Infertility

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Objectives

- Classify the different types of female and male infertility
- Choose appropriate diagnostic tests based on history
- Recognize limitations of each test and when further testing is necessary
- Describe appropriate treatment

Infertility: Definitions

- Failure to conceive with regular intercourse
  - < 35 yo: 12 months
  - ≥ 35 yo: 6 months
- Inability to conceive on own or with partner
- Type
  - Primary: No history of pregnancy
  - Secondary: History of pregnancy

Definitions of infertility and recurrent pregnancy loss: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

This document contains the definitions of infertility and recurrent pregnancy loss as defined by the Practice Committee of the American Society for Reproductive Medicine. It replaces the document, "Definitions of Infertility and Recurrent Pregnancy Loss: a Committee Opinion," last published in 2013 (Fertil Steril 2013;99:63). (Fertil Steril® 2020;113:533–5. ©2019 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/56482-29354

Infertility is categorized as a disease by the World Health Organization, a designation supported by numerous professional associations including the American Medical Association, the European Society for Human Reproduction and Embryology, the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) and the American Society for Reproductive Medicine (1–4).

Infertility is a disease* historically defined by the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with her/his partner.

Infertility is a disease which generates disability as an impairment of function. Diagnostic testing for infertility should be initiated without delay treatment may be, initiated at 12 months in women under 35 years of age and at 6 months in women age 35 or older. In women over 40 more immediate evaluation and treatment may be warranted (2).

Donor Insemination is the process of placing laboratory-processed sperm into the reproductive tract of a woman from a man who is not her intimate sexual partner for the purpose of initiating a pregnancy (2). Cycle fecundity is significantly lower when donor insemination is performed using cryopreserved donor sperm when compared to use of fresh sperm (5). In individuals or couples using cryopreserved donor sperm who fail to achieve pregnancy consideration should be given to performing an evaluation and initiating treatment sooner than 12 months for women under 35 years of age and 6 months for ed) as, "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body as manifested by characteristic symptoms and signs; the etiology, pathology, and prognosis may be known or unknown" (6). Each pregnancy loss merits careful review to determine whether specific evaluation of the woman or couple may be appropriate (2).

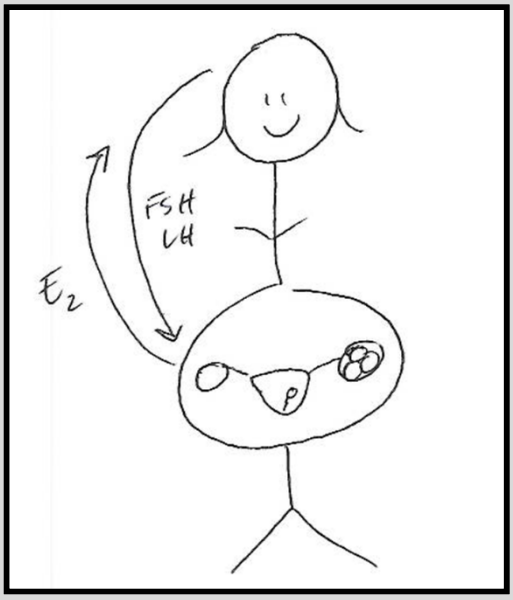
Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only

When should the evaluation begin?

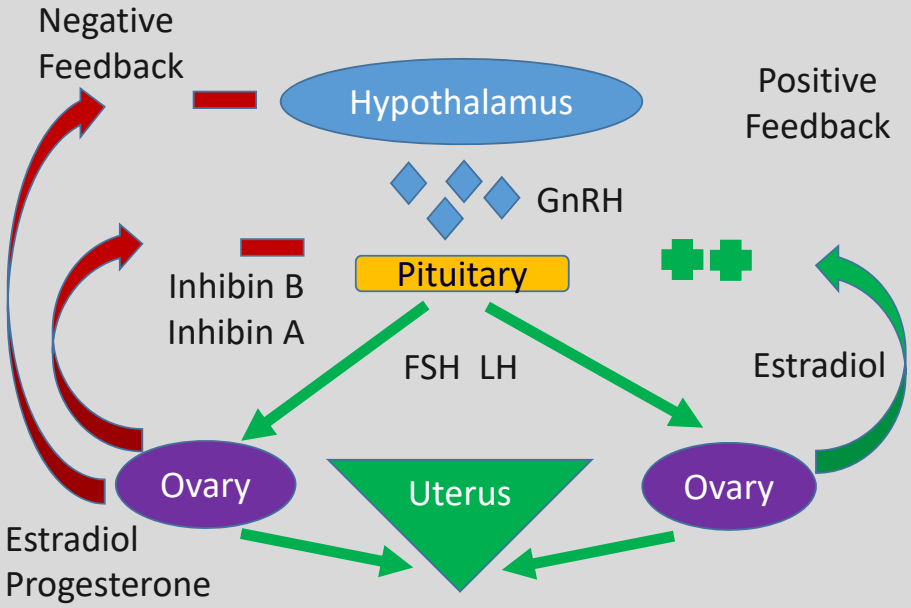
- < 35 yo: 12 months
- 35-39 yo: 6 months
- ≥ 40 yo: Immediately
  - Age-related fertility decline, increase incidence of disorders that impair fertility, higher risk of pregnancy loss
- Evaluate sooner based on history
  - Oligo/amenorrhea, chemotherapy/radiation, endometriosis, tubal disease, male risk factors

Fertility

- What is needed to conceive?
  - Oocytes of good quality
  - Sperm of good quality and quantity
  - Patency of 1 tube
  - Normal uterine cavity

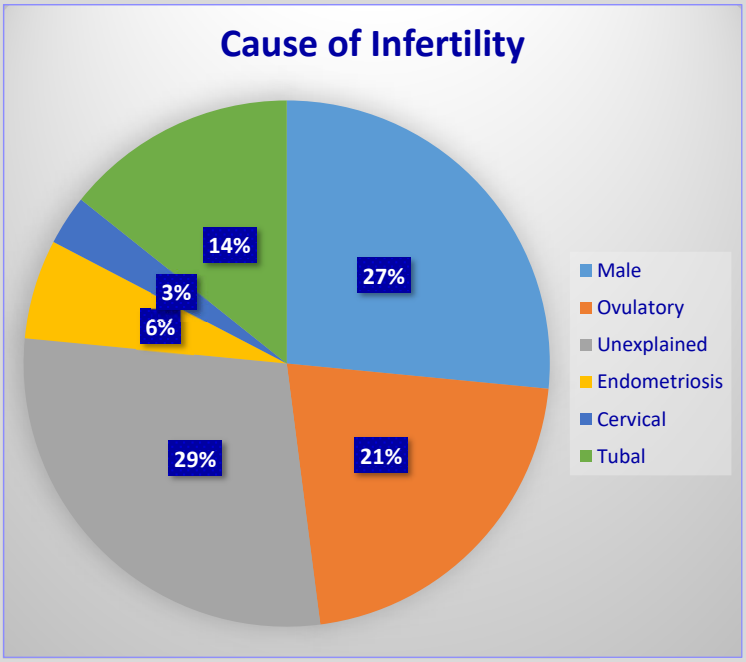


Ovarian follicular development



Infertility

- May have more than contributing factor



Infertility: Female history

- Duration of infertility, previous evaluation/ treatment
- Pregnancy history
- Menstrual history
- Previous contraception
- Coital frequency and sexual dysfunction
- Gynecologic history
- Medications

Infertility: Female history

- Chemotherapy, radiation
- Medical/ surgical history (especially pelvic and abdominal)
- Social history, environmental and occupational exposures
- Family history of birth defects, intellectual disability, or reproductive failure
- Details of intercourse including lubricants
- Exercise, dietary history

Infertility: Female history

- Chemotherapy, radiation
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How is the stress level?
How is the couple doing?
Are they supported?

Diagnostic tests

- Assessment of:
  - Ovulation
  - Ovarian reserve
  - Tubal patency
  - Uterine cavity

Infertility tests that should not be routinely ordered, unless specifically indicated (33).

- Laparoscopy for unexplained infertility
- Advance sperm function testing (e.g., DNA fragmentation testing)
- Postcoital testing
- Thrombophilia testing
- Immunologic testing
- Karyotype
- Endometrial biopsy
- Prolactin
- Progesterone
- Estradiol
- Follicle-stimulating hormone
- Luteinizing hormone

ASRM. Fertility evaluation of infertile women. Fertil Steril 2021.

- Preconception screening
  - Genetic carrier screening, immunization

Diagnostic tests: Ovulation

- Ovulation
  - Menstrual history may be reliable
  - Mid-luteal “day 21” progesterone
    - Check 7 days post ovulation
    - >3 ng/mL defines ovulation
      - No “good” or “bad” level due to pulsatility

WHO Classification of anovulation

Class	Physiology	Clinical presentation	FSH	Estradiol
Class 1	Hypogonadotropic hypogonadism	Hypothalamic amenorrhea Hyperprolactinemia	Low	Low
Class 2	Normogonadotropic normoestrogenic	Polycystic ovary syndrome (PCOS)	Normal	Normal
Class 3	Hypergonadotropic hypoestrogenic	Primary ovarian insufficiency (POI)	High	Low

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Diagnostic tests: Ovarian reserve

- Indications
  - > 35 years yo
  - Family history of POI
  - History of ovarian surgery, chemotherapy, pelvic radiation
  - Unexplained infertility
  - IVF
- Ovarian reserve testing
  - Day 3 FSH + estradiol, antral follicle count, CCCT
    - Normal: < FSH 10 IU/ mL, estradiol 80 pg/mL
  - Anti-mullerian hormone

- Only use for treatment planning and expectations
- Does not imply inability to conceive

ASRM. Fertil Steril.2020

Diagnostic tests: Tubal and uterine

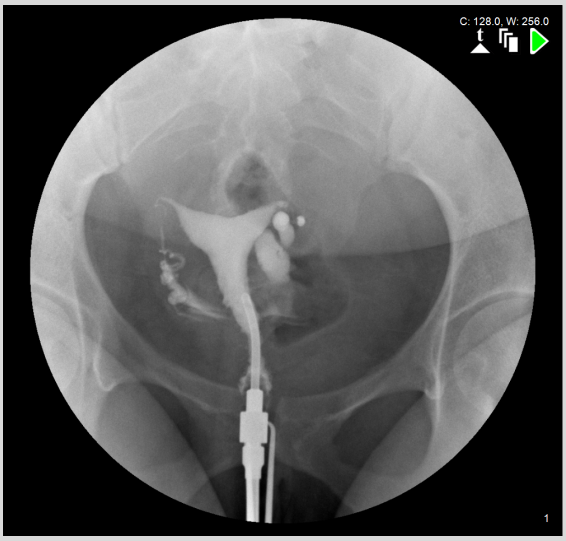
- Tubal patency/ uterine cavity evaluation

- Hysterosalpingogram
  - Fluoroscopy with contrast
  - May be therapeutic

- Hysterosalpingo-contrast sonography
  - Ultrasound of uterus, tubes, adnexa before and after transcervical injection of echogenic contrast media

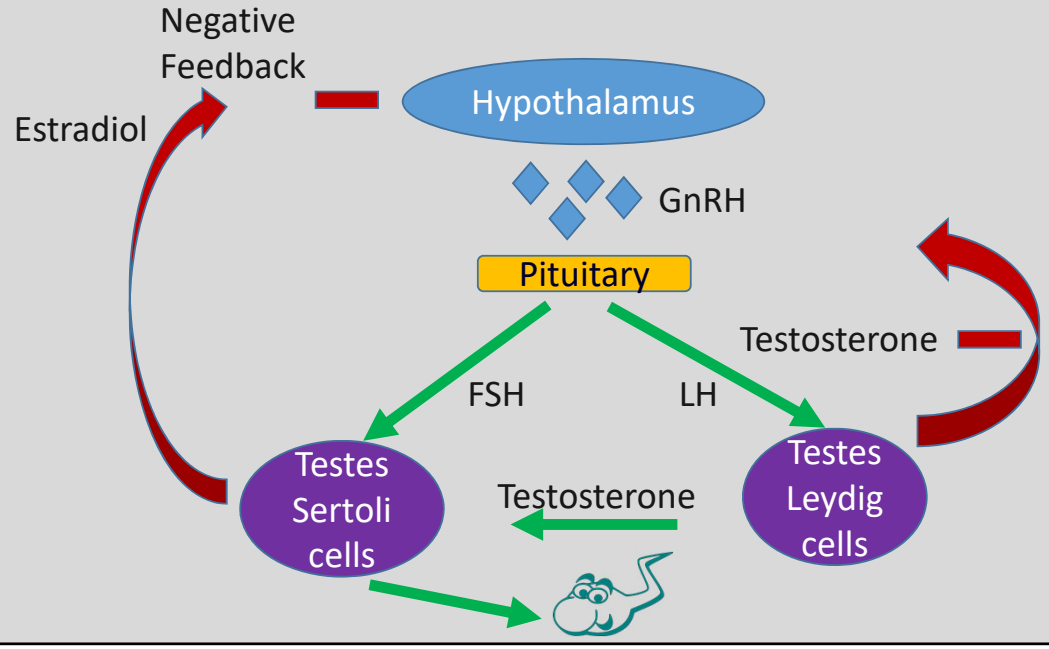
- Saline infusion sonohysterography/ flexible hysteroscopy if tubal patency not needed

Hysterosalpingogram



Male Evaluation

Testosterone Production and Spermatogenesis



Infertility: Male history

- Duration of infertility, prior evaluation or treatment
- Fertility in other relationships
- Medical/surgical history, testicular surgery/ injury, history of mumps
- Chemotherapy, radiation
- Medical/ surgical history
- Social history, environmental and occupational exposures
- Family history of birth defects
- Details of intercourse, lubricants
- Exercise, dietary history
- Sexual dysfunction

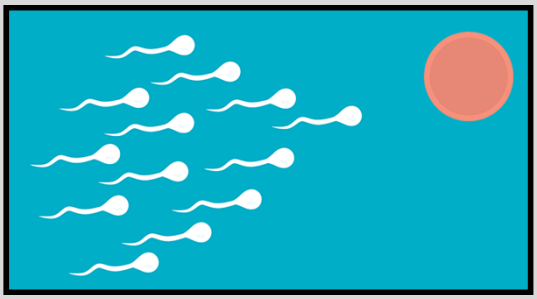
Diagnostic testing: Male

- Semen analysis
- Physical exam
  - Secondary sexual characteristics
  - Testicular volume
- Scrotal ultrasound
- Hormonal testing
  - Sperm count < 16 million
  - Serum total testosterone (between 8-10 AM), FSH, LH
  - TSH, prolactin

Semen analysis

- Home or in-office collection
- 2-3 days of abstinence
- May need to repeat if abnormal

- Useful if abnormal



Semen analysis: WHO 2021

Semen volume (ml)	**1.4 (1.3-1.5)**
Total sperm number (million)	**39 (35-40)**
Sperm concentration (million/ ml)	**15-16**
Total motility (%)	**42 (40-43)**
Progressive motility (%)	**30 (29-31)**
Normal forms (%)	**4 (3.9-4)**

Diagnostic testing: Male

- Chromosomal testing
  - Karyotype
    - Sperm concentration ≤10 million/mL
      - Klinefelter syndrome
      - Chromosomal translocations
  - Y-chromosome microdeletions
    - Sperm concentration ≤5 million/mL
  - Cystic fibrosis transmembrane-conductance regulator (*CFTR*) mutations
    - Obstructive azoospermia with congenital absence of the vas deferens
    - Also test female partner

Male hormonal evaluation

Clinical condition	FSH	LH	Testosterone	Prolactin
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Complete testicular failure/ hypergonadotropic hypogonadism	High	High	Normal/low	Normal
Prolactin-secreting pituitary tumor	Normal/low	Normal/ low	Low	High

Basic fertility evaluation

Female		
History		
Physical		
Pre-pregnancy evaluation		
Additional testing for cause of infertility	Diminished ovarian reserve	Day 2-4 FSH, estradiol Antimullerian hormone (AMH) Antral follicle count by transvaginal ultrasound
	Ovulatory dysfunction	Luteal progesterone level
	Tubal factor	HSG, hysterosalpingo-contrast sonography
	Uterine factor	HSG, hysteroscopy, sonohysterography, transvaginal ultrasound
Male		
History		
Semen analysis		

ACOG Obstet Gynecol. 2019

What can't you find?

- 10-20% have unexplained infertility!

- Endometriosis
  - Laparoscopy
- Pelvic adhesions
  - Laparoscopy
- Issues with sperm function/ fertilization issues
  - In vitro fertilization
- Implantation issues
  - No testing available
- Egg quality
  - ? In vitro fertilization

Infertility management and treatment

- Correction of life-style or coital practice
- Ovulation induction
- Intrauterine insemination
- Hysteroscopy and/or laparoscopy
- In vitro fertilization
- 3rd party reproduction

Management: Lifestyle modification

- Functional hypothalamic amenorrhea
  - Reduce stress (exercise, activity)
- PCOS
  - Weight loss, exercise
    - Is there time considering age?
- Hyperprolactinemia
  - Ensure no other factor is increasing prolactin
- Environmental risks
  - Tobacco, alcohol, diet

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Management: Oral agents

- Lead to increase in FSH and follicular development
- Lower risk of multiple gestation
- Low-cost, easy administration

- Clomiphene citrate
  - SERM
- Letrozole
  - Aromatase inhibitor
  - Off-label use
- Dopamine agonists

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Management: Oral agents

- Clomiphene citrate/ letrozole
  - Low cost, 5 day course
  - Cumulative pregnancy rate 30-40%
- Risks
  - Twins 7-9%, triplets <1%
  - Mild side effects
- Can be paired with intercourse or insemination
- Letrozole recommended for PCOS

Management: Gonadotropins

- Increase FSH concentration to exceed threshold to recruit follicles
- Recombinant FSH
- Human menopausal gonadotropins (hMG) (FSH+LH)
  - Needed for both folliculogenesis and steroidogenesis
    - Hypogonadotropic hypogonadism
- Indications
  - PCOS resistant to other treatments
  - Hypogonadotropic hypogonadism
  - Controlled ovarian hyperstimulation

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Management: Gonadotropins

- Outcomes
  - Pregnancy rate 15-25%/cycle
- Risks
  - Multiple gestation
    - Responsible most high order multiple gestation among all treatments
      - 5% triplets or more
  - Ovarian hyperstimulation syndrome
  - Costly
- No increased risk of cancer, birth defects, SAB

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Management: Hyperprolactinemia

- Dopamine agonists
  - Bromocriptine
    - Side-effects likely
  - Cabergoline
- High chance of ovulation and pregnancy once PRL falls
- Stop when patient conceives

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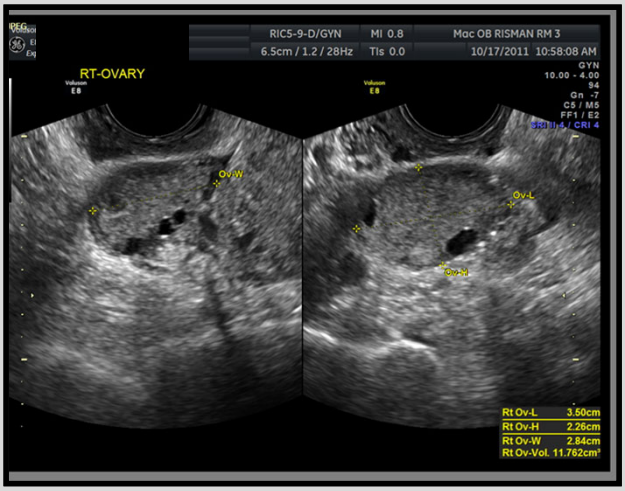
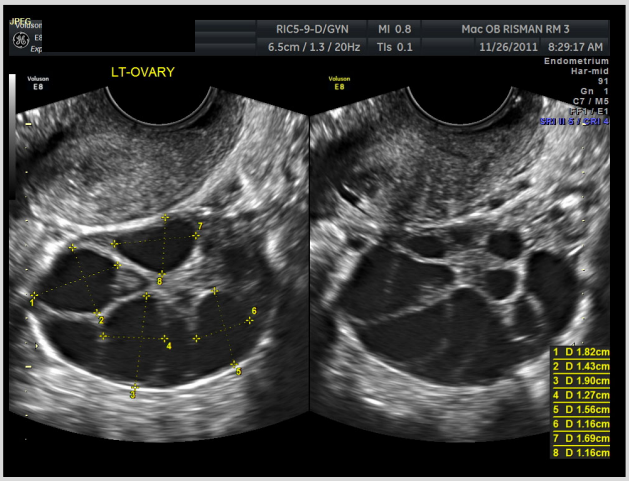
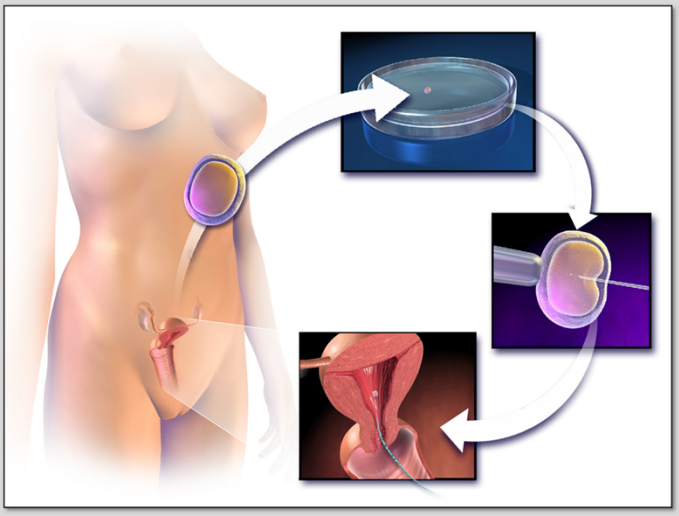
IVF: Controlled ovarian hyperstimulation





IVF: Oocyte retrieval and embryo transfer

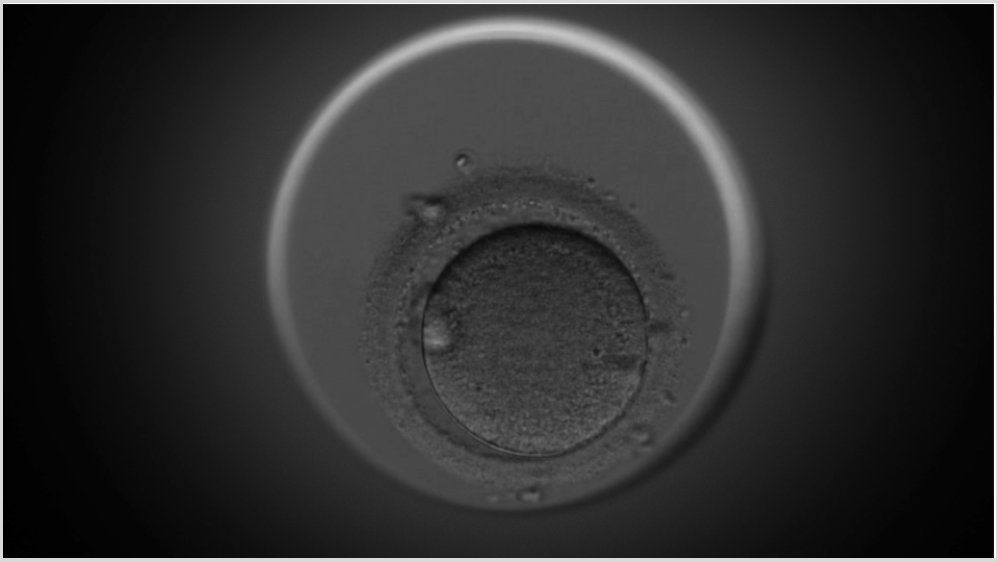
- Transvaginal retrieval
- Fertilization and embryo culture in the laboratory
- Embryo transfer, embryo biopsy, and/or embryo freeze



Blausen.com staff (2014)

Intracytoplasmic sperm injection (ICSI)

Embryo development to blastocyst

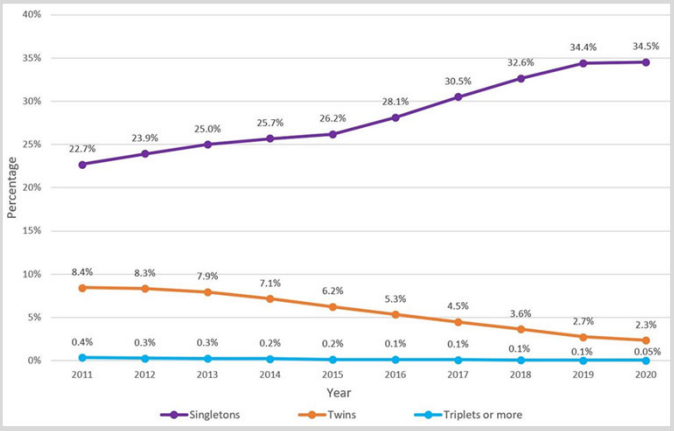


Who needs IVF/ICSI?

- Tubal factor infertility
- Severe male factor infertility
- Failed other fertility treatments
  - Unexplained infertility
  - Endometriosis
  - Decreased ovarian reserve
  - Recurrent pregnancy loss
- Patients with genetic mutations who want to avoid passing on mutations to child
- Fertility preservation
  - Oocytes or embryos

Current trends in ART

- Blastocyst culture
- Reduction of OHSS
  - GnRH antagonist cycles with GnRH agonist trigger
- Preimplantation genetic testing (PGT)
- Elective single embryo transfer (eSET)
- Freeze-all cycles
- Increasing oocyte cryopreservation



https://www.cdc.gov/art/reports/2020/

Preimplatation genetic testing (PGT)

- PGT-A
  - Aneuploidy (trisomy 21, trisomy 18, etc.)
- PGT-M
  - Monogenetic disease (cystic fibrosis, SMA)
  - Recessive, dominant, x-linked
- PGT-SR
  - Balanced translocation

Embryo biopsy for PGT

PGT: Indications

- Increased risk of having a child with a genetic condition
- Avoiding a sex-linked genetic condition
- Have a child that is a HLA type match for a sibling needing stem cell therapy
- Avoid pregnancy loss if patient/ partner has a balanced translocation
- Older patients requesting single embryo to be transferred

Summary

- Initiation of the infertility evaluation is based on age and history
- History is key
- About 20-30% of couples will have normal testing
- Treatment may include correction or bypass of medical issue
- Most patients, in time, will be successful

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