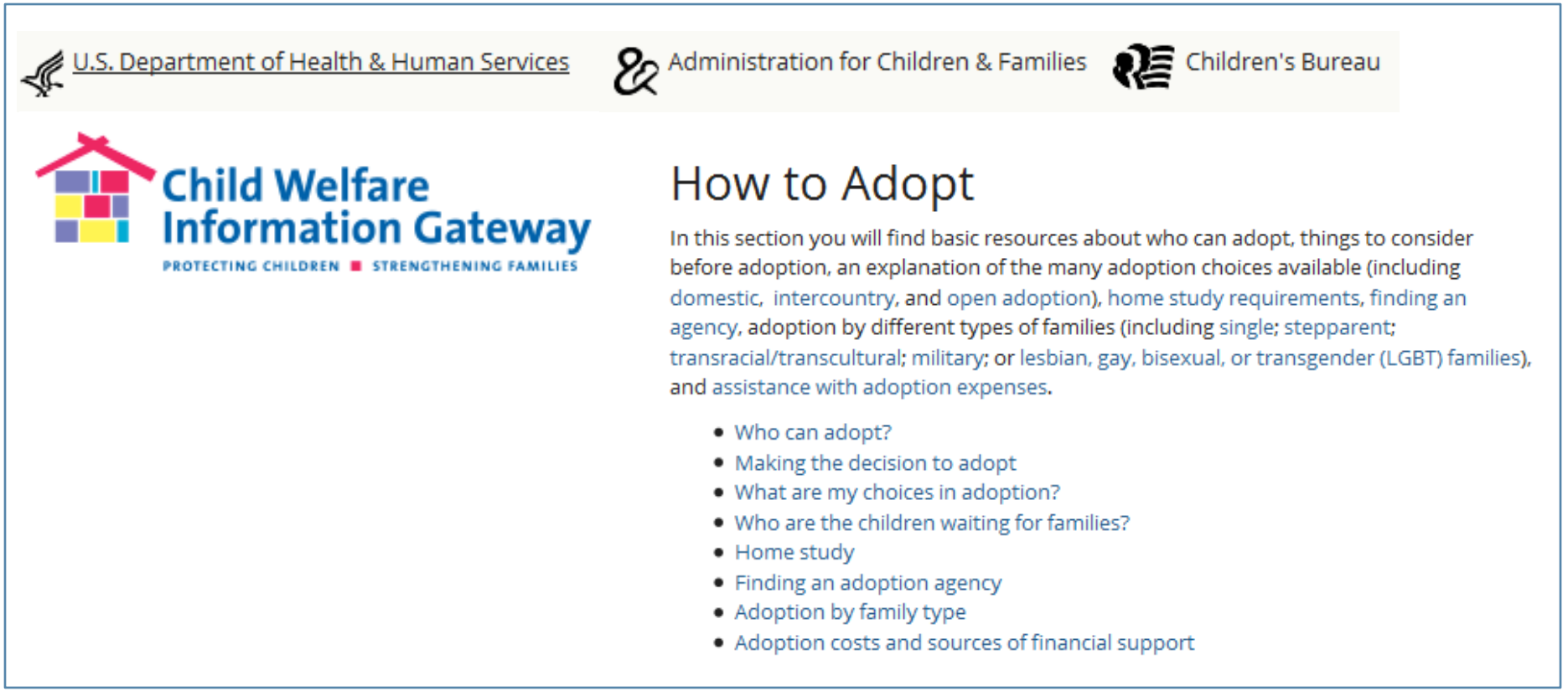
- Child is not genetically related to one parent
- May not be covered by insurance

Adoption

- Many different types of adoption
  - Domestic or international
  - Closed or open
  - Foster to adoption
- Financial resources and tax credits available
- http://www.resolve.org/family-building-options/adoption/

Adoption

- https://www.childwelfare.gov/topics/adoption/



Adoption: Pros & Cons

ADVANTAGES

- Guaranteed child without DM, no need for genetic testing of embryo or fetus
- Provide home and family to child who needs one ☺

DISADVANTAGES

- Child is not genetically related to either parent, woman does not carry pregnancy

Family-Building Options

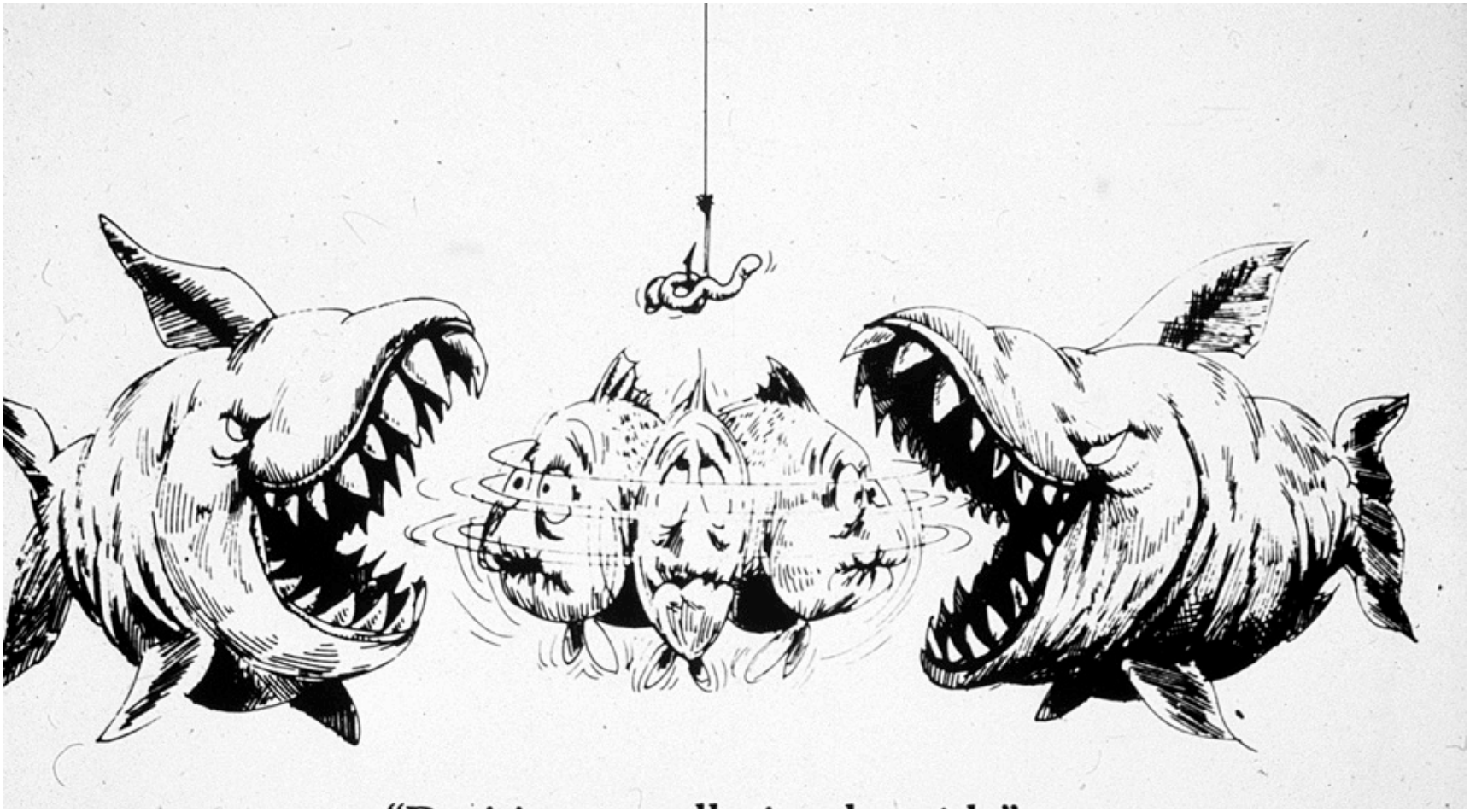
IVF + PGD

Donor Eggs/ Sperm

Prenatal Testing

Adoption

Decision-Making



Decision-Making

- When deciding whether to take action to prevent passing on a genetic condition, individuals consider
  - Nature and severity of disease
  - Age of onset
  - Quality of life
  - Availability of treatment currently and future prospects
- Many of these aspects are subjective and/or uncertain
- Influenced by lived experience with the condition

Choosing among the options

- How important is it that the child be genetically related to you?
- How important is it that you or your partner carry a pregnancy?
- Would you be willing to terminate an affected pregnancy?
- What will your finances allow?

General advice

- "Try on" each option – spend time imagining how it would feel and what your life would look like if you go that route
- Different family members do not always agree – this is normal
- There is no absolute "right" or "wrong" choice
- If you are really struggling with a decision, seek out individual or couples counseling

Resources

- National Society of Genetic Counselors
  - www.nsgc.org

- Resolve
  - www.resolve.org

- Genetics Fact Sheets
  - http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets

Resources

MATERNAL MYOTONIC DYSTROPHY AND PREGNANCY

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Karin J. Blakemore, M.D.

Director, Prenatal Genetics

Division of Maternal-Fetal Medicine

Johns Hopkins University School of Medicine

Myotonic Dystrophy

- DM1
  - Distal muscle weakness and wasting
  - Facial muscle involvement
    - Ptosis
    - Tent-shaped mouth
  - CTG trinucleotide repeat DM protein kinase gene (DMPK)

- DM2
  - Proximal muscle weakness of lower limbs
  - Later onset and more favorable course
  - CCTG tetranucleotide repeat Zinc finger 9 protein gene (CNBP)

- **Phenotypes of DM1 and DM2 overlap** somewhat

Myotonic Dystrophy Type I DM1

- Most common heritable neuromuscular disorder
  - 1 in 8,000
- Progressive muscle weakness and wasting
- Myotonia
- Cataract Formation
- Endocrine abnormalities
  - Diabetes mellitus
  - Gonadal dysfunction in men

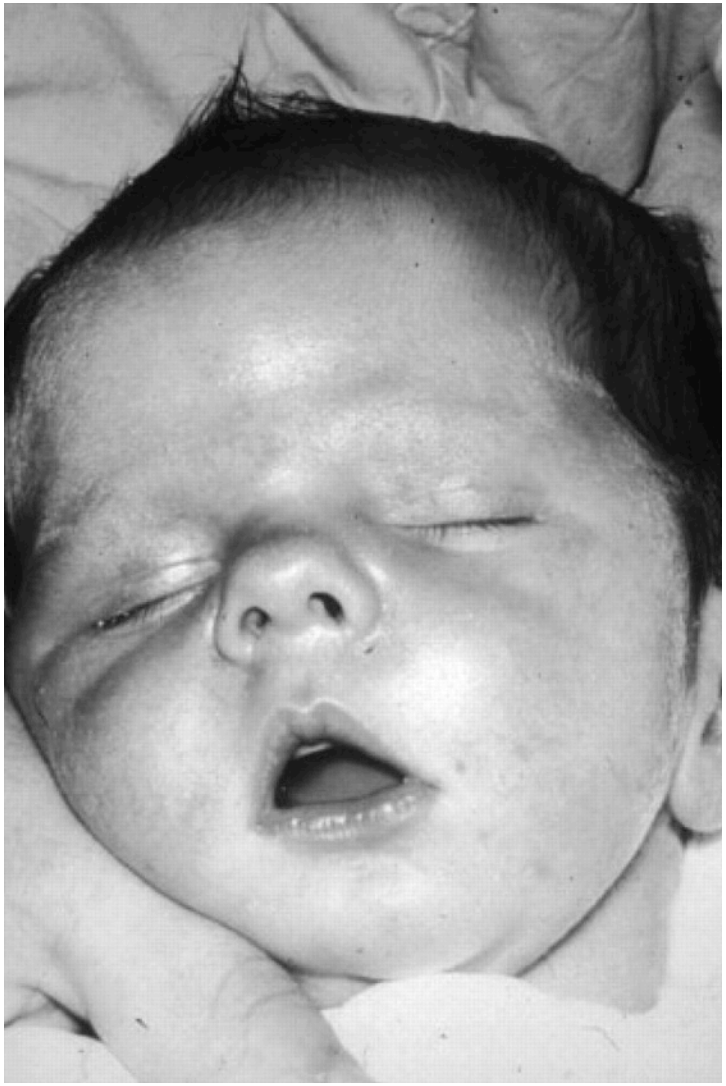
Myotonic Dystrophy Type I
DM1

- DM1 is caused by a triplet repeat expansion (CTG) in non-coding region of the "myotonin" gene, the DM protein kinase gene (DMPK) at 19q13.3
- Normal repeat size 5 – 34
- Affected individuals have 50 – thousands of repeats
  - Severity correlates with number of repeats
- Congenital form nearly always occurs to an affected mother (i.e. rarely to an affected father)
  - Premutation alleles 35-49 repeats in unaffected parent

Myotonic Dystrophy Type I
DM1

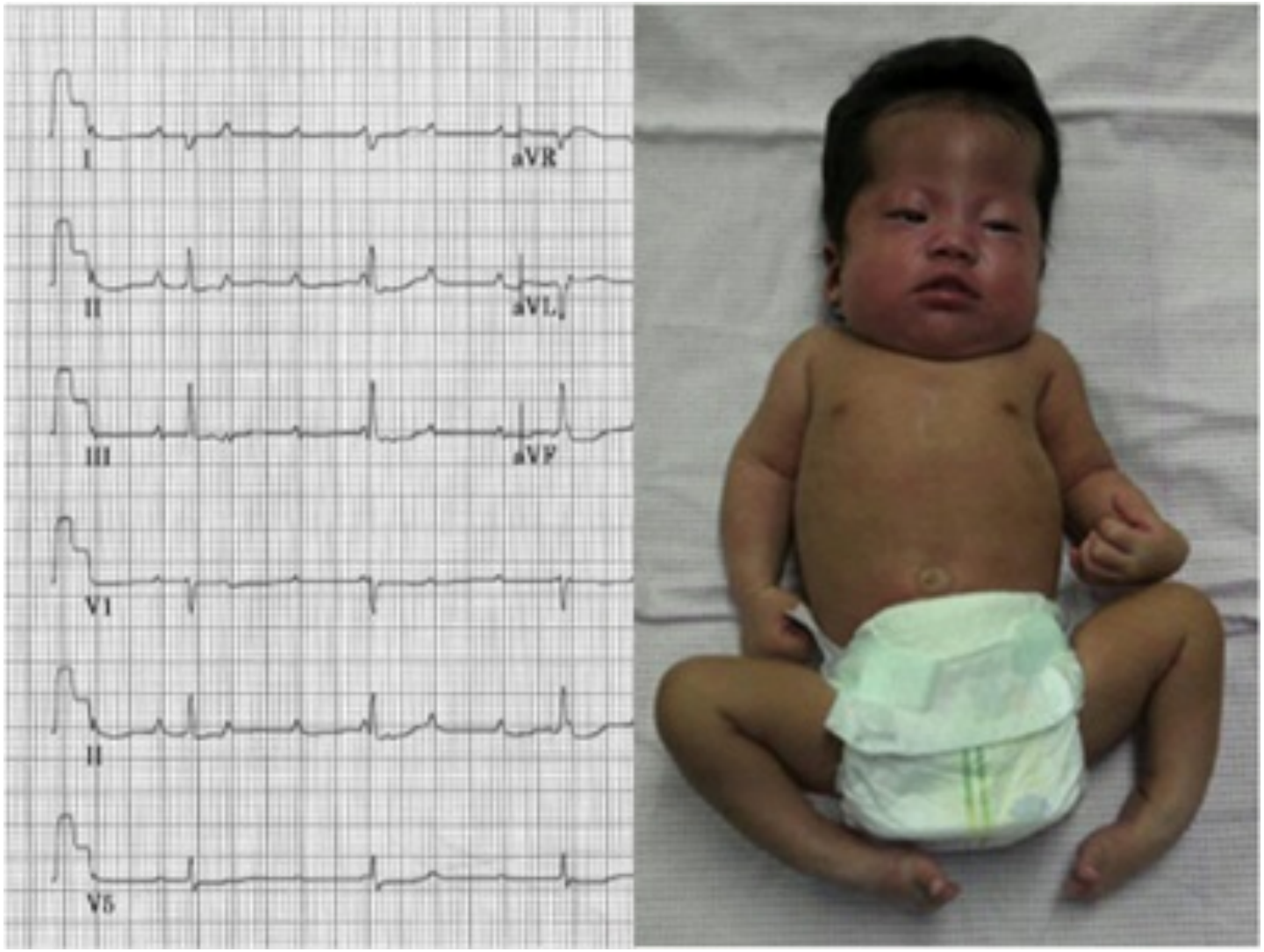
3 Types:

- **Mild**
- **Classic**
- **Congenital**



Congenital DM1 Neonatal Characteristics

- Floppy
- Facial diplegia and tent-shaped mouth
- Talipes
- Respiratory difficulties
  - Diaphragmatic hypoplasia
  - Improves with time
- 20% Neonatal Mortality
- GI Dysmotility
- Cerebral ventriculomegaly rarely requiring V-P shunt
- Survivors have significant learning disability


I
aVR
II
aVL
III
aVF
V1
II
V5

Classic DM1

Neurology / Volume 17 / February 1967

The effect of pregnancy on dystrophia myotonica

Anthony Hopkins, M.R.C.P., and Shirley Wray, M.R.C.P.

Maternal DM1 and Pregnancy

- Muscle weakness and myotonia stay the same or worsen
  - Usually manifests in third trimester, if at all
  - Progesterone effect?
  - Improves in the puerperium / postpartum

- Regular moderate exercise encouraged
  - Prolonged inactivity worsens symptoms

Maternal DM1 and Pregnancy

Caution (or avoidance) in use of Magnesium Sulfate

- **Anti-seizure prophylaxis for Preeclampsia**
- **Fetal "Neuroprotection" in Preterm Labor**
- **Tocolysis for Preterm Labor**

Maternal DM1
Anesthetic Considerations

- Impaired pulmonary ventilation may be aggravated by even small doses of respiratory depressants
- General anesthesia of particular risk
  - Exaggerated responses to paralytic agents
- Occasionally prolonged post-op intubation is required
- Diminished cough reflex increases risk for aspiration pneumonia
- Cardiac arrhythmias associated with DM1

DM1 and Cardiac Arrhythmias

- **Intraventricular Conduction Defects**
- **First-degree Heart Block**
- **Non-sustained Supraventricular Tachycardia**

  and

  Non-sustained Ventricular Tachycardia

  } **Both more common in DM2**

- ***Risk of sudden cardiac death.***
- **ECG and Holter monitoring are recommended.**

Acta Obstet Gynecol Scand 65:667–668, 1986

CASE REPORT

OBSTETRIC COMPLICATIONS AS THE FIRST SIGN OF MYOTONIC DYSTROPHY

Ditlev Fossen and Leif Gjerstad

From the Department of Obstetrics & Gynecology, Sarpsborg Sykehus, Sarpsborg, and the Department of Neurology, Rikshospitalet, The National Hospital, University of Oslo, Oslo, Norway

Maternal DM1 and Pregnancy

Problems can occur in all 3 stages of labor & postpartum

- **Attributable to generalized muscle weakness and *decreased myometrial contractility***
- **Increased risk for cesarean section and postpartum hemorrhage**
  - **Failure to progress**
  - **Failure to descend**
  - **Uterine atony**

Maternal DM1 and Pregnancy

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  - **Failure to descend**
  - **Uterine atony**

The affected congenital DM1 fetus *also* promotes maternal obstetrical complications.

Maternal DM1 and Pregnancy

Problems can occur in all 3 stages of labor & postpartum

- **Attributable to generalized muscle weakness and *decreased myometrial contractility***
- **Increased risk for cesarean section and postpartum hemorrhage**
  - **Failure to progress**
  - **Failure to descend**
  - **Uterine atony**

The affected congenital DM1 fetus *also* promotes maternal obstetrical complications.

Many pregnant women with DM1 are undiagnosed!

BRITISH MEDICAL JOURNAL VOLUME 289 25 AUGUST 1984

Lesson of the Week

Do you shake hands with mothers of floppy babies?

T H H G KOH

Congenital DM1 Neonatal Characteristics

- Floppy
- Facial diplegia and tent-shaped mouth
- Talipes
- Respiratory difficulties
  - Diaphragmatic hypoplasia
  - Improves with time
- 20% Neonatal Mortality
- GI Dysmotility
- Cerebral ventriculomegaly rarely requiring V-P shunt
- Survivors have significant learning disability

In utero the fetus with Congenital DM1 presents in a very similar way as the neonate.

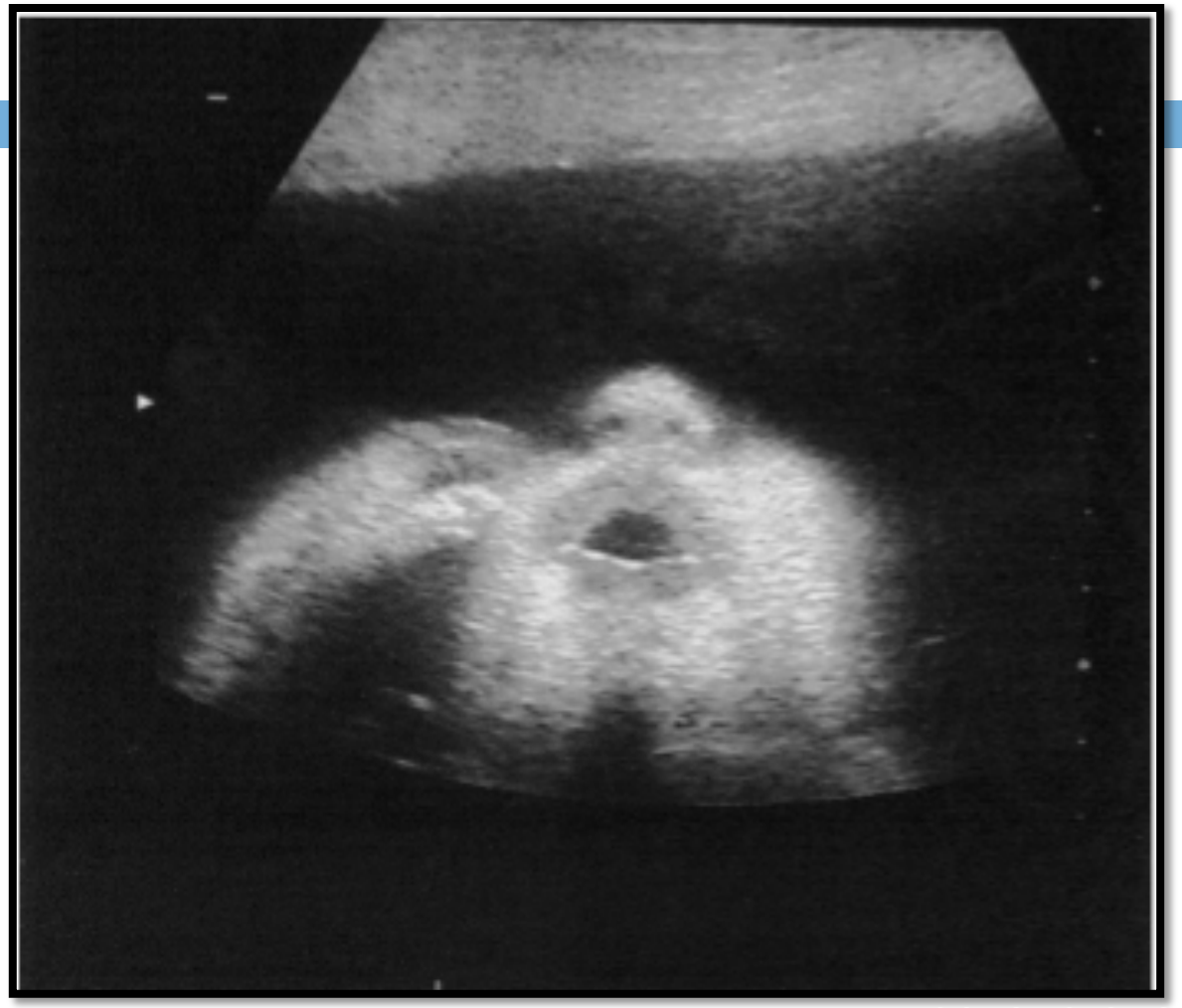
Most women experience decreased fetal movement.

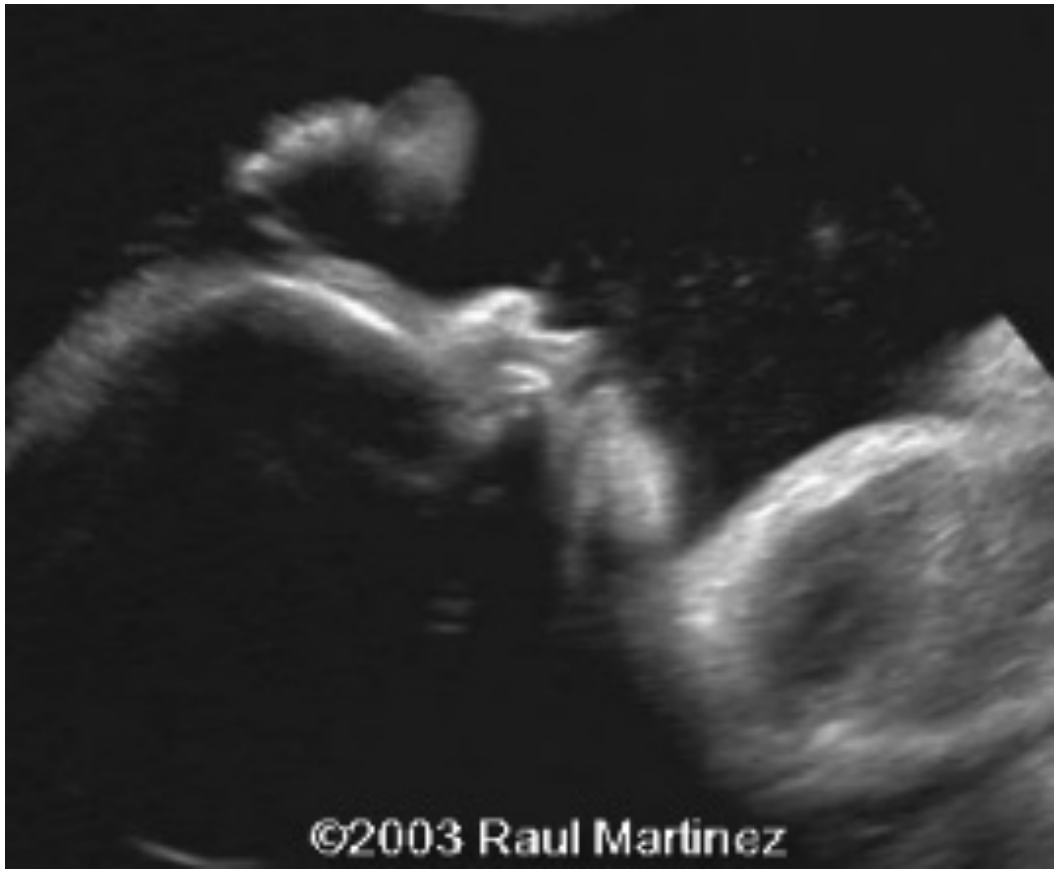
This and the other fetal manifestations are able to be visualized by prenatal ultrasound.

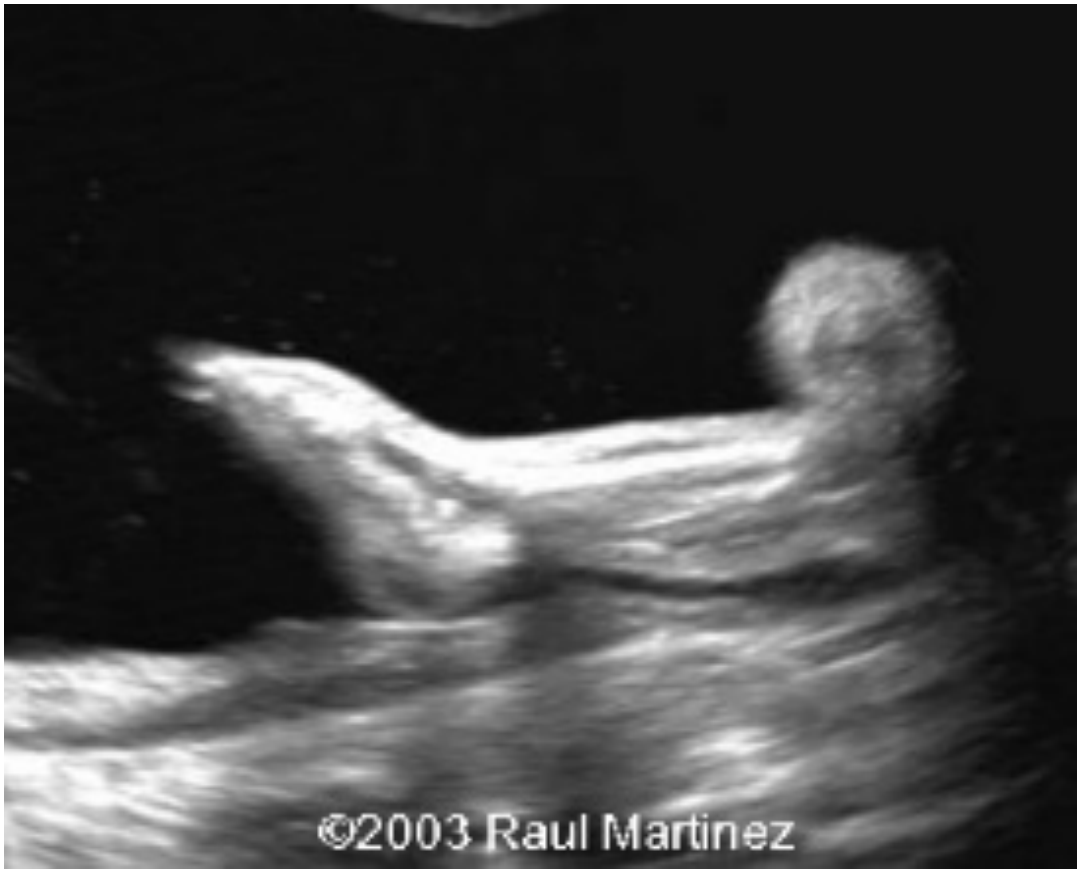
Fetal Effects of Congenital DM1

Fetal hypotonia/myotonia leads to:

- **Decreased fetal movement**
  - **Facial diplegia and tent-shaped mouth**
  - **Talipes**
  - **Breech presentation**
- **Decreased fetal swallowing**
  - **POLYHYDRAMNIOS**




©2003 Raul Martinez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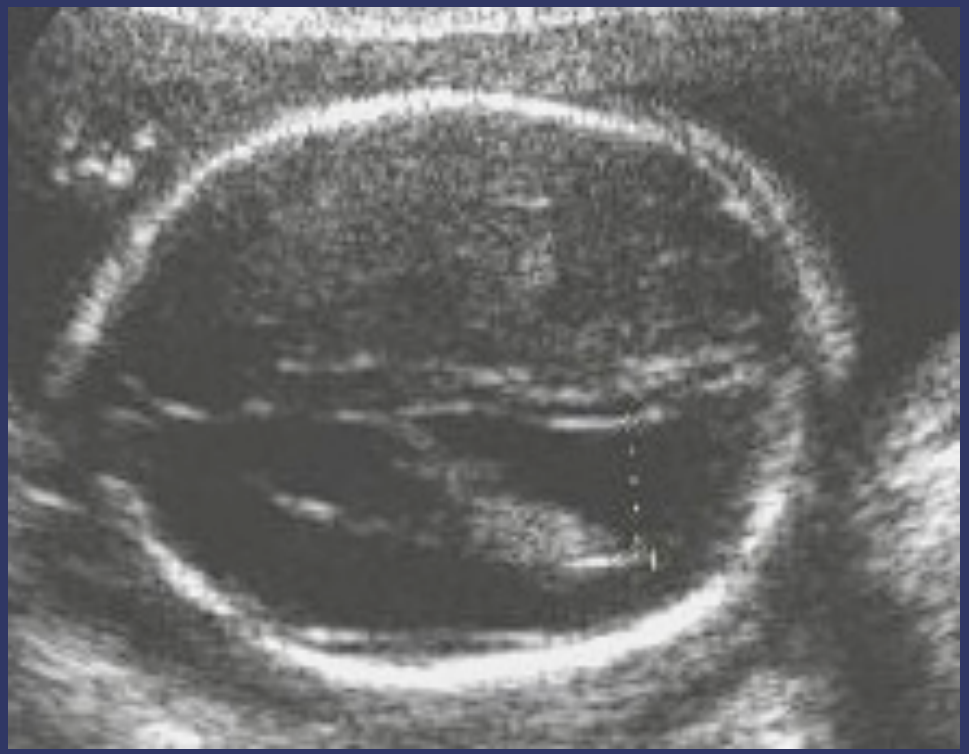


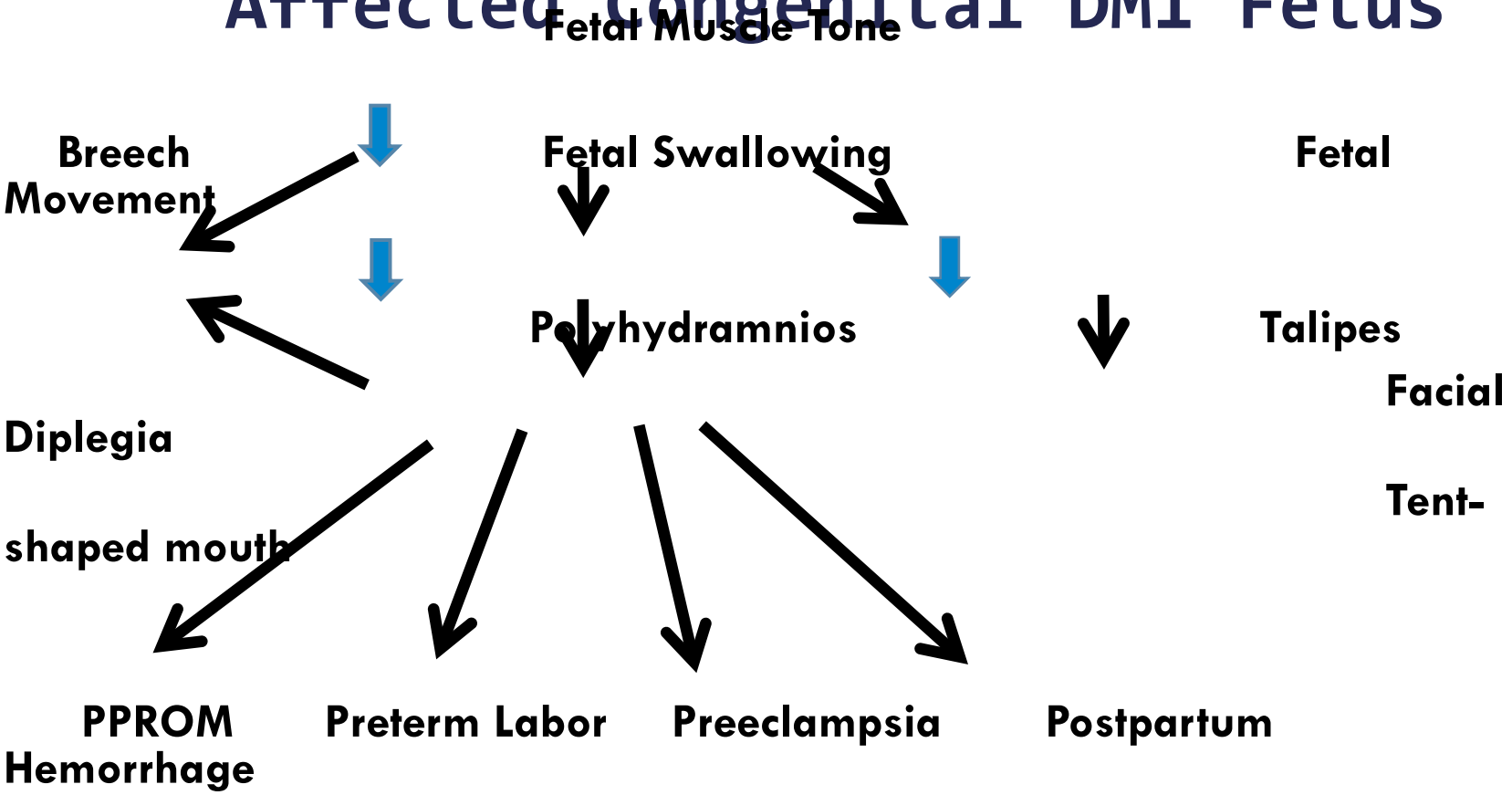
Mild Cerebral Ventricluomegaly

Fetal Effects of Congenital DM1 on Obstetrical Outcomes

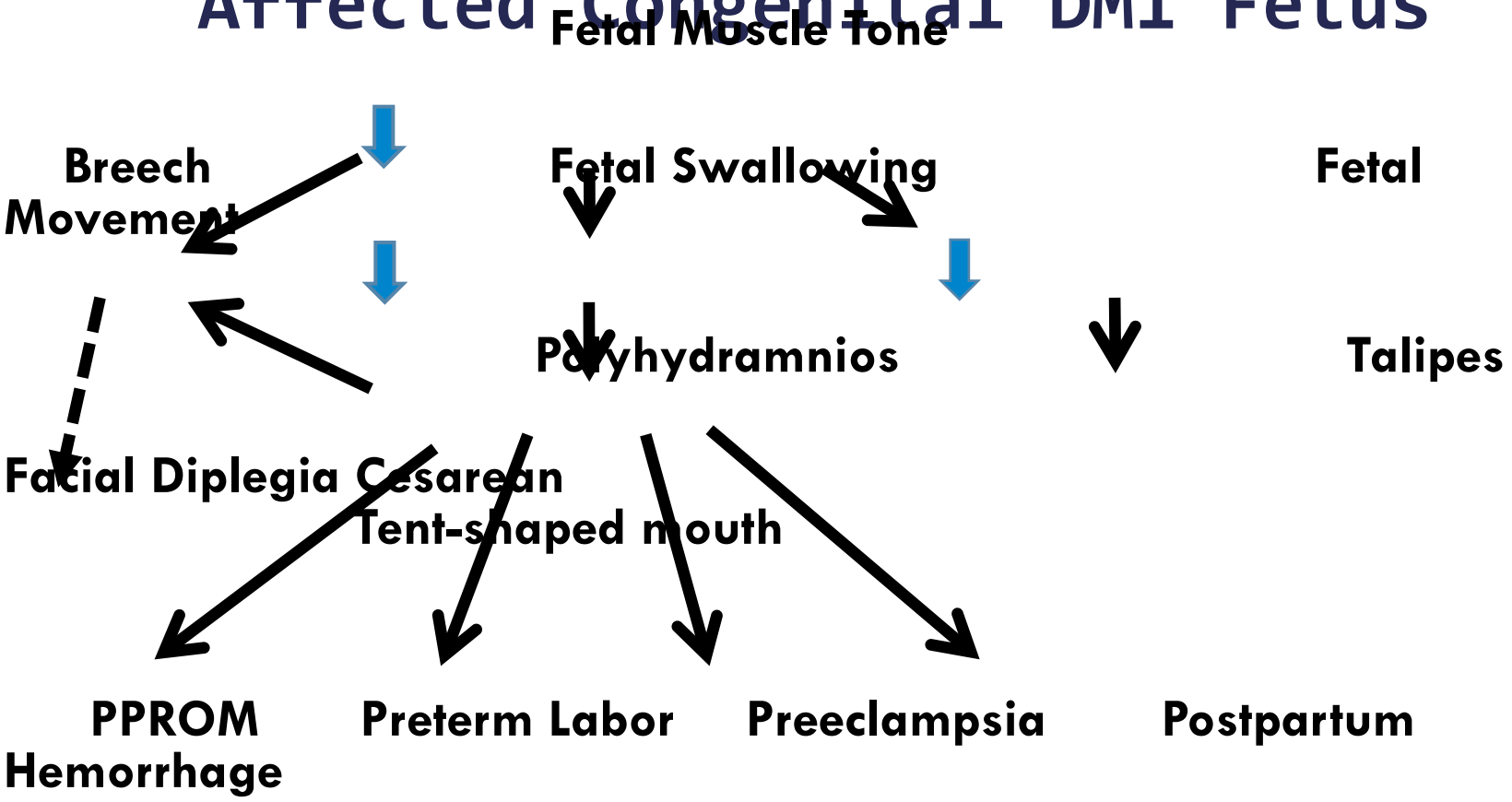
Fetal hypotonia/myotonia leads to:

- **Decreased fetal movement**
  - **Facial diplegia and tent-shaped mouth**
  - **Talipes**
  - **Breech presentation**
    - **Increased cesarean section rate**
- **Decreased fetal swallowing**
  - **POLYHYDRAMNIOS**
    - **Preterm Premature Rupture of Membranes (PPROM)**
    - **Preterm labor**
    - **Preeclampsia**
    - **Uterine Atony**
      - **Postpartum Hemorrhage**

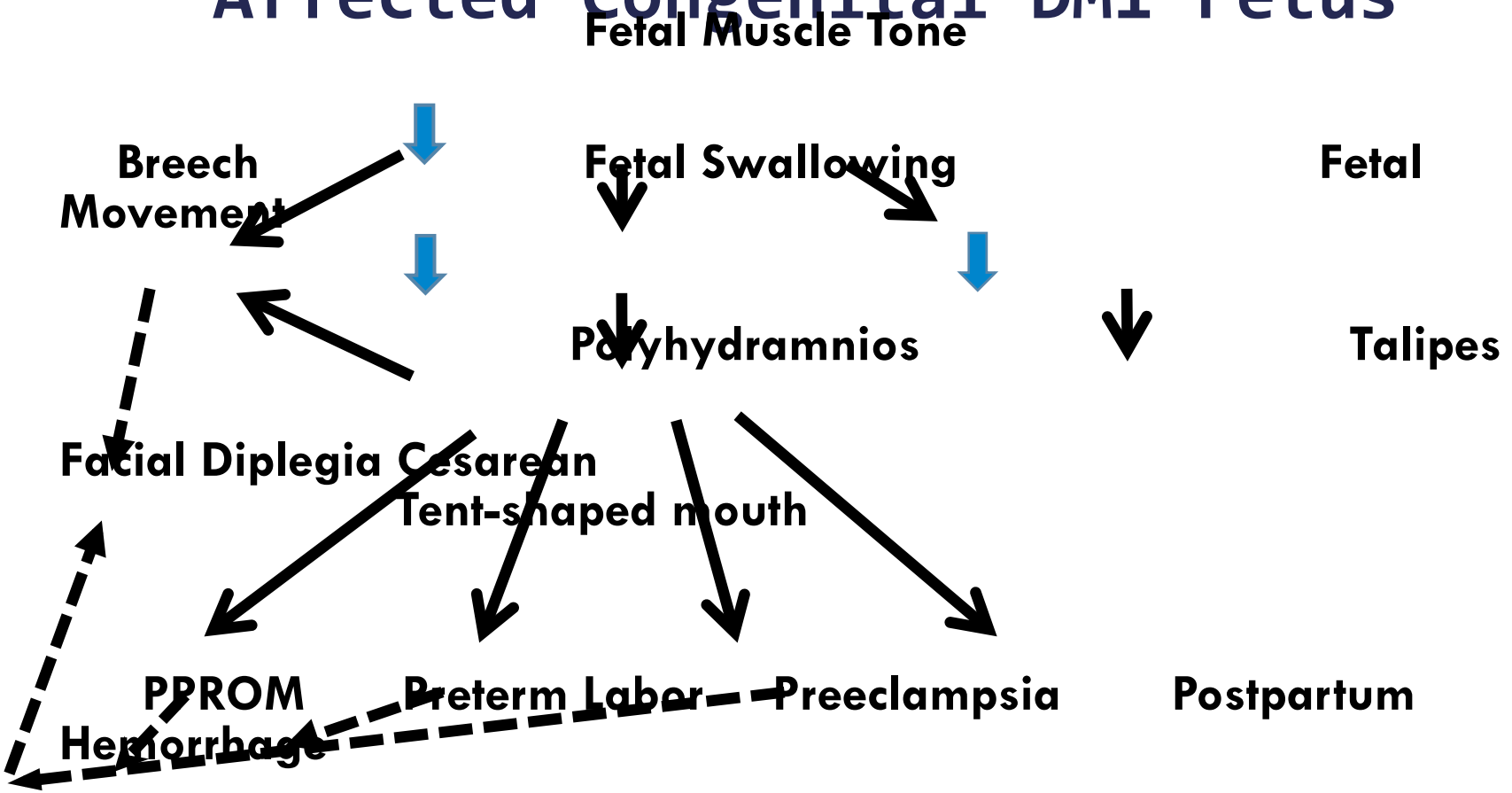
Affected Congenital DM1 Fetus



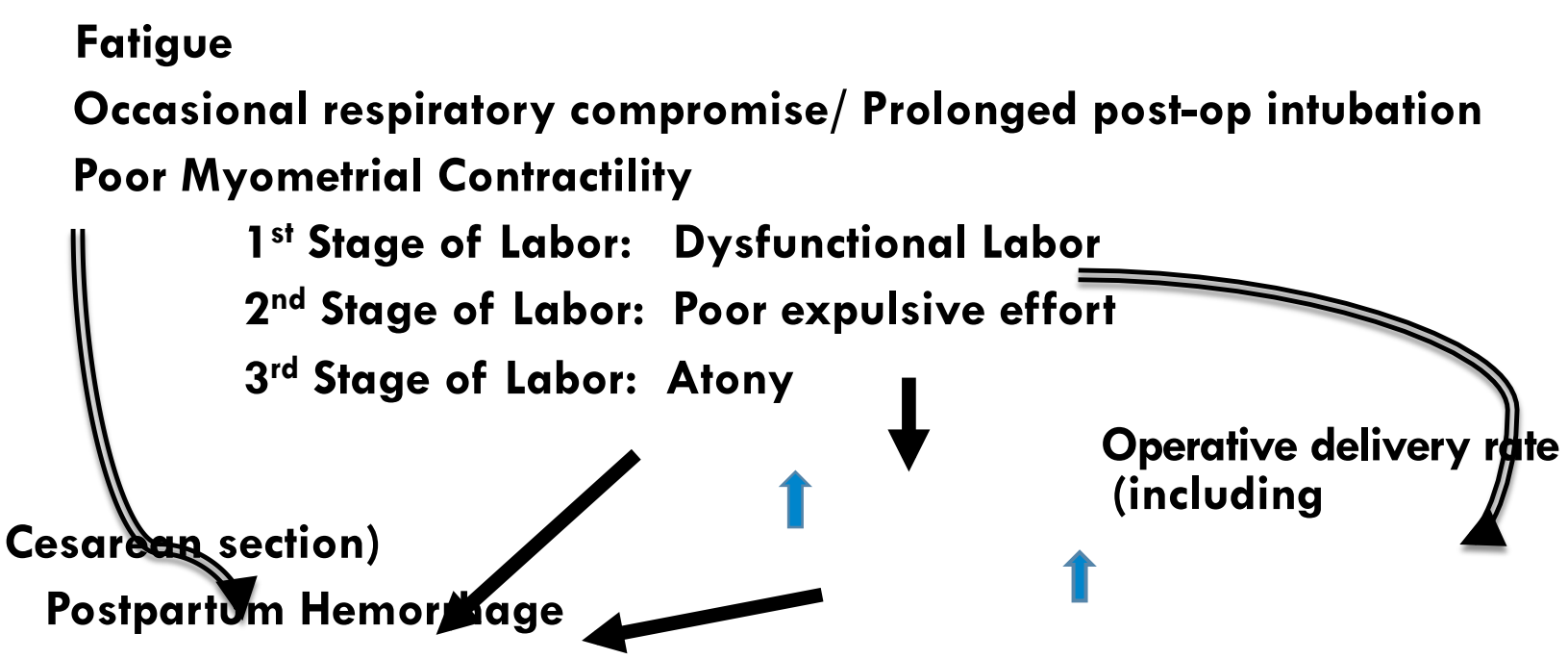
Affected Congenital DM1 Fetus



Affected Congenital DM1 Fetus



Affected Mother (Symptomatic)



Contraception in Women with DM1

- **While progesterone is postulated to possibly aggravate DM1 symptoms in pregnancy, there is no literature to support avoiding progesterone in the smaller doses associated with contraceptive methods (e.g. oral contraceptives, progestin injection, and progestin-containing implants or IUDs).**
- **Non-hormonal IUDs can cause increased menstrual flow, which may be an undesirable side-effect in patients whose myometrial contractility may be diminished.**

Contraception in Women with DM1

- **No form of contraception is contraindicated in DM1, and patient response to the method chosen will vary, as in the general population.**
- **Individual's DM1 disease progression with increasing age may influence family planning decision-making in terms of timing (consider not delaying child-bearing to be healthy for pregnancy).**
- **Postpartum Tubal Ligation under epidural may be preferable to interval tubal ligation under general anesthesia.**

Summary

Many women with Classic DM1 are relatively asymptomatic and are undiagnosed before conceiving a pregnancy.

Maternal DM1 can lead to obstetrical complications even if the fetus if not affected.

Congenital DM1 can *further* complicate her pregnancy, labor, delivery, and postpartum course.

Summary

Even recent cases series describe ~50% of maternal Classic DM1 only being diagnosed through an offspring affected with Congenital DM1

--During pregnancy, through the fetal presentation of polyhydramnios, decreased fetal movement, talipes, facial diplegia, and mild cerebral ventriculomegaly

--Or postpartum, by the neonatal presentation of hypotonia, respiratory insufficiency, facial diplegia, and talipes.

In light of the potentially life-threatening and avoidable obstetrical complications that may ensue, prenatal recognition of Congenital DM1 is highly important not only for the fetus, but also for the mother.

Summary

As devastating as it is, the diagnosis of Congenital DM1 in the baby can provide the key to appropriate planning and obstetrical management decisions which can be life-saving to the mother.

BRITISH MEDICAL JOURNAL VOLUME 289 25 AUGUST 1984

Lesson of the Week

Do you shake hands with mothers of floppy babies?

T H H G KOH

Do you shake hands with mothers with polyhydramnios, decreased fetal movement and sonographic signs of fetal hypotonia?

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