Ovaries and Oocytes and Embryos...Oh My! An Introduction to Infertility Evaluation and Management

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Disclosures

I have no disclosures to report.

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Objectives

At the conclusion of this session, the participant will be able to:

1. Define infertility and recognize its psychological, emotional, ethical, economic, and legal implications.
2. Identify when to begin the infertility evaluation and complete the initial work up prior to referral to a specialist.
3. Review infertility treatment options and their respective risks/complications.

Which of the following patients meet the diagnostic criteria for primary infertility?

A) A 29-year-old who has been unable to conceive after 10 months of unprotected intercourse.
B) A 31-year-old who has been unable to conceive after 10 months of donor inseminations.
C) A 35-year-old who has been unable to conceive after 6 months of unprotected intercourse with a history of a miscarriage in the first trimester last year.
D) A 37-year-old who has been unable to conceive after 6 months of unprotected intercourse.

What is the best initial evaluation of the etiology of infertility in a 25-year-old female who has been trying to conceive for > 12 months?

A) Endometrial biopsy
B) Hysterosalpingogram (HSG)
C) Ovulation predictor kits
D) Basal body temperature charts

The most important prognostic factor affecting fertility is:

A) Day 3 FSH and estradiol levels
B) Female age
C) Sperm count
D) BMI

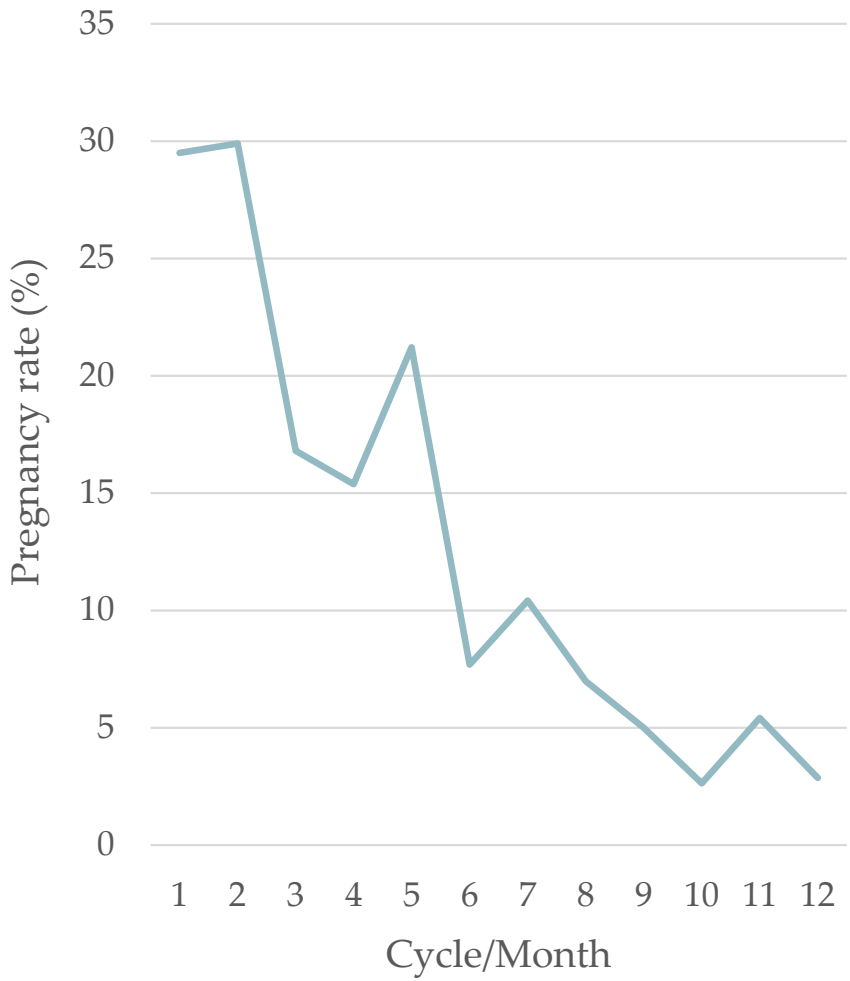
Overview

- Infertility has psychological, emotional, ethical, economic, and legal implications
- 2018 marked the 40th anniversary of the 1st birth of a baby conceived via IVF

Photo credit: *Lauren Walker* (*facebook.com/lauren.g.walker.9*)

Overview

- Fecundity, fertility, & fecundability
- *Infertility* is defined as the inability to conceive after:
  - > 12 months of regular intercourse or donor insemination without use of contraception in women < 35 years old
  - > 6 months of regular intercourse or donor insemination without use of contraception in women ≥ 35 years old
- Primary vs. secondary infertility
- Recurrent pregnancy loss



Zinaman MJ, Clegg ED, Brown CC, et al. Estimates of human fertility and pregnancy loss. Fertility and Sterility 1996.

Epidemiology

- The WHO estimates 1 in 6 adults has experienced infertility based on global data
- Demand for infertility services has increased
  - ART use has doubled in the past decade
  - 1.7% of all babies born every year are conceived using ART

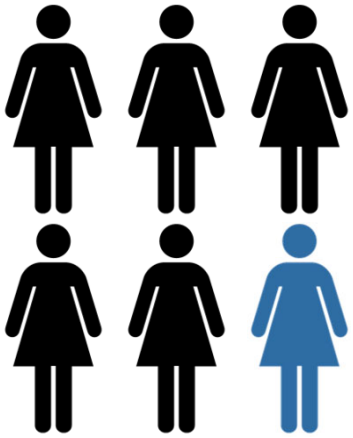
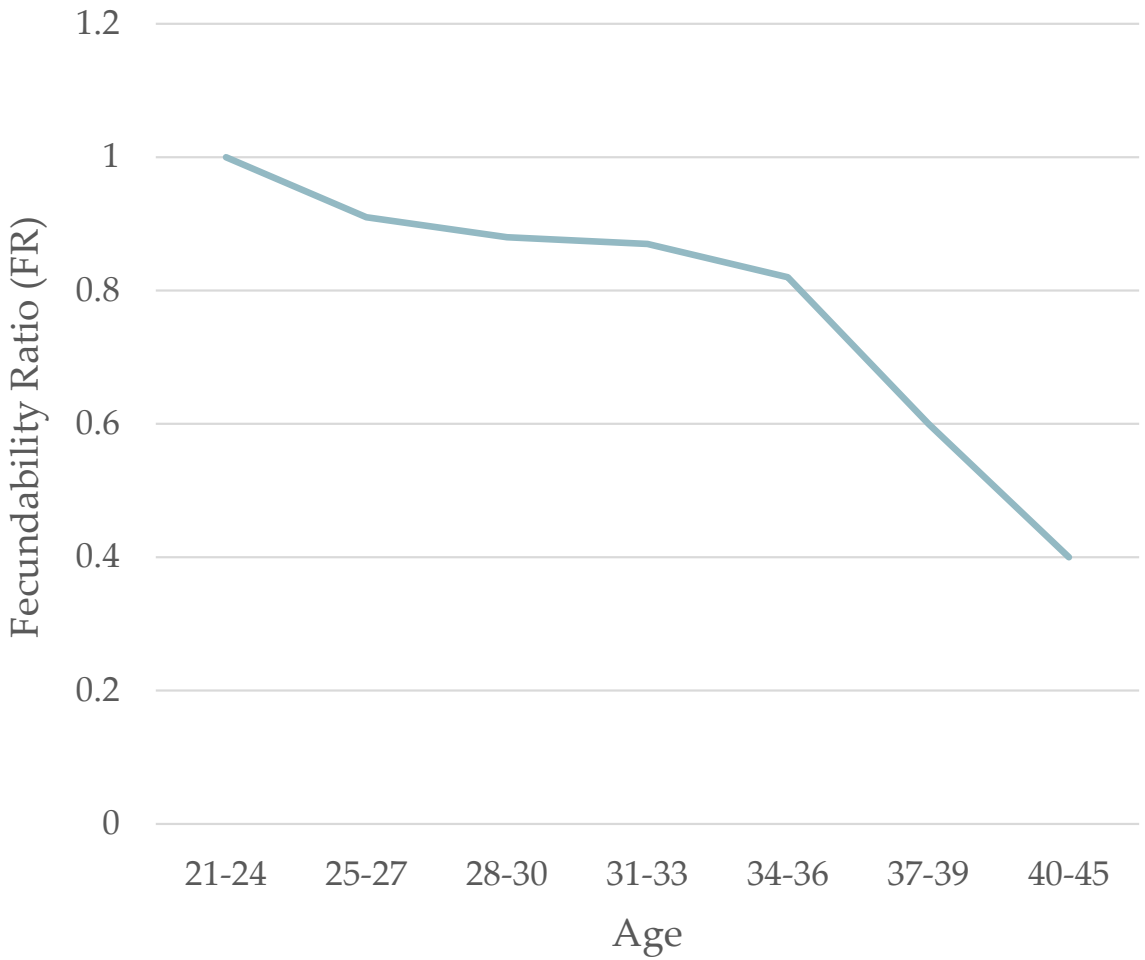


Photo credit: *AIGA (https://www.aiga.org/globalassets/symbol-signs/13_toiletsq_women.gif)*

Impact of AGE on fertility

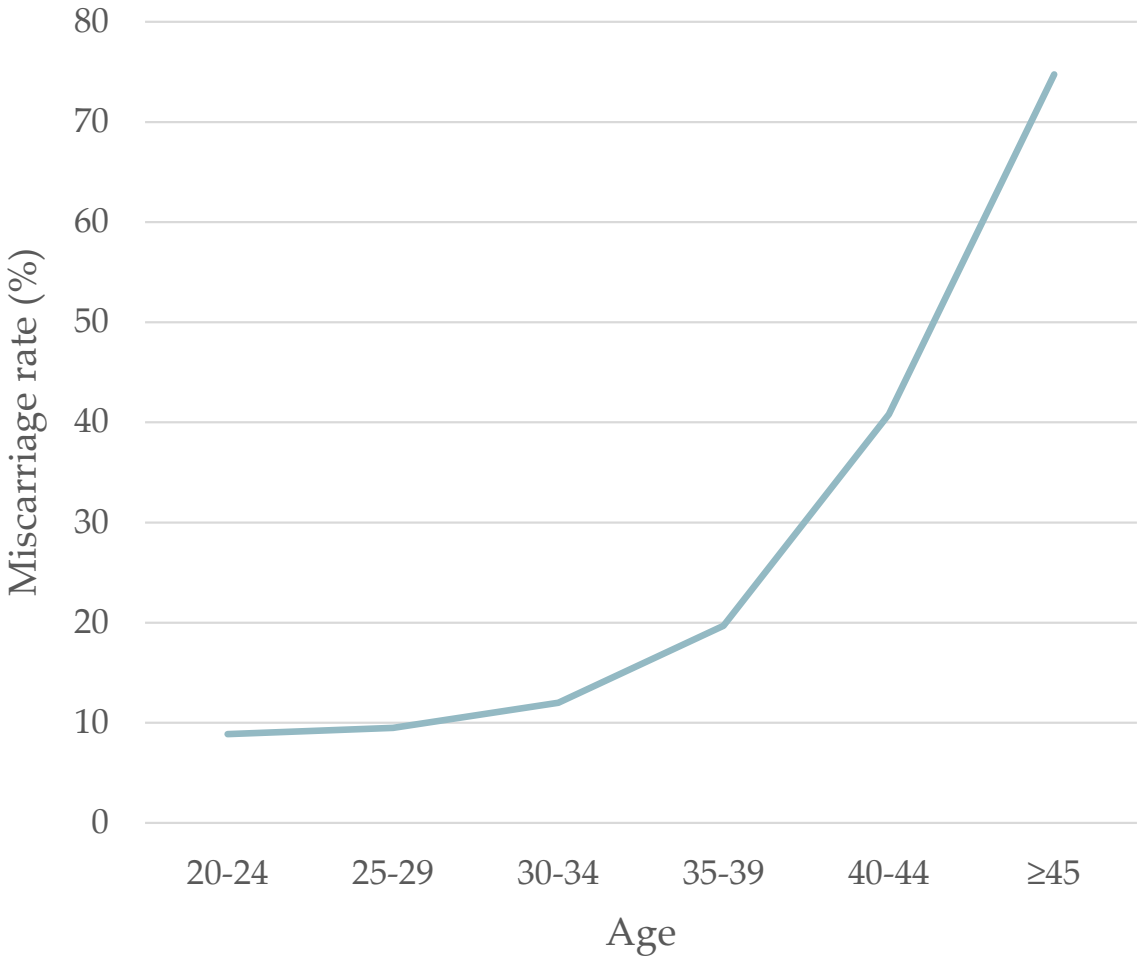
- Quantity and quality of follicles and oocytes decreases with increasing age
- Fecundability decreases with increasing age



Wesselink AK, Rothman KJ, Hatch EE, et al. Age and fecundability in a North American preconception cohort study. American Journal of Obstetrics & Gynecology 2017.

Impact of AGE on fertility

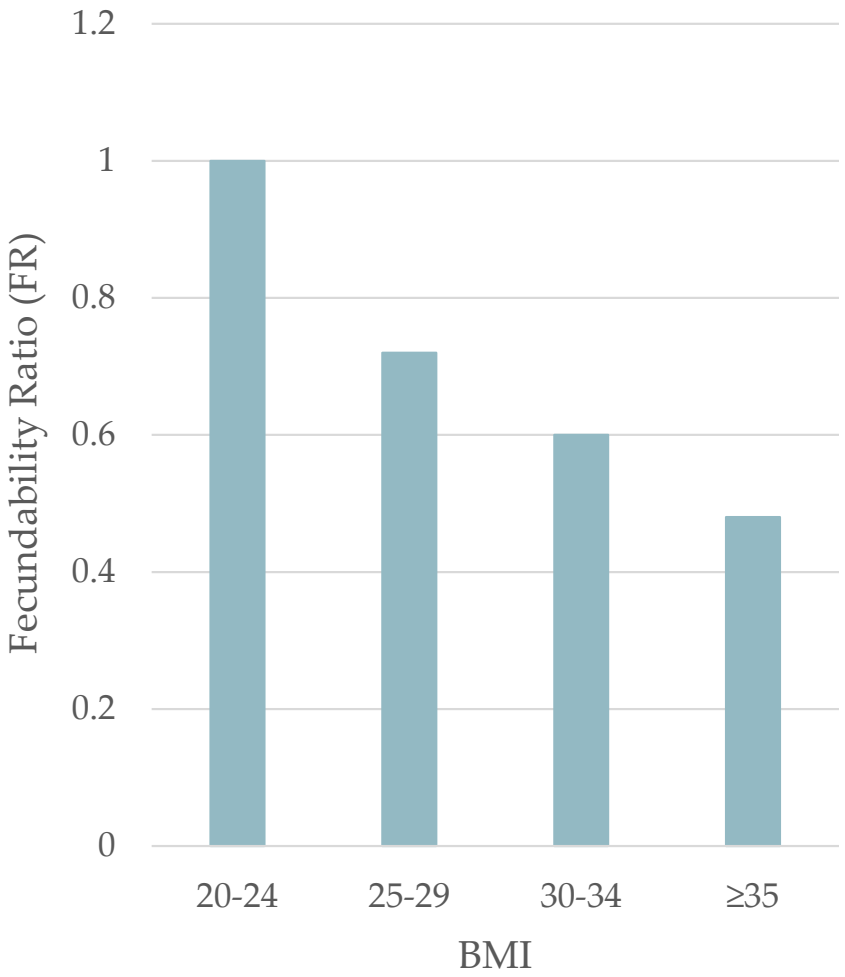
- Miscarriage rate increases with increasing age
- Unclear if age plays a significant role in males



Andersen A-MN, Wohlfahrt J, Christens P, et al. Maternal age and fetal loss: population based register linkage study. BMJ 2000.

Impact of BMI on fertility

- Fecundability decreases with increasing BMI



Wise LA, Rothman KJ, Mikkelsen EM, et al. An internet-based prospective study of body size and time-to-pregnancy. Human reproduction 2010.

Impact of SMOKING on fertility

- Increased risk of infertility and decreased pregnancy rates in cigarette smokers as compared to non-smokers
- What about marijuana use?

Photo credit: *PIXABAY (https://pixabay.com/photos/cigarette-broken-unhealthy-smoking-3112657/)*

Impact of ALCOHOL on fertility

- Effect of alcohol on fertility has not been clearly established
- High levels of alcohol consumption are probably best avoided if attempting pregnancy

Photo credit: *http://pngimg.com/download/17469*

Impact of CAFFEINE on fertility

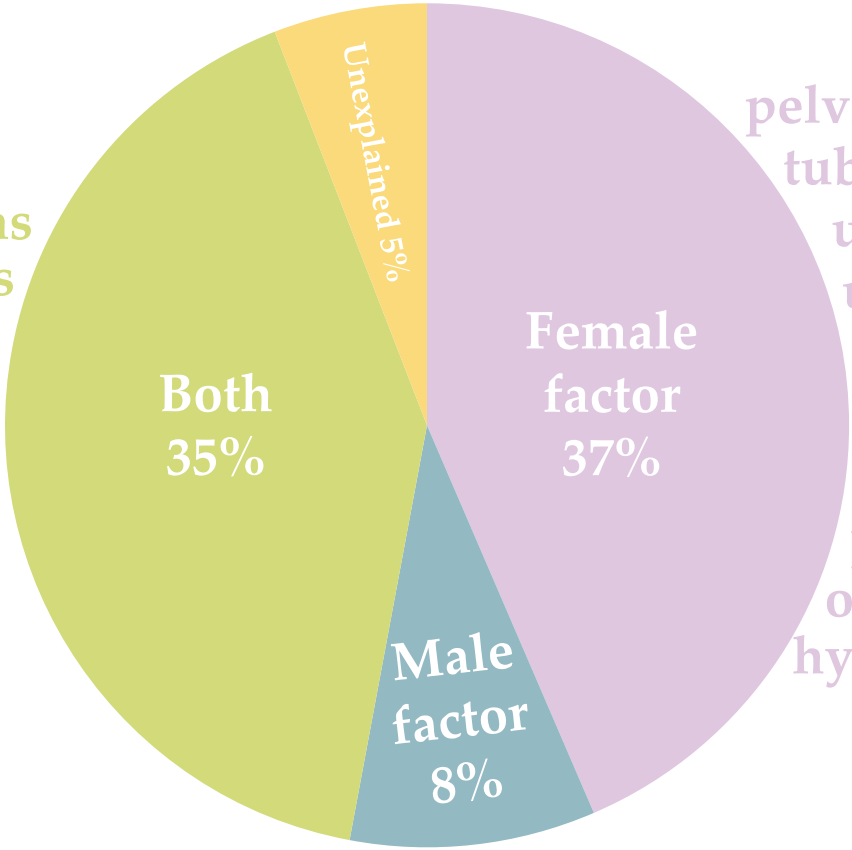
- High levels (> 500 mg per day) of caffeine consumption associated with decreased fertility

Photo credit: *ALPHA STOCK IMAGES (http://alphastockimages.com/)*

How to optimize natural conception

- Encourage use of ovulation predictor kits and timed intercourse (1-2 days preceding ovulation)
- Educate patients on age-related decline in fertility
- Lifestyle modifications
  - Limit stress and excessive exercise
  - Weight management
  - Smoking cessation
  - Limit excessive alcohol and caffeine use
- Don't forget a prenatal vitamin!

Etiology



pelvic inflammatory disease
tubal obstruction or damage
uterine adhesions
uterine anomalies
fibroids
endometriosis
cervical factors
premature ovarian failure
ovulatory dysfunction
hyperprolactinemia

environmental toxins
lifestyle factors
stress
genetics

hypogonadism cryptorchidism
erectile dysfunction oligospermia
varicocele azoospermia
testicular trauma or infection

Recent advances in medically assisted conception. World Health Organization 1992.

When to evaluate

< 35 years old	→	> 12 months of regular intercourse or donor insemination without use of contraception
35 – 39 years old	→	> 6 months of regular intercourse or donor insemination without use of contraception
≥ 40 years old	→	immediate
at any age with risk factors	→	immediate

"We're off to see the ~~wizard~~ reproductive endocrinologist!"

- Who should evaluate?
- What are the initial steps involved in the infertility work up?

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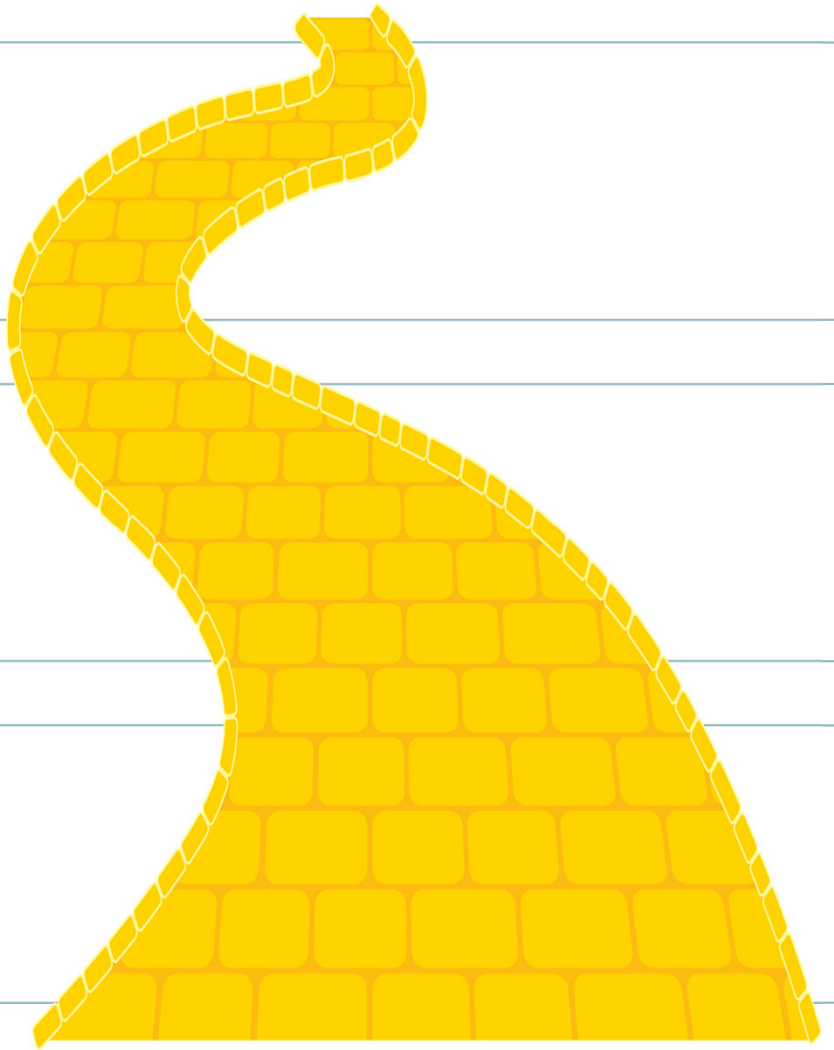
Infertility Work Up

History & Physical Examination
- duration of infertility
- demonstrated fertility in other relationships

Female Evaluation
- ovarian evaluation
- uterine evaluation

Male Evaluation
- semen analysis



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Infertility Work Up

History

- Medications & Allergies
- Medical History
- Surgical History
- Social History (Stress, Exercise/Diet/BMI, Tobacco, Alcohol, Drugs)
- Family History (Early menopause? Infertility? Fragile X or developmental delay?)
- Sexual History (Frequency and timing of intercourse? Lubricant use? Sexual dysfunction? Dyspareunia? STIs? PID? Contraception use?)
- Menstrual History (Menarche? Cycle length and characteristics? Dysmenorrhea? Molimina?)
- Gynecologic History (Abnormal pap smears?)
- Obstetric History

Infertility Work Up

Physical Examination

- Vital signs (including BMI)
- Skin exam
- Thyroid exam
- Breast exam
- Pelvic exam

Infertility Work Up

Female Evaluation: LABS

- Prolactin
- TSH
- CBC
- ABO, Rh, & antibody screening
- STI screening (HIV, hepatitis B, hepatitis C, syphilis, +/- chlamydia & gonorrhea)
- Rubella, varicella, and measles immunity
- Pap smear (and mammogram if indicated)
- Genetic carrier screening

Infertility Work Up

Female Evaluation: OVARIAN EVALUATION

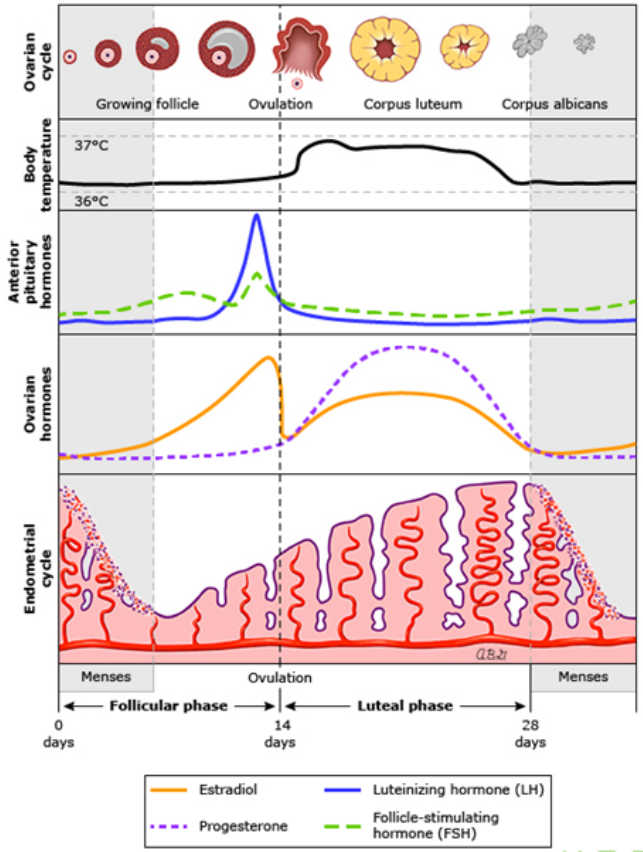
- Antral Follicle Count (AFC)
- Anti-Mullerian Hormone (AMH)
- Day 3 labs (FSH & estradiol)
- Clomiphene Citrate Challenge Test (CCCT)

Antral Follicle Count (AFC)

Anti-Mullerian Hormone (AMH)

- Small peptide hormone produced by the granulosa cells of the preantral and antral follicles of the ovary that influences follicle recruitment
- Stable levels throughout the menstrual cycle
- Normal is ≥ 1.06 ng/mL

Day 3 labs (FSH & estradiol) and Clomiphene Citrate Challenge Test (CCCT)



FSH	Normal < 10 mIU/mL Borderline 10-15 mIU/mL Abnormal > 15 mIU/mL
estradiol	Normal < 70-80 pg/mL

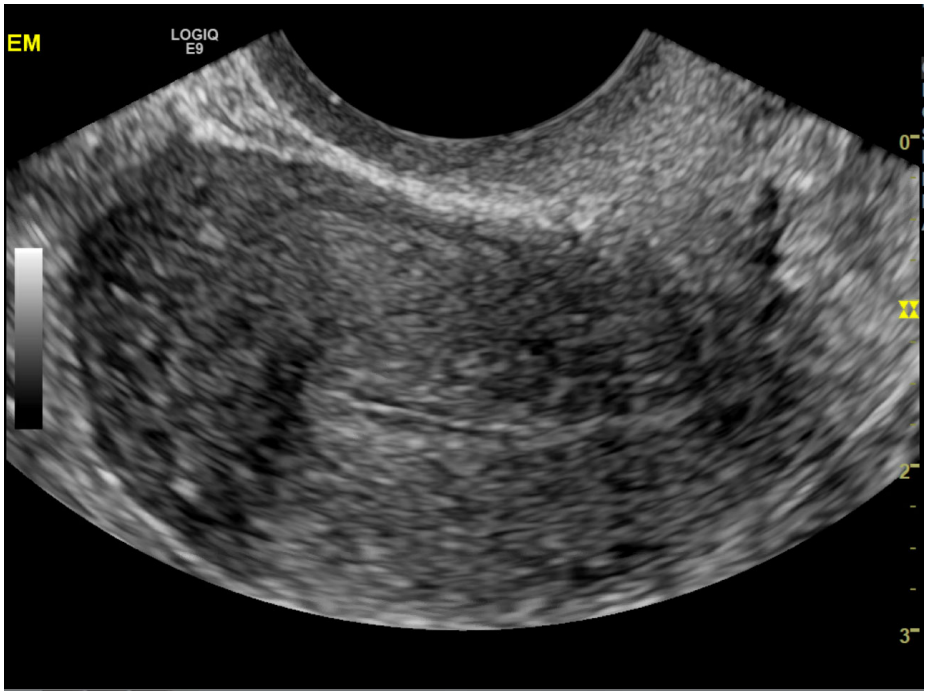
Infertility Work Up

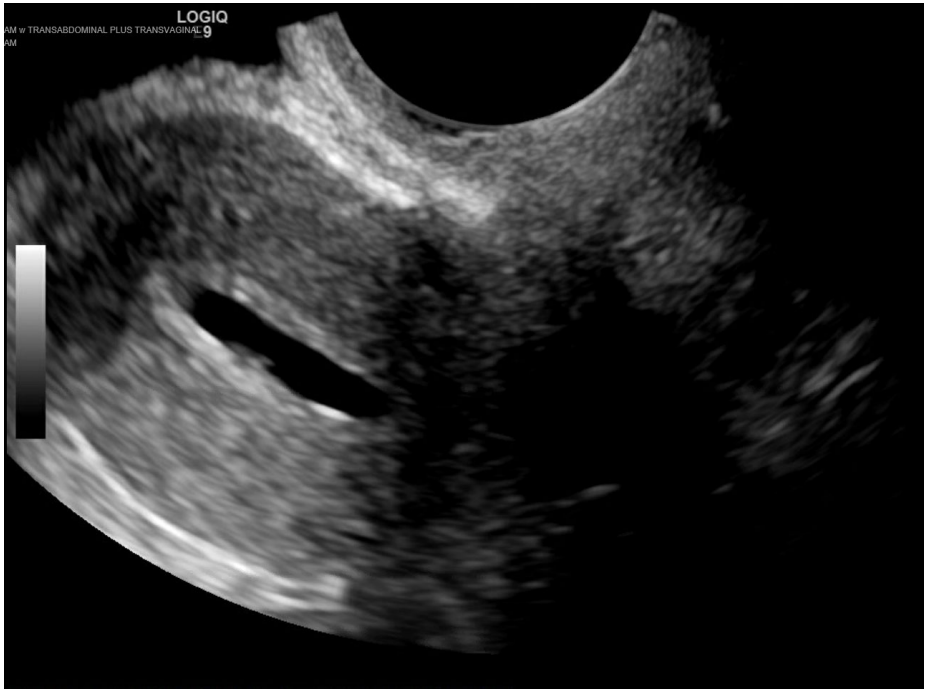
Female Evaluation: UTERINE EVALUATION

- Hysterosalpingogram (HSG)
- Sonohysterogram/Sonohystogram
- Hysterosalpingo-contrast-sonography (HyCoSy)
- Pelvic ultrasound
- Hysteroscopy
- Laparoscopy

Hysterosalpingogram (HSG)

Sonohysterogram/Sonohystogram





Hysteroscopy

Infertility Work Up

Male Evaluation: SEMEN ANALYSIS

Volume	2-5 mL
Concentration	20-500 million/mL
Motility	50-100%
Morphology	≥ 5%

Oligospermia: low concentration of sperm in ejaculate
Azoospermia: complete absence of sperm
Asthenospermia: abnormal motility
Teratospermia: abnormal morphology

Infertility Work Up

Male Evaluation

- STI screening
- Genetic carrier screening
- Endocrine labs
- Scrotal ultrasound
- Urology referral

} if indicated

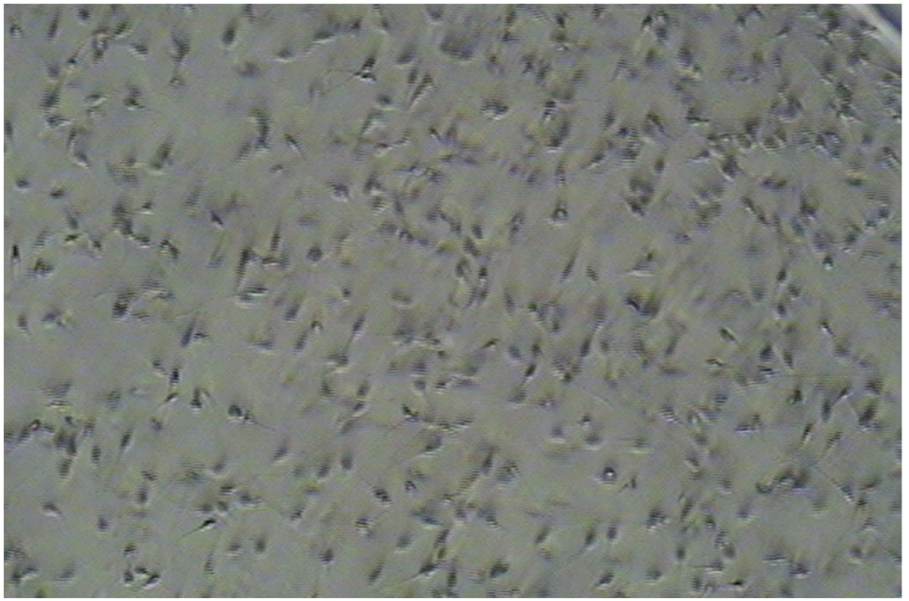
Treatment

- Based on the underlying pathology
- Based on the manipulation of the HPO axis via *Ovulation Induction* vs. *Controlled Ovarian Stimulation* in combination with timed intercourse (TI), intrauterine insemination (IUI), or assisted reproductive technologies (ART)
- Lifestyle modifications and psychological/emotional support are important

Photo credit: *https://upload.wikimedia.org/wikipedia/commons/d/d6/The_Wizard_of_Oz_Judy_Garland_Terry_1939.jpg*

Intrauterine Insemination (IUI)

- Also called artificial insemination
- Semen is spun down in the lab, washed, and injected into the uterine cavity via catheter threaded through the cervix

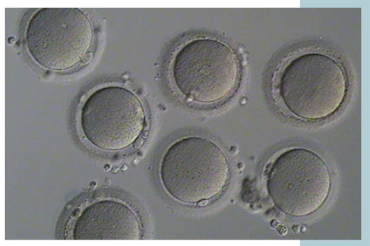


In Vitro Fertilization (IVF)

Medications administered for controlled ovarian stim[illegible]tion

Labs and ultraso[illegible]onitor follicle/oocyte de[illegible]aries

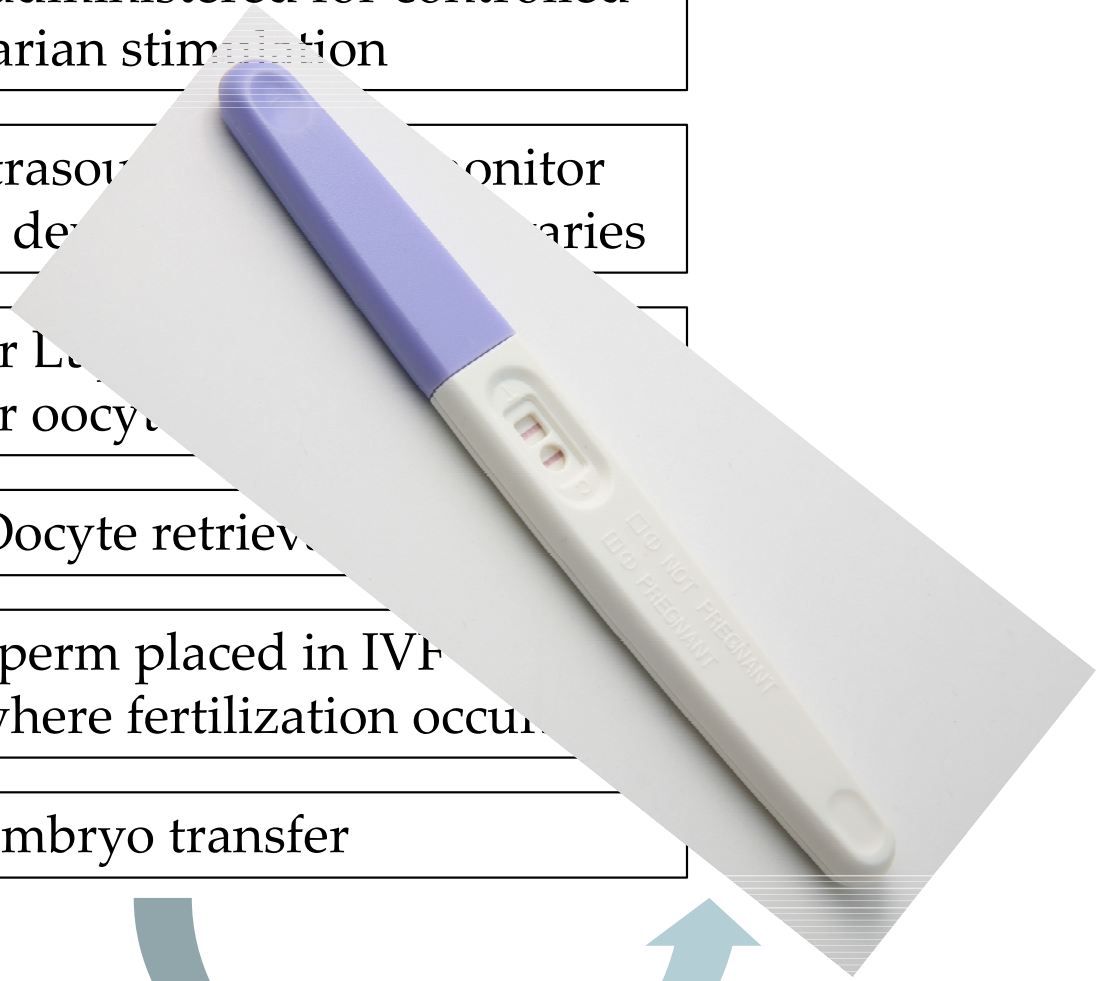
HCG and/or L[illegible] trigger oocyt[illegible]



Oocyte retriev[illegible]

Oocyte and sperm placed in IVF[illegible] medium where fertilization occu[illegible]

Embryo transfer



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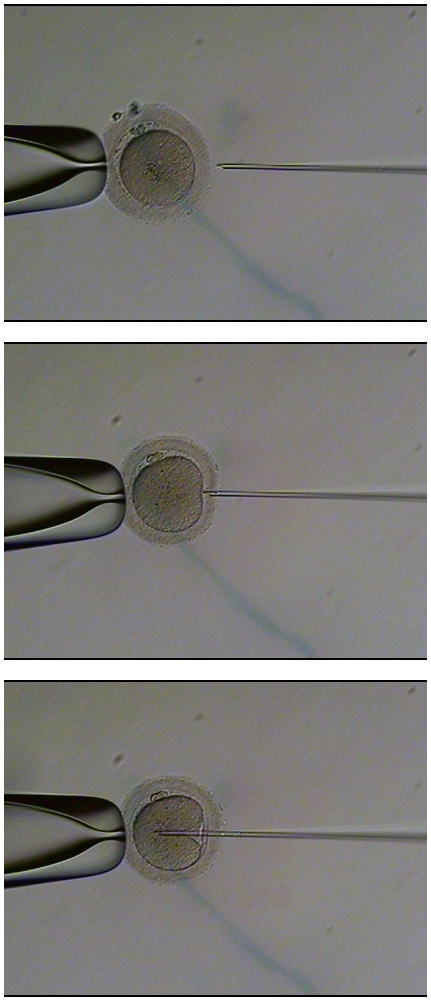
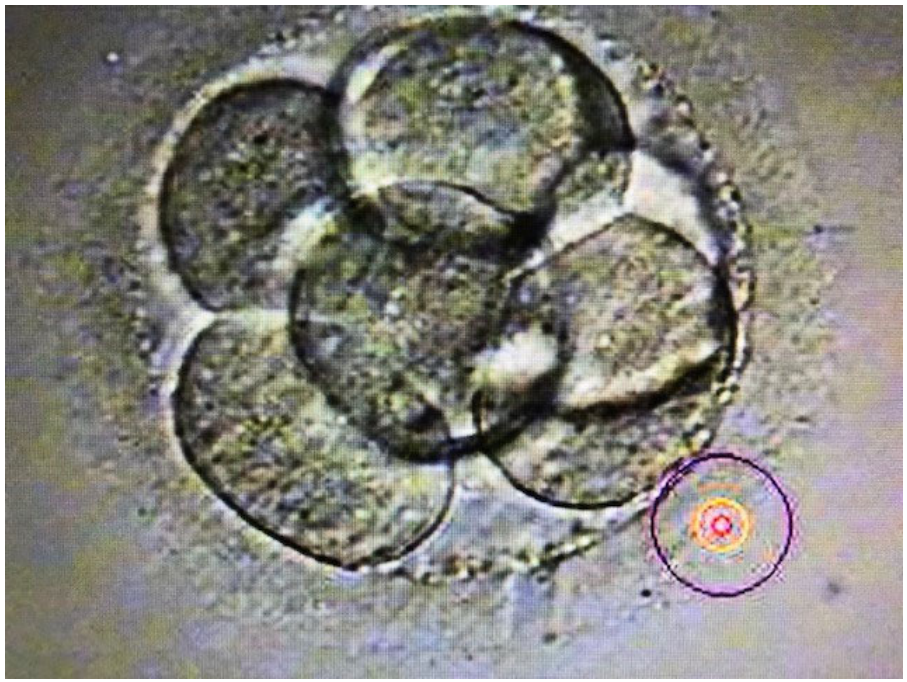
Intracytoplasmic Sperm Injection (ICSI)

- Procedure in which a single sperm is directly injected into each mature egg
- May be used for male factor infertility, poor oocyte quality, and when there is a likelihood of poor or failed fertilization



Assisted Hatching (AH)

- Procedure in which a hole is made in the outer membrane (zona pellucida) of the embryo via laser just prior to transfer to facilitate hatching
- May be used for couples who have had unsuccessful prior IVF attempts

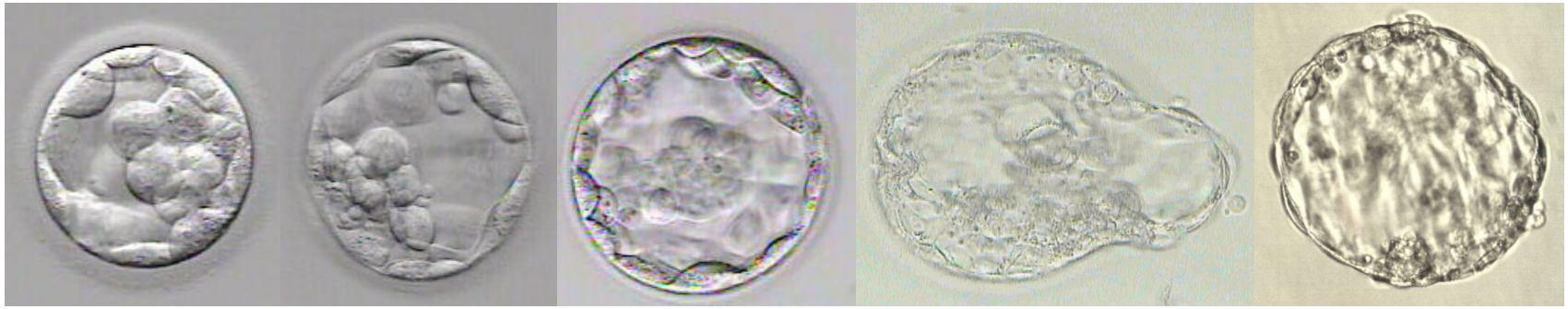


Preimplantation Genetic Testing (PGT)

…for aneuploidy (PGT-A)	▪ Both parents are chromosomally normal ▪ Screens embryos for aneuploidy (chromosomal abnormalities)
…for structural rearrangements (PGT-SR)	▪ One or both parents have a structural chromosomal abnormality (such as a translocation or deletion/duplication)
…for monogenic (single gene) disorders (PGT-M)	▪ One or both parents carry a specific genetic mutation ▪ Screens embryos for specific genetic mutation

Cryopreservation

- Ovarian tissue
- Oocytes
- Sperm
- Embryos



Third Party Reproduction

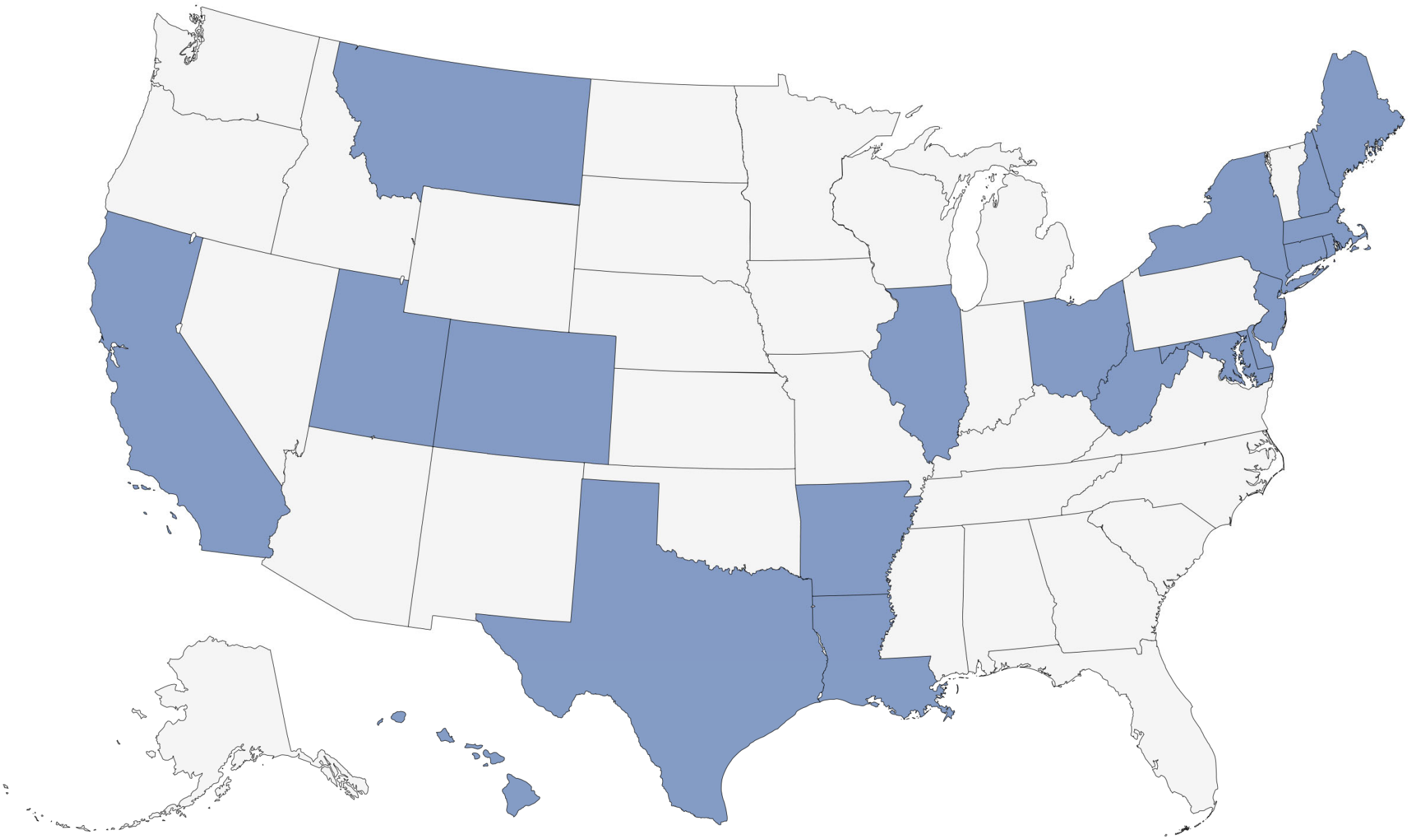
- Gestational carrier
- Donor egg
- Donor sperm
- Donor embryo

Risks

- Medication side effects
- Injection site reactions (bruising, swelling, discomfort) and/or infections
- Surgical risks (anesthesia, bleeding, infection, damage to surrounding anatomical structures, etc.)
- Ovarian Hyperstimulation Syndrome (OHSS)
- Ovarian torsion
- High-order multiples
- Ectopic or heterotopic pregnancy

Controversies

- Direct to consumer fertility testing
- Ethical issues
  - Advanced parental age – how old is too old?
  - PGT issues such as gender selection
  - Donor gamete compensation
- Religious issues
  - Embryo disposition – what do we do with leftover embryos?
- Legal issues
  - Embryo disposition in cases of separation, divorce, or death
- Cost & insurance coverage



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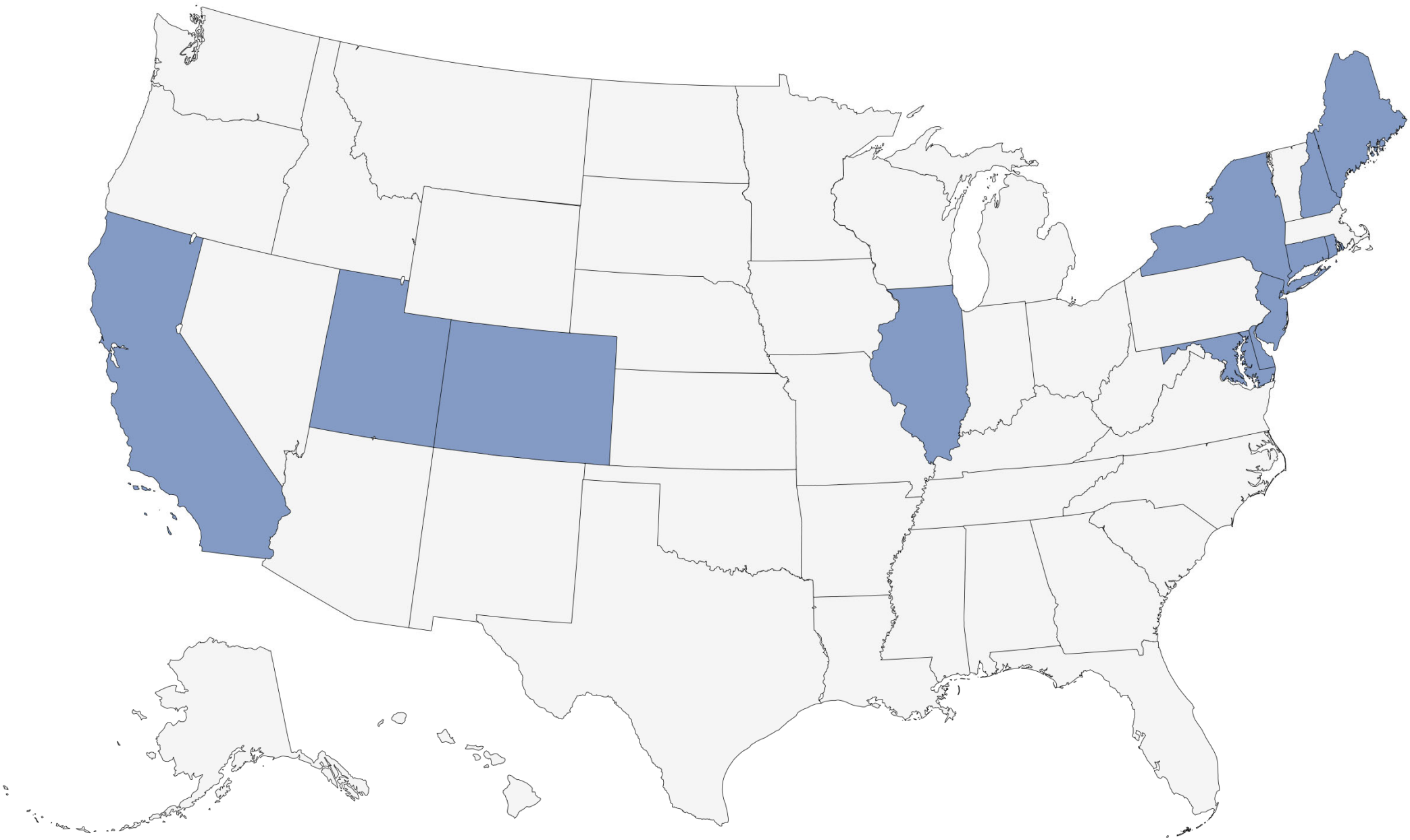
CHIM EMPLOYER OF EXCELLENCE 2018-19

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL



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Resources for your patients

Resolve: The National Infertility Association

www.resolve.org

Society For Assisted Reproductive Technology (SART)

www.sart.org

American Society for Reproductive Medicine (ASRM)

www.reproductivefacts.org

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The most important prognostic factor affecting fertility is:

A) Day 3 FSH and estradiol levels
B) Female age
C) Sperm count
D) BMI

Thank you!

Questions?

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