





Fertility

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Stephanie Dahl, MD

CCRM Minneapolis

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Fertility Testing

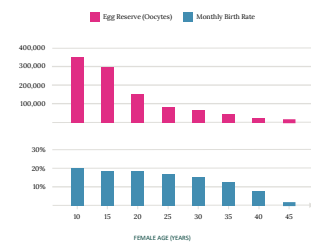
- When is it indicated?
 - Women <35 years
 - Failure to achieve successful pregnancy after 12 months of unprotected intercourse
 - Women 35-40 years
 - Failure to achieve successful pregnancy after 6 months of unprotected intercourse
 - Women >40 years
 - Failure to achieve successful pregnancy after 3 months of unprotected intercourse
 - Right away if:
 - History of oligo/amenorrhea, PCOS
 - Hx chemotherapy/radiation either partner
 - Known or suspected uterine issues, tubal disease, or stage III-IV endometriosis
 - Known or suspected male infertility
 - Recurrent pregnancy loss
 - Special instances: Same sex couples



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Age Related Infertility

Egg quantity declines with age, impacting chance of pregnancy.




On a month to month basis, healthy women in their teens and 20s have an 18-20% chance of getting pregnant each month, But that declines after age 35 to 10%.

Source:
 Dr. Mandy Katz-Jaffe, Scientific and Genetics Director for CCRM Fertility
 Andrea Rodrigo BSc, MSc (Embryologist)
 Mark P. Trollice MD, FACOG, FACS, FACE (Reproductive Endocrinologist)
 Miguel Dolz Arroyo MD, PhD (Gynecologist)
 Sandra Fernández BA, MA (Fertility Counselor)

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Steps of evaluation


- Evaluation of both partners should begin at the same time



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Male Factor Infertility

- Male factor
 - Common
 - Sole factor in 30% of infertile couples
 - Contributes in an additional 30%– 40% of couples



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Important to obtain Hx

- Childhood issues
 - Undescended testicles
 - High fevers, Infections (mumps)
- Medical Problems (DM, HTN, cancer)
- Previous surgery
 - Vasectomy, hernia repair, cancer, trauma
- Medications
 - Antidepressants (affect libido).
 - Chemotherapy/ radiation tx
- Reproductive history
 - Previous pregnancies, prior children
 - STDs, prostatitis, trauma to groin, ED, low libido
- Exposures to gonadotoxins: STEROIDS
 - ETOH, tobacco, pesticides, herbicides, chemicals
- Family/ genetic history
 - Cystic Fibrosis, Y-chromosome microdeletions, Klinefelter's

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Evaluation of the male: Physical exam

- Physical Exam
 - Vitals
 - Height, weight, body habitus
 - Routine physical exam
- Genital exam
 - Examination of the penis, noting the location of the urethral meatus
 - Palpation and measurement of the testes
 - Presence of vas and epididymides
 - Presence or absence of a varicocele
 - Secondary sex characteristics
 - Prostate examination where indicated

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Evaluation of the male

- Semen analysis
 - Abstinence interval 2–5 days
 - Collection:
 - Masturbation into a specimen cup
 - Intercourse with condoms free of spermicide
 - 3 major parameters
 - Concentration (mil/mL)
 - Motility %
 - Morphology %

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SA: Normal Values

TABLE 1

Lower limits of the accepted reference values for semen analysis.

Parameter	Reference value
On at least two occasions	
Ejaculate volume	1.5 mL
pH	7.2
Sperm concentration	15 × 10 ⁶ spermatozoa/mL
Total sperm number	39 × 10 ⁶ spermatozoa/ejaculate
Percentage motility	40%
Forward progression	32%
Normal morphology	4% normal
And	
Sperm agglutination	Absent
Viscosity	≤2 cm thread after liquefaction

Parameters that actually predict male fertility:

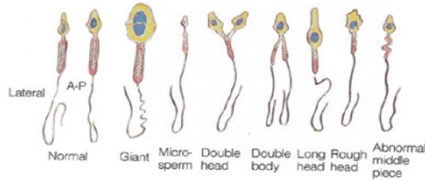
- Concentration >48 million/mL
- Motility >63%
- Morphology >8 %

Note: Data from World Health Organization, 2010 (10).
Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.

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Evaluation of the male


- Semen Analysis
 - Kruger "strict" morphology criteria
 - 8-10% of sperm demonstrate normal morphology, even in semen obtained from fertile men
 - Identifies risk for poor/failed fertilization with the use of standard in vitro fertilization (IVF) techniques
 - Dictates use of intracytoplasmic sperm injection (ICSI)



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Sperm terminology

- Asthenozoospermia
 - Astheno = weak
 - Poor motility
- Teratospermia
 - Terato = monster
 - Low normal sperm morphology
- Hypospermia
 - Reduced semen volume
- Aspermia
 - Complete lack of seminal fluid and sperm
- Oligospermia < 15 mil/mL
 - Oligo = few
 - Low sperm count
- Severe Oligospermia < 5 mil/mL
 - Very low sperm count
- Azoospermia
 - No sperm in seminal fluid



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Male Infertility

- Repeat SA
- Endocrine Evaluation
 - Indications:
 - Sperm concentration <5 million/mL
 - Any sperm count with otherwise unexplained impaired sexual function (ED, low libido)
 - Labs:
 - FSH, LH, TSH, PRL, CBC, chem panel, Hgb A1c
 - Total testosterone (T)
 - Must be drawn in the morning
 - total T level <300 ng/mL warrants further evaluation

*****NEVER GIVE TESTOSTERONE SUPPLEMENTATION TO MEN WHO ARE ATTEMPTING TO CONCEIVE*****

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Male Vitamin Cocktail

- Multivitamin with minerals- Centrum
- Vitamin E 400 IU daily
- Vitamin C 1000mg daily
- L-Carnitine 500mg daily
- DHA (Omega 3 FA) 1000 mg daily
- Vitamin D 400-800 IU daily
- CoEnzyme Q 200 mg bid
- HEALTHY LIVING
- No body building or herbal supplements
- Eliminate Tobacco, drugs. Decrease ETOH

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“But his sperm count was normal.”

1. Always obtain the report
2. Men with normal semen parameters can have sperm that are incapable of fertilizing an egg
3. Men with obesity and men > 50 demonstrate lower sperm counts and higher rates of infertility

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Other Abnormalities on SA

- Round cells in Seminal fluid
 - Under wet-mount microscopy, leukocytes and immature sperm appear similar and are properly called “round cells”
 - Many laboratories improperly report all round cells as “white blood cells”
 - Can distinguish with:
 - » Traditional cytological staining and immunohistochemical techniques
 - Men with true pyospermia (>1 million leukocytes/mL) should be evaluated for genital tract infection
 - Increased white blood cells in semen have been associated with:
 - Deficiencies in sperm function and motility.
 - May be linked to chronic prostatitis, tx 4-6 wks abx

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Other Abnormalities on SA

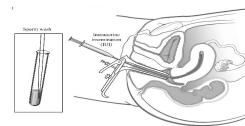
- Sperm Agglutination
 - Suggests Antisperm antibodies
 - Formed when there is a breach in the blood-testis barrier and the immune system is exposed to large quantities of sperm antigens
 - Trauma
 - Torsion
 - Biopsy
 - Orchitis
 - Testicular cancer
 - Vasectomy
- Tx IUI
- IVF with ICSI



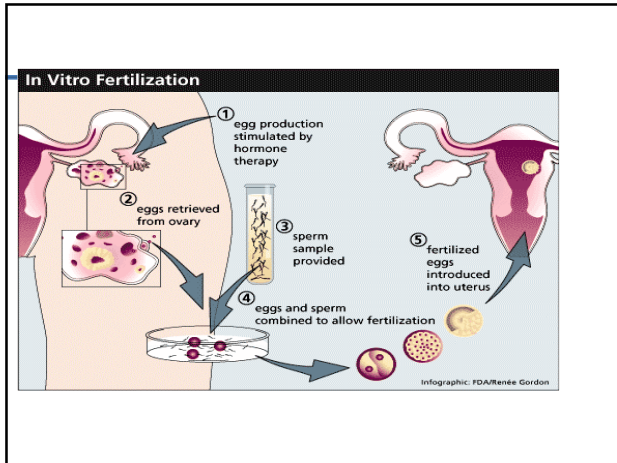
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Intrauterine insemination (IUI)

- Sperm collected
- Sample washed and prepped
- Total Motile Count (TMC) 10 mil post-wash
- Counts < 5 mil = decreased success
- Counts < 2 mil = IVF



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Azoospermia



- Normal FSH/LH
 - Obstructive Azoospermia
 - Vasectomy ??
 - Carrier screening for Cystic Fibrosis (Counsyl test, Natera)
 - Mutation in Cystic fibrosis trans- membrane conductance regulator (CFTR) gene
 - Located on chromosome 7
 - 80% of men with CBAVD have documented mutations of the CFTR gene.
 - Men with CBAVD should be assumed to have a CFTR gene mutation unless they have renal anomalies
- Elevated FSH/LH- (Low T) Hypergonadotropic hypogonadism
 - Non-obstructive Azoospermia
 - Y chromosome microdeletions
 - Chromosome analysis.
 - Klinefelter's; 47 XXY
- Low FSH/LH- (Low T) Hypogonadotropic hypogonadism
 - Non-obstructive Azoospermia
 - Hypogonadal
 - Kallman syndrome (GnRH deficiency)
- Low FSH/LH (High T)
 - Non-obstructive Azoospermia
 - Exogenous steroids
 - Clomid use

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Evaluation of the infertile male

- Abnormal male reproductive history or semen parameters warrants evaluation by a urologist



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Azoospermia

- **Obstructive: Sperm are being produced in the testicles but are not present in ejaculate**
 - Vasectomy
 - Congenital Bilateral Absence of Vas- CF Carriers
 - Cystic fibrosis trans- membrane conductance regulator (CFTR) gene
 - Located on chromosome 7
 - 80% of men with CBAVD have mutations of the CFTR gene
- **Non-obstructive: Sperm are not being produced**
 - Klinefelter's : 47XXY
 - Y-chromosome microdeletions
 - Sertoli-only syndrome

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Azoospermia

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 - Vasectomy ??
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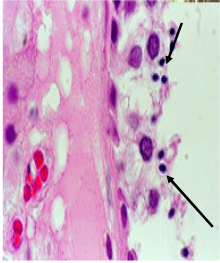
Y-chromosome microdeletions

- Prevalence
 - 7% of infertile men with severely impaired spermatogenesis
 - 2% of normal men
 - 16% of men with azoospermia
 - Identified with with PCR
- Most deletions causing azoospermia or oligozoospermia occur in regions of the long arm of the Y chromosome
 - Azoospermia factor (AZF) regions
 - Contain multiple genes necessary for spermatogenesis
 - Three regions screened for mutations:
 - AZFa (proximal)
 - » very poor prognosis for sperm retrieval
 - AZFb (central)
 - » very poor prognosis for sperm retrieval
 - AZFc (distal)
 - » May still produce sufficient numbers of sperm to allow testicular sperm extraction
 - » Results of ICSI are not affected adversely
 - » Sons of individuals with Y-chromosome microdeletions will inherit the abnormality and, therefore, may also be infertile

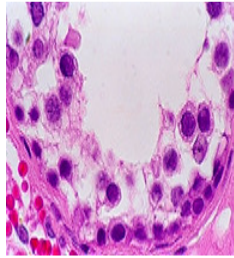
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Testicular biopsy

Sites with spermatogenesis



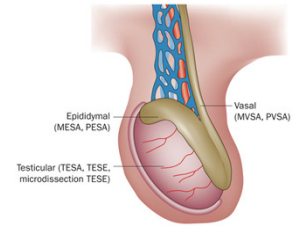
Sites without spermatogenesis



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Treatment of azoospermia

- **Sperm extraction:**
 - **PESA:** percutaneous epididymal sperm aspiration
 - **MESA:** microsurgical epididymal sperm aspiration
 - **TESA:** testicular sperm aspiration
 - **TESE:** testicular sperm extraction
 - **MicroTESE:** microsurgical testicular sperm extraction

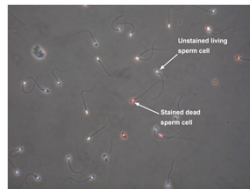


These sperm are not functional and must be used with IVF/ICSI. IUI IS NOT AN OPTION!

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Sperm viability tests

- Sperm Viability Tests
 - Used to see if non-motile sperm are viable
- Types of tests
 - Dyes
 - Eosin Y or trypan blue
 - Viable sperm exclude the dye and remain colorless
 - Sperm used for dye tests cannot be used for IVF
 - Hypoosmotic swelling (HOS) test
 - Sperm incubated with hypo osmotic solution
 - Sperm can be used for ICSI
 - Pentoxifylline Test
 - Viable sperm will develop motility after exposure to evaluation of the infertile male
 - Can be used for ICSI



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IVF with ICSI



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Special testing

- Post-ejaculatory urinalysis
 - Indications: HISTORY OF DM
 - Low volume ejaculate (<1.0mL)
 - Men typically notice decreasing fluid in ejaculate over time and eventually there's no fluid
 - Causes of low volume ejaculate
 - Incomplete semen collection
 - Very short abstinence interval (<1 day)
 - **Retrograde ejaculation**
 - Lack of emission
 - Ejaculatory duct obstruction
 - Hypogonadism
 - CBAVD
 - How its performed:
 - Ejaculate. Immediately collect urine sample.
 - Centrifuge the post ejaculate urine specimen
 - Microscopic examination of the pellet for sperm



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Evaluation for severe MF oligospermia (< 5 mil/mL) is the same as azoospermia

- FSH, LH, am testosterone, TSH
- Hyperprolactinemia- refer to endocrinology
- CBC- hemochromatosis, blood disorders
- Chem panel- Liver disease, ETOH abuse,
- Hemoglobin A1c- diabetes.
 - Retrograde ejaculation
- Urology consultation
- Offer Chromosome analysis, Y-chromosome microdeletions, Counsyl test (CF testing)

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How common are genetic abnormalities

- Karyotypic chromosomal abnormalities
 - Prevalence:
 - 10%–15% in non-obstructive azoospermic men
 - 5% in men with severe oligozoospermia (<5 million/mL)
 - <1% in men with normal sperm concentrations
 - 2/3 of all chromosomal abnormalities are sex chromosome related (Klinefelter syndrome; 47,XXY)
 - Increased risk for miscarriages
 - Increased risk for children with chromosomal and congenital defects
- Men with nonobstructive azoospermia or severe oligozoospermia should be offered high- resolution karyotype and Y-chromosome microdeletions before using their sperm to perform ICSI

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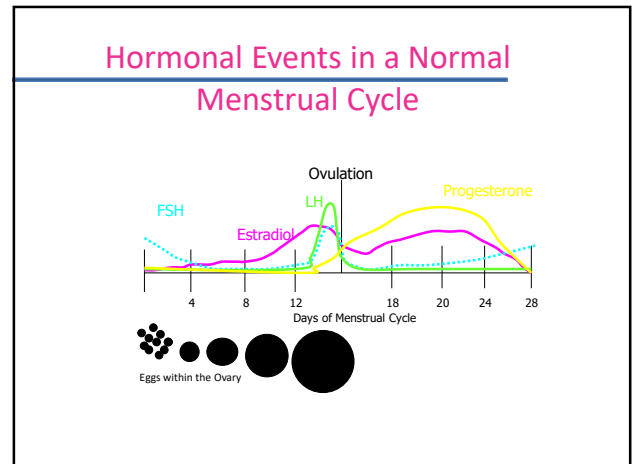
What about Imaging?

- Ultrasonography Indications
 - Low volume ejaculate
 - Transrectal ultrasonography for seminal vesicle location and volume, ejaculatory ducts dilation
 - Scrotal pathology
 - Scrotal ultrasonography
 - Varicoceles
 - Spermatoceles
 - Absent vasa
 - Epididymal induration
 - Testicular masses
 - Defining vague or ambiguous physical examination findings or abnormalities

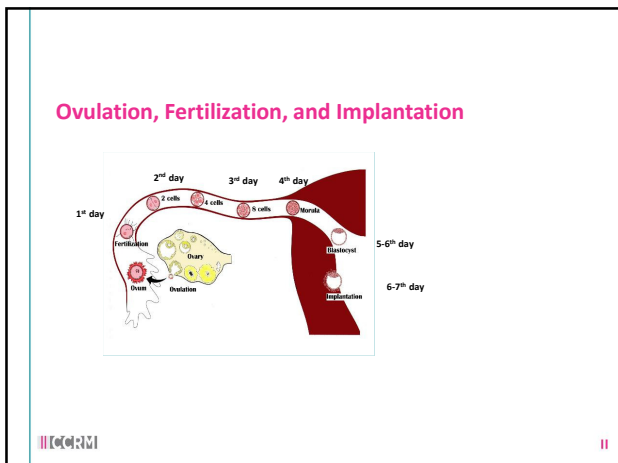
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LET'S TALK FEMALE FERTILITY

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HEALTHY PATIENT, HEALTHY PREGNANCY, HEALTHY BABY

- Eat healthy! well balanced diet
- Prenatal vitamins
- Stop smoking, alcohol, recreational drugs
- Reduce stress
- Low impact exercise
- Healthy weight
- Avoid toxic environmental exposures
- Vitamin D
- Vitamin C
- DHA (Fish oil)
- Internet Resources:
 - ACOG.org/patient
 - ASRM.org/Patient
 - www.ccrnivf.com

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When to seek help

- Women <35 years
Failure to achieve successful pregnancy after 12 months of unprotected intercourse
- Women 35-40 years
Failure to achieve successful pregnancy after 6 months of unprotected intercourse
- Women >40 years
Failure to achieve successful pregnancy after 1-3 months of unprotected intercourse

Right away if:

- History of oligo/amenorrhea, PCOS
- Hx chemotherapy/radiation either partner
- Known or suspected uterine issues, tubal disease, or stage III-IV endometriosis
- Known or suspected male infertility
- Recurrent pregnancy loss
- Special instances: Same sex couples
- Women >41 years

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OVARIAN RESERVE DECLINES WITH AGE

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Female Diagnostic Evaluation Ovulatory Function

- Serum antimullerian hormone (AMH)
 - Produced by granulosa cells of early follicles
 - Gonadotropin-independent
 - Relatively consistent within and between menstrual cycles
 - Can be obtained on any day of the menstrual cycle and on OCPs
- AMH levels <1 ng/mL
 - Poor response to ovarian stimulation
 - Poor embryo quality
 - Poor pregnancy outcomes after IVF

Age	Count
24	209
25	204
26	260
27	471
28	587
29	737
30	805
31	812
32	805
33	860
34	1019
35	1141
36	1297
37	1234
38	1333
39	1170
40	1088
41	983
42	883
43	808
44	727
45	615
46	491
47	411
48	302
49	202

Seifer DB et al. Fertil Steril 95(2) 747-50. 2011

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Most Common Causes of Infertility

- Age
- PCOS
- Amenorrhea/ oligomenorrhea
- Endometriosis
- Uterine Fibroids/polyps
- Uterine anomalies
- Hyperprolactinemia
- Male factor infertility
- Unexplained infertility

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Often Multiple Diagnosis/Problems

Female Diagnosis: <ul style="list-style-type: none"> Age related infertility (DOR) Ovulation Disorders (PCOS, thyroid disease, hyperprolactinemia) Fallopian Tube Damage Cervical Factors Uterine Abnormalities (Asherman, fibroids, polyps, septum, Bicornuate, unicornuate, didelphys, Adenomyosis) Endometriosis Pelvic or Uterine Adhesions (scar tissue) Low or elevated BMI Genetic disorders Medical history- cancer, loss of reproductive organs, chronic medical conditions, medications Exposures to toxins (tobacco, ETOH, chemicals) 	Male Diagnosis: <ul style="list-style-type: none"> Sperm Abnormalities Absence of sperm Obstruction (CF Carriers, vasectomy) Endocrine Dysfunction Varicocele Metabolic Factors Low or elevated BMI Genetic disorders Age related infertility Medical history- cancer, loss of male reproductive anato abnormal organ development Exposures to toxins (tobacco, ETOH, drugs)
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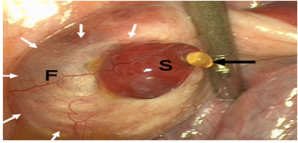
Female Diagnostic Evaluation Ovulatory Function

- 40% of infertility in women
- Common causes:
 - Polycystic ovary syndrome
 - Obesity
 - Weight gain or loss
 - Strenuous exercise
 - Thyroid dysfunction
 - Hyperprolactinemia

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Female Diagnostic Evaluation Ovulatory Function


- Methods of determining ovulation:
 - History
 - Basal Body Temperature (BBT)
 - Ovulation predictor (LH) kits
 - Serum progesterone



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Female Diagnostic Evaluation Ovulatory Function

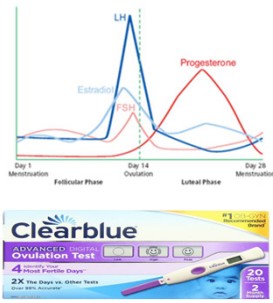
- Basal Body Temperature (BBT)
 - Cannot determine time of ovulation
 - 0.4-1.0°F 24 hours **AFTER** ovulation
 - Period of highest fertility 5-7 days prior to temp rise



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Female Diagnostic Evaluation Ovulatory Function

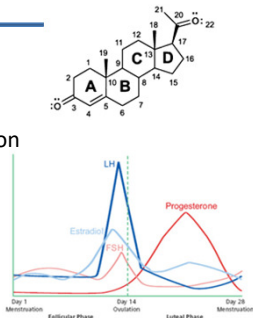
- Ovulation Predictor (LH) kits
 - Detect urinary LH
 - Identify the midcycle LH surge that precedes ovulation by ~36 hours
 - Best chance of conceiving:
 - Day of LH surge and following 2 days
 - Correlate well with the peak in serum LH (midday or evening urine)



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Female Diagnostic Evaluation Ovulatory Function

- Luteal serum progesterone concentration
 - Check one week after ovulation
 - Often cycle day 21
 - Progesterone greater than 3 ng/mL corresponds reliably with ovulation



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Fertility testing Female

- In addition to the usual PMH, Surg Hx, Meds, Fam Hx, Soc Hx, ROS:
 - Pregnancy History
 - Time to conceive. New partner?
 - Miscarriages, ectopics, # of term/preterm,
 - Complications with pregnancy/delivery
 - Previous Fertility evaluation and treatments
 - Extensive Gyn hx
 - Age at menarche
 - Cycle regularity. PCOS
 - Cycle characteristics (duration of bleeding, molimina, dysmenorrhea)
 - Previous Methods of Contraception/ coital frequency
 - Sexual Dysfunction (decreased libido, dyspareunia)

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Evaluation of the infertile female

- History continued
 - Sexually transmitted infections/PID
 - Hx fibroids, polyps, endometriosis, ovarian cysts
 - SX Endocrine disease
 - Thyroid, Galactorrhea, Hirsutism, Acne, hot flashes
 - Abnormal paps/subsequent treatment
 - Tob, ETOH, caffeine, drug use
 - Family history of birth defects, delayed development, early menopause, RPL
 - Occupation and exposure to environmental hazards (chemo tx, radiation tx)

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Evaluation of the infertile female

- Physical Exam
 - Weight, BMI, blood pressure, pulse
 - Thyroid enlargement and presence of any nodules or tenderness
 - Breast secretions
 - Signs of androgen excess
 - Vaginal or cervical abnormalities
 - Uterine size, shape, position, and mobility
 - Adnexal masses or tenderness
 - Cul-de-sac masses, tenderness, or nodularity



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Female Diagnostic Evaluation

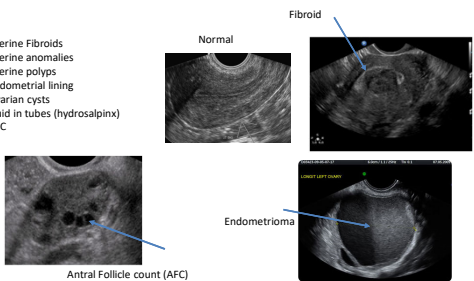
- Labs:
 - TSH, Prolactin (refer if abnormal)
 - Anti-Mullerian hormone (AMH)
 - Day three labs
 - FSH, E2, LH
 - Day 21 progesterone
 - Carrier Screening
- Prenatal labs: Blood type, Rubella titer, ID
- Transvaginal Ultrasound
- HSG- ok to delay 2-3 months for anovulatory pts

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Diagnostic Testing

Ultrasound-

- Uterine Fibroids
- Uterine anomalies
- Uterine polyps
- Endometrial lining
- Ovarian cysts
- Fluid in tubes (hydrosalpinx)
- AFC




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Female Diagnostic Evaluation

Ovulatory Function

- Antral follicle count (AFC)
 - Early follicular phase transvaginal ultrasound
 - Sum of antral follicles in both ovaries
 - AFC <10
 - Poor ovarian stimulation
 - Failure to conceive more likely

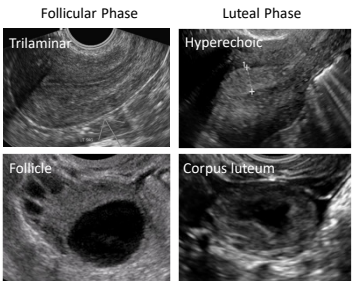


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Female Diagnostic Evaluation

Anatomical

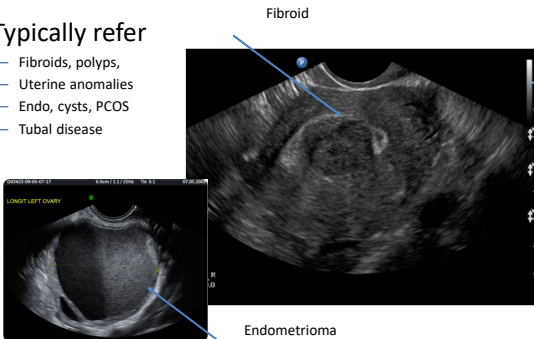
- Transvaginal ultrasound Day 2-3
 - Endometrium Thickness
 - Normal <6mm
 - >10mm= eval
 - Ovaries
 - No cysts
 - Normal uterus



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Ultrasound abnormalities

- Typically refer
 - Fibroids, polyps
 - Uterine anomalies
 - Endo, cysts, PCOS
 - Tubal disease



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Clomiphene citrate

- FDA approved for ovulation induction
- Selective Estrogen Receptor Modulator (SERM)



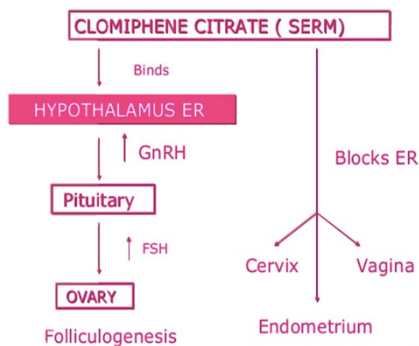
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Clomiphene Citrate -

- Structural similarity to estrogen allows CC to bind to estrogen receptors (ER)
- CC binds nuclear ER for an extended period of time and ultimately depletes ER concentrations
- Depletion of hypothalamic ER prevents correct interpretation of circulating estrogen levels
- Reduced levels of estrogen feedback trigger pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion
- This triggers increased pituitary gonadotropin release
- The LH surge occurs 5–12 days after the last dose of CC is taken.

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Clomiphene citrate



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Clomiphene citrate – when to start?

- Patients having menstrual cycles:
 - Early follicular phase
 - Start Clomid Day 3-5 start
 - 50 mg for 5 days
- Anovulatory PCOS patients:
 - Induce a menstrual cycle
 - Consider EMB if prolonged unopposed estrogen exposure first
 - Neg bhcg. Then Prometrium 400 mg for 10 days

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How to instruct your patients to time intercourse

- Use LH predictor kits
- Or simply prescribe intercourse cycle days 10, 12, 14, 16
 - More frequent intercourse is not necessary
 - Sperm survive 72 hours in the reproductive tract
- Midluteal progesterone > 5
- Among anovulatory women who ovulate with CC, the cumulative conception rates for 50 mg/d, 100 mg/d, or 150 mg/d at 3 months are 50%, 45%, and 33%, respectively

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Clomiphene citrate dosing

- Clomiphene comes in 50mg tabs
- For patients doing unmonitored clomid cycles, stick with 50mg
- If the patient is not responding, refer to a REI
 - Increasing the dose of clomiphene citrate often has a negative effect on the endometrial lining which needs to be monitored (SERM)



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Risks of Clomid

- Twins
 - 8% in anovulatory women
- Triplets
 - 1%
- No increased risk of congenital malformations

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Clomid side effects

- Mood swings are the most common side effect
 - 64%–78%
- Vasomotor flushes
 - 10%
- Visual disturbances
 - Blurred or double vision, scotomata, and light sensitivity, generally are uncommon (<2% prevalence)
 - Reports of optic neuropathy
 - If these symptoms occur must STOP CLOMID
- Less specific side effects (2-5%)
 - Breast tenderness
 - Pelvic discomfort
 - Nausea

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What about using other ovulation induction agents?

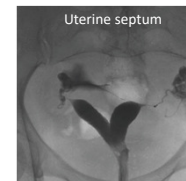
- Risks of Femara/Letrozole
 - ? Risks of birth defects if taken during pregnancy
 - Not FDA approved for ovulation induction
 - Must have a negative pregnancy test each month
 - Works well with PCOS
- Injectable gonadotropins- very risky
 - These should only be administered by a physician experienced with these medications under close ultrasound monitoring due to risks of multiple follicular recruitment
 - Risk multiples (25% twins, 5% triplets, <1% 4+)
 - Risk of severe OHSS
 - massive ovarian enlargement, progressive weight gain, severe abdominal pain, nausea and vomiting, hypovolemia, ascites, and oliguria

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Female Diagnostic Evaluation

Uterine Abnormalities

- Hysterosalpingography (HSG)
 - Defines the size and shape of the uterine cavity
 - Can reveal developmental anomalies
 - unicornuate, septate, bicornuate uteri
 - Can reveal acquired abnormalities
 - endometrial polyps, submucous myomas, synechiae

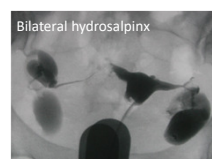
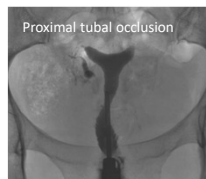


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Female Diagnostic Evaluation

Tubal Patency

- Tubal disease is an important cause of infertility
- Methods for evaluation:
 - HSG
 - SIS for fluid in the cul de sac
 - Laparoscopy/chromotubation
 - Fluoroscopic/hysteroscopic selective tubal cannulation
 - Chlamydia trachomatis antibodies:
 - Modest PPV (60%)
 - High NPV (80–90%) for detection of distal tubal disease



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Female Diagnostic Evaluation

Uterine Abnormalities

- Transvaginal saline sonogram
 - Better defines the size and shape of the uterine cavity
 - High PPV (>90%) and NPV for detection of intrauterine pathology

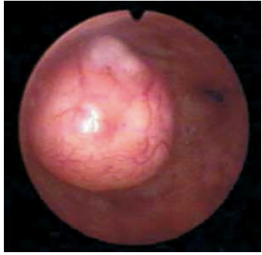


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Female Diagnostic Evaluation

Uterine Abnormalities

- Hysteroscopy
 - Definitive method for the diagnosis and treatment of intrauterine pathology



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To Refer or not to Refer

- Immediate referrals:
 - Age 35 or greater
 - AMH <1.0
 - FSH >10
 - Blocked fallopian tubes
 - Abnormal semen analysis

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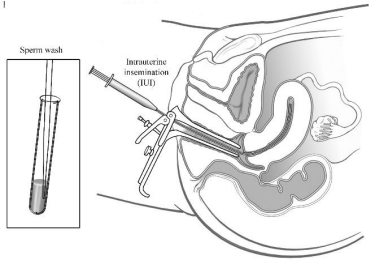


INTRAUTERINE INSEMINATION (IUI)

- IUI is one of the simpler treatments for infertility
 - Increases the chances of sperm reaching the egg(s)
 - Similar to pap smear
 - Low risk
 - IUI is only utilized after fertility evaluation and after it has been demonstrated that at least one fallopian tube is open
- Most patients will only undergo up to 3 IUI's.
- IUI can be completed with follicle stimulation with the use of medications called Clomid, Letrozole and ultrasound monitoring with trigger shot (Ovidrel)




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INTRAUTERINE INSEMINATION (IUI)

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- **Advanced treatment:**
 - In Vitro Fertilization (IVF)
 - IntraCytoplasmic Sperm Injection (ICSI)
 - Pre Implantation Genetic Testing (PGT)
 - Sperm retrieval (MESA, TESE)
- **Fertility Preservation**
 - Egg or Embryo Freezing
 - Sperm freezing
- **Third Party Reproduction**
 - Donor Egg
 - Donor Sperm
 - Donor Embryos
 - Gestational Carriers (Gestational Surrogacy)

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INDICATIONS FOR IVF

- **Women**
 - Decreased ovarian reserve
 - Polycystic ovarian syndrome
 - Tubal occlusion
 - Advanced age
 - Recurrent pregnancy loss
 - Heritable Genetic Disorders
 - Endometriosis
 - Failure of success from other types of fertility treatment
- **Men**
 - Male factor infertility
 - Mechanical factor (blockage)
 - Heritable disorders

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Steps involved In IVF:

The steps involved in the IVF cycle are:

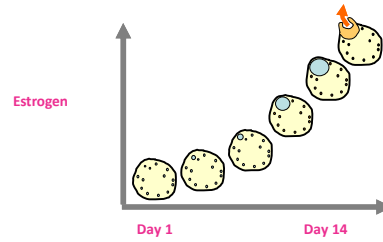
- Hormonal stimulation of the ovaries to develop multiple oocytes (eggs) which grow in follicles in the ovary
- Monitoring ovaries to assess the follicle growth
- Retrieval (removal) of oocytes
- Oocytes and sperm preparation, incubation, and fertilization (ICSI)
- Possible biopsy and screening embryos for CCS/PGD
- Cryopreservation of embryos
- Embryo Transfer



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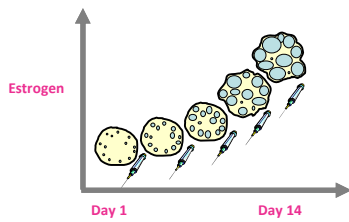
NORMAL FOLLICULAR PHASE



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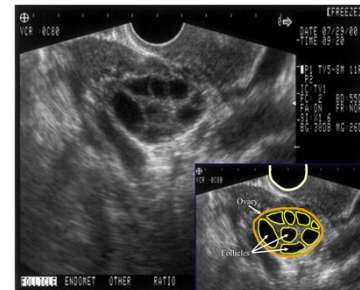
STIMULATED CYCLE



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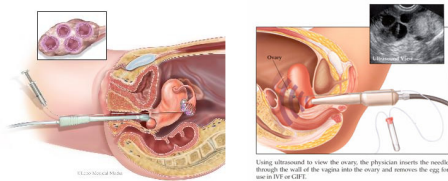
MONITORING PHASE



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IVF EGG HARVESTING PROCEDURE



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Video: Manipulation of eggs/sperm



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FREEZE EGGS OR CREATE EMBRYOS

|| ||

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STAGES OF EMBRYO DEVELOPMENT

Day 1
2 pronuclei

Day 3
Cleavage stage

Day 5 or 6
Blastocyst

|| ||

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FRESH OR FROZEN EMBRYO TRANSFER?

- Fresh embryo transfer: Day 3 or Day 5
 - Based on appearance only
 - Hyperstimulated ovaries
 - Hyperstimulated uterus
 - Lower success rates
- Frozen embryo transfer
 - Day 5 or day 6 embryos
 - Chromosomal or Single Gene testing
 - More physiological
 - Make sure uterus is optimal

|| ||

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THE FROZEN ADVANTAGE

- ↑ Implantation rates
- ↑ Ongoing pregnancy rates
- ↑ Live birth rates
- ↓ Discomfort when ovaries are not hyperstimulated

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FROZEN EMBRYO TRANSFER TIMING

Blastocyst is transferred after several days of progesterone supplementation
Can control timing using estrogen and progesterone

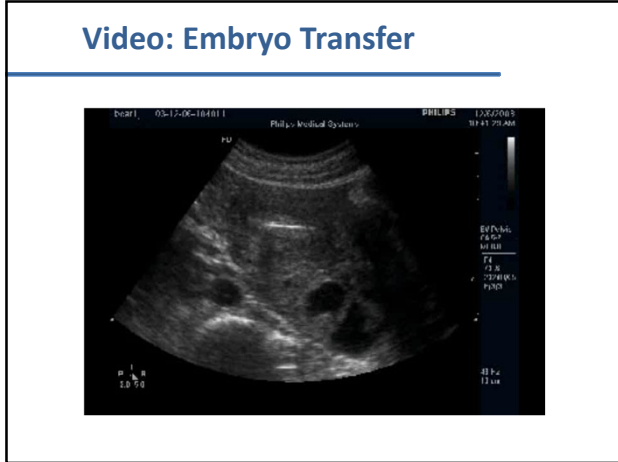
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The uterine lining (endometrium) is important

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PREIMPLANTATION GENETIC TESTING

- Early form of prenatal screening
- Done in conjunction with IVF
- ICSI is performed to decrease genetic contamination

Goal: Identify embryos with normal chromosomes (Euploid) for transfer to improve pregnancy outcomes

- Embryo biopsy performed to assess chromosome number
- Embryos are frozen while results of the biopsy are awaited
- Only embryos that have the correct number of chromosomes are selected for frozen embryo transfer (FET)

Illustration by Alex Baker, DNA Illustrations, Inc. Dr.

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Biopsy of Embryos for PGT Testing

Preliminary IVF outcome data for normal-responder patients following single-embryo transfer.

	Group A	Group B	Group C
Maternal age (y)	36.1 ± 4.7	36.8 ± 4.8	37.9 ± 3.7*
Implantation rate (FHT)	49.2%	52.6%	65.1%*
MAB	14.3%	14.4%	4.6%*
Ongoing pregnancy rate	40.7%	43.8%	60.0%*

Note: Group A (n = 118): day 5 fresh single-blastocyst transfer based on morphology alone; group B (n = 272): frozen single-blastocyst transfer based on morphology alone; group C (n = 347): frozen single-blastocyst transfer based on comprehensive chromosome screening results. FHT = fetal heart tone; MAB = missed abortion.
* P < .05.
Schoolcraft. Single-embryo transfer for older women. Fertil Steril 2013.

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ABNORMAL CHROMOSOME NUMBER (ANEUPLOIDY) IS THE LEADING CAUSE OF INFERTILITY

Aneuploid Embryo = Abnormal # of Chromosomes

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BENEFITS OF PGT-ANEUPLOIDY SCREENING

- ✓ Chromosome aneuploidies cause infertility and are the major cause of maternal age related decline in fertility
- ✓ >70% of spontaneous miscarriages are due to chromosome aneuploidies (inefficiency of human reproduction)
- ✓ Miscarriages = critical loss of time, cost and emotional trauma (~15% pregnancy loss after routine IVF cycle. That drops to 5% with euploid blastocyst transfer)
- ✓ Euploid embryos result in the highest ongoing implantation rates (maternal age independent)
- ✓ Single Euploid Embryo Transfer results in the **fastest path** to a singleton chromosomally normal live birth

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ELECTIVE SINGLE EMBRYO TRANSFER (eSET)

- Minimizes negative outcomes:
 - Multiple births
 - Pre-term labor
 - Miscarriage
 - Pre-eclampsia
 - Gestational diabetes
 - Neonatal morbidity

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Fertility preservation

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History of freezing sperm/eggs

- Attempts to freeze sperm date back to 1800s
- 1953- First successful pregnancy from frozen sperm (reported 10 years later due to legal/social climate at the time)
- 1977- First US sperm bank
- 1999- First successful pregnancy with egg vitrification
- 2012 ASRM removed “experimental” label for egg freezing

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Who should consider freezing eggs?

- Cancer patients
 - Chemo/Radiation tx can result in infertility and early menopause
- Women concerned about age-related infertility
- Family hx/ Genetic hx/ Exposures to toxins
- Transgender patients prior to initiating Tx
- Women who want to donate their eggs

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Allen W. Lorion, Pamela B. Marqu, Lindsay Nohr Beck, Lawrence Brenner, Anthony J. Magdalinski, Ann H. Partridge, Gwendolyn Quinn, W. Hamish Wallace, and Kudlak Oktay

Allen W. Lorion, Professor-School of Medicine at the University of Pennsylvania, Philadelphia; Anthony J. Magdalinski, Fertility Practice, Suburban, PA; Pamela B. Marqu, American Society of Clinical Oncology, Alexandria, VA; Kudlak

ABSTRACT

Purpose
To update guidance for health care providers about fertility preservation for adults and children with cancer.

“As part of education and informed consent before cancer therapy, health care providers ...should address the possibility of infertility with patients treated during their reproductive years.”

“...Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation.”



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Thank you!



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