Infertility Evaluation

RES013

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

RESIDENT EDUCATION

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Course Overview

ACTIVITY NUMBER: RES013

ACTIVITY TITLE: Infertility Evaluation

ACCREDITATION STATEMENT
The American Society for Reproductive Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Release Date: August 15, 2013
Expiration Date: August 14, 2016
Reviewed: July, 2013

Estimated Time to Complete Activity: 1.0 hour

NEEDS ASSESSMENT and IDENTIFICATION OF PRACTICE GAP
Infertility is a disease defined by the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years.[1] Infertility affects about 7.3 million women and their partners in the U.S., about 12% of the reproductive-age population.[2] A basic infertility evaluation of the couple is essential to determine the cause(s) and the appropriate treatment or need for referral. Unfortunately, there are limited data from rigorous, controlled, clinical trials evaluating the efficacy of infertility screening tests in relation to clinical outcome, leading physicians to use other sources of guidance for their clinical practice decisions.[3] Surveys of practicing board-certified reproductive endocrinologists have shown variability in the details of the performance of most testing and practice pattern differences, especially with regards to age and geographic location.[3] In addition, there is lack of agreement on the roles of newer and more controversial modes of testing.[4]

This presentation addresses the causes of primary and secondary infertility, with guidance for performing a pertinent physical examination and patient history. The presentation also covers the basic diagnostic tests for assessing the most common causes of infertility, and their interpretation. Treatments discussed include nongonadotropin therapies and the role of selected surgical procedures. Also discussed are indications for referral to a board-certified reproductive endocrinologist and counseling for patients regarding their prognosis and options for family building.

1. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril. 2008 Nov;90(5 Suppl):S60.
2. Centers for Disease Control and Prevention, National Center for Health Statistics. *2002 National Survey of Family Growth*. U.S. Department of Health and Human Services Web site.
3. Glatstein IZ, Harlow BL, Hornstein MD. Practice patterns among reproductive endocrinologists: the infertility evaluation. Fertil Steril. 1997 Mar;67(3):443-51.
4. Glatstein IZ, Harlow BL, Hornstein MD. Practice patterns among reproductive endocrinologists: further aspects of the infertility evaluation. Fertil Steril. 1998 Aug;70(2):263-9.

This educational activity is designed to address the Unit 5 Reproductive Endocrinology educational objectives from the Council on Resident Education in Obstetrics and Gynecology (CREOG) on this topic.

EDUCATIONAL OBJECTIVES

At the conclusion of the educational activity, participants should be able to:

1. Describe the classification and principal causes of infertility.
2. Elicit a pertinent history and list the components of a focused physical examination to evaluate infertility.
3. Select and interpret diagnostic tests to determine the most likely cause of infertility.
4. Describe appropriate treatment for infertile patients who have irregular ovulation with nongonadotropin therapy.
5. Describe appropriate surgical procedures to correct anatomic conditions that cause infertility.
6. Counsel patients about the prognosis for their condition and alternatives to childbearing such as adoption, donor gametes, and use of a surrogate or gestational carrier.
7. Describe the indications for referral to a subspecialist for treatment.

TARGET AUDIENCE

This activity is designed to meet the educational needs of resident physicians in obstetrics and gynecology and other related specialties.

ACGME COMPETENCIES

Medical Knowledge
Patient Care
Interpersonal and Communication Skills

SUCCESSFUL COMPLETION REQUIREMENTS

Successful completion of this educational activity requires the learner to:

- View a course overview page, containing all CME and disclosure information, including acknowledgement of commercial support and disclosure of unlabeled use, prior to the start of each module.
- Complete a 10-question pre-exam prior to the module. Learners should note any pre-exam questions answered incorrectly for clarification during module study.
- Be given the option of downloading a printed syllabus containing the presentation and narrative.
- Participate in the interactive activity: Audio narration is synchronized with PowerPoint presentation that can be advanced, stopped or reversed as desired.
- Complete a 10-question post-exam, with feedback of correct/incorrect answers, **scoring a minimum of 70% in two attempts.**
- Complete the evaluation survey.
- Print certificate of completion.

DISCLOSURES FOR PLANNERS AND FACULTY

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James P. Toner, M.D., Ph.D. - Research support from Columbia Laboratories
Ellen Wilson, MD – Nothing to Disclose
Bo Yu, MD – Nothing to Disclose

It is the policy of the ASRM to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All faculty/authors participating in this activity were required to disclose any relationships they may have with commercial entities whose products or services are used to treat patients so that participants may evaluate the objectivity of the presentations. The content and views presented in this activity are those of the faculty/authors and do not necessarily reflect those of the ASRM or CREOG. Any discussion of off-label, experimental, or investigational use of drugs or devices will also be disclosed. The disclosure statements were reviewed by the Subcommittee for Standards of Commercial Support of the CME Committee of ASRM and any perceived conflicts of interest were resolved in accordance with the policies of the ACCME.

STATEMENT OF SUPPORT
No commercial support has been provided for this activity.

Exam Questions

1. A 25-year-old woman presents for a fertility evaluation. She has been trying to conceive for the past 1.5 years with her 28-year-old husband. He has two children from a previous relationship. She has regular 28 day menstrual cycles, a history of pelvic inflammatory disease and hypothyroidism treated with levothyroxine. The test most likely to reveal the etiology of the couple's infertility is:
    a. Early follicular phase serum FSH
    b. Semen analysis
    c. Hysterosalpingogram
    d. Serum TSH

2. A couple is undergoing an evaluation for fertility. The male partner's semen analysis returns with the following results:

    - Volume 2.0 mL
    - Count 2 million/mL
    - Motility 25%

    What is the most appropriate next step?

    a. Fertility treatment with intrauterine inseminations
    b. Prescribe clomiphene citrate therapy
    c. Initiation of antioxidant and vitamin therapy
    d. Referral to a urologist or male reproductive specialist for evaluation

3. A 34-year-old woman has a history of 2 prior miscarriages. She had retained products of conception following her second miscarriage, requiring a dilation and curettage. She was thought to have endomyometritis at the time of the procedure. Periods since her last miscarriage have been light, possibly secondary to Asherman syndrome. The test that will evaluate her uterine cavity as well as assess tubal status is:
    a. Hysterosalpingogram
    b. Hysteroscopy
    c. CT scan
    d. MRI

4. A 38-year-old woman presents to her Ob/Gyn. She was married last year and stopped her birth control pills 7 months ago to try to conceive. She has 27-28 day menstrual cycles, and she and her husband have been having intercourse every other day for one week starting on cycle day 9. What is the next appropriate step?
    a. Advise her to return after one year of unprotected intercourse.
    b. Have them increase intercourse to daily around the time of ovulation.
    c. Instruct her to wait to have intercourse until an ovulation predictor kit is positive.
    d. Initiate a fertility evaluation.

5. A 39-year-old single woman presents for a fertility consultation. She states that she wants to check on the health of her eggs. She would like to know how much time she has as her "biological clock is ticking." Which one of the following laboratory assessments can be used to assess ovarian reserve?
    a. Fasting prolactin
    b. Early follicular phase serum FSH and estradiol
    c. Total testosterone
    d. TSH

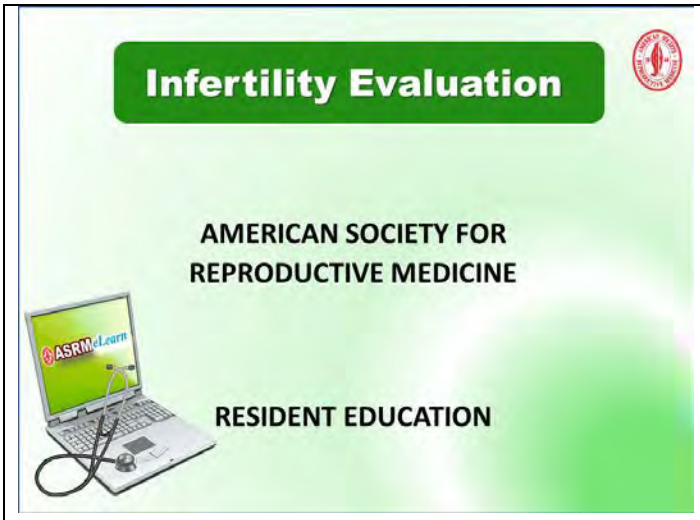
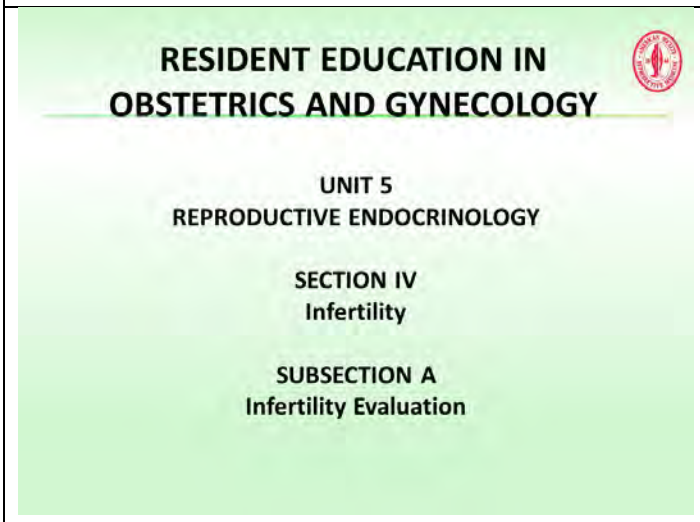
6. A 32-year-old woman presents with 1.5 years of primary infertility. Her menstrual cycles fall every 45-50 days, and she has hirsutism. She has no prior pelvic surgery and no known history of STIs. Her husband has a child from a previous relationship. The most appropriate therapy for this couple is:
    a. Clomiphene citrate
    b. Bromocriptine
    c. Intrauterine insemination
    d. In vitro fertilization

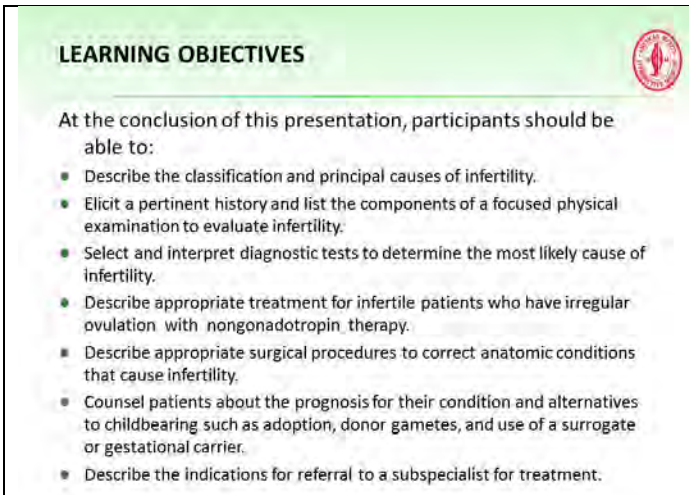
7. Which of the following is an appropriate method to determine ovulation status?
    a. Early follicular FSH and estradiol
    b. Antral follicle count
    c. Early follicular antimüllerian hormone level
    d. Mid-luteal serum progesterone level

8. A couple presents with 1 year of primary infertility. The female partner is 26 years old, cycles every 28 days and has a normal hysterosalpingogram. A semen analysis reveals a volume of 2mL, concentration of 9 million/mL, 40% motility and normal morphology. The male patient is referred to a urologist; his physical exam is normal and a repeat semen analysis reveals a similar result. The most reasonable initial therapy for this couple with mild male factor infertility is:
    a. Clomiphene citrate to induce ovulation.
    b. Reassurance and recommendation to continue unassisted efforts to conceive.
    c. Intrauterine insemination
    d. In vitro fertilization with intracytoplasmic sperm injection

9. Infertility affects what percentage of couples having regular unprotected intercourse?
    a. 5%
    b. 10%
    c. 25%
    d. 40%

10. A 27-year-old woman presents with 2 years of primary infertility. She was on birth control pills for the past 8 years for severe dysmenorrhea and currently uses prescription-strength ibuprofen for the painful cramping with her periods. Menstrual cycles occur every 28 days. She has no history of STDs, and her husband has a normal semen analysis. She has tried 6 months of clomiphene citrate without success. The best approach to evaluate for tubal patency in this patient is:
    a. Hysterosalpingogram
    b. Sonohysterogram
    c. Laparoscopy with chromopertubation
    d. Magnetic resonance imaging

	Welcome to the American Society for Reproductive Medicine's eLearning modules in reproductive endocrinology.
	The subject of this presentation is Unit 5 of the CREOG Educational Objectives – Reproductive Endocrinology, Section IV – Infertility, Subsection A – Infertility Evaluation.



At the conclusion of this presentation, participants should be able to:

-Describe the classification and principal causes of infertility.

-Elicit a pertinent history and list the components of a focused physical examination to evaluate infertility.

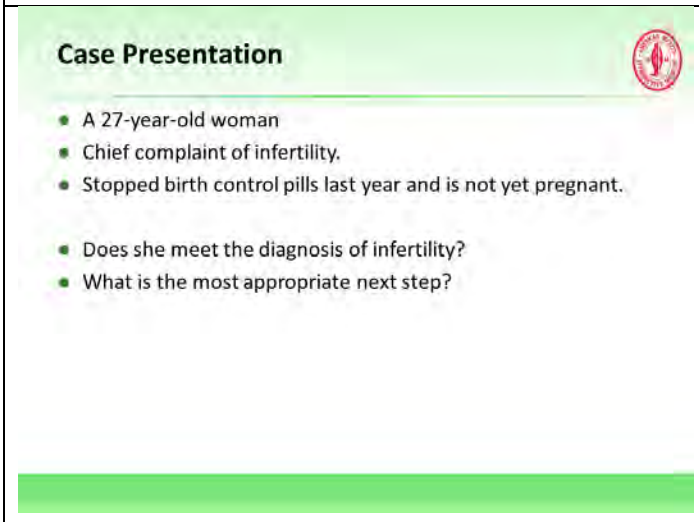
-Select and interpret diagnostic tests to determine the most likely cause of infertility.

-Describe appropriate treatment for infertile patients who have irregular ovulation with nongonadotropin therapy.

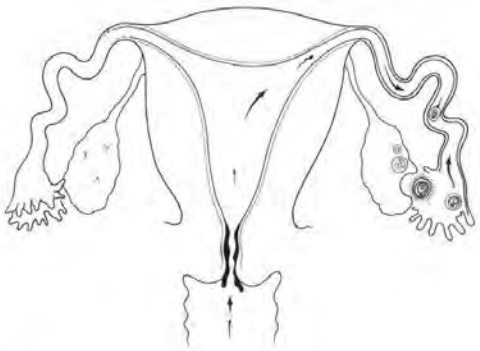
-Describe appropriate surgical procedures to correct anatomic conditions that cause infertility.

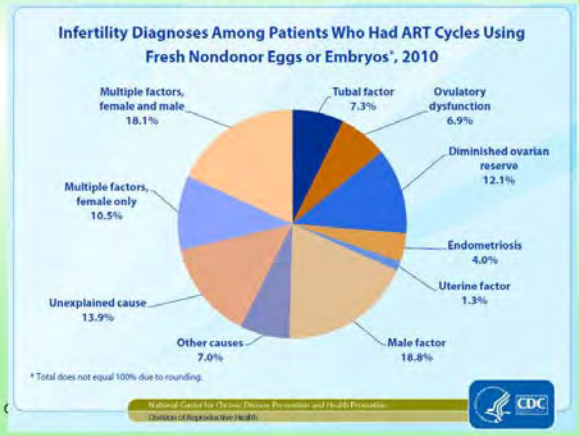
-Counsel patients about the prognosis for their condition and alternatives to childbearing such as adoption, donor gametes, and use of a surrogate or gestational carrier.

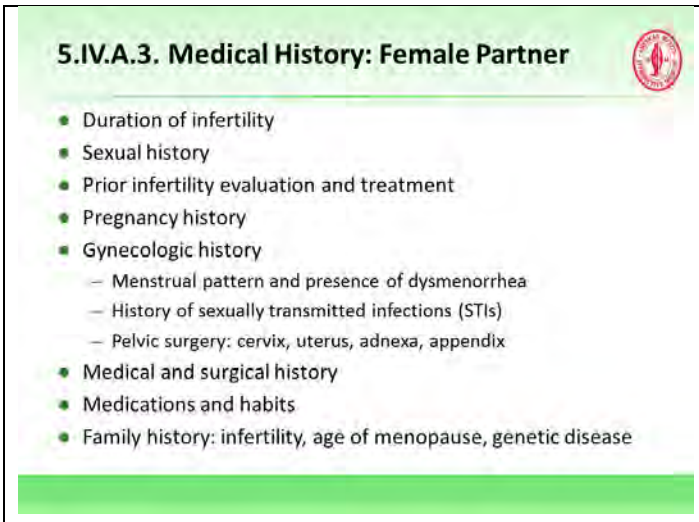
-Describe the indications for referral to a subspecialist for treatment.



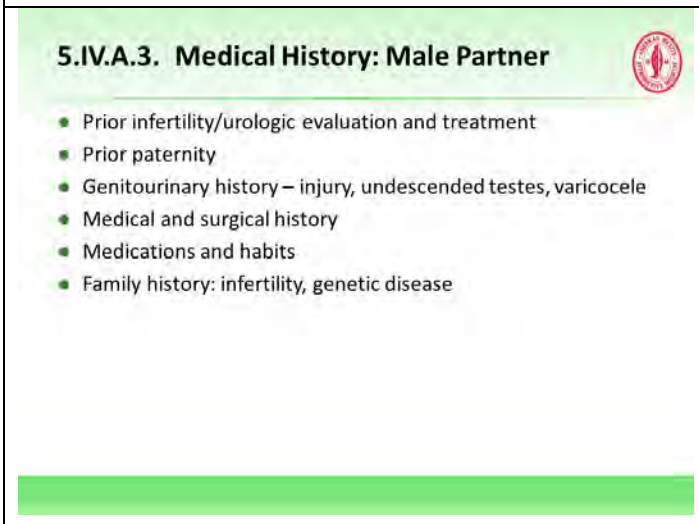
The case for this presentation is a 27-year-old woman who presents with the chief complaint of infertility. She reports that she stopped her birth control pills last year and is not yet pregnant. Does she meet the diagnosis of infertility? What is the appropriate next step?

5.IV. A.1. Definition of Infertility • Couples having regular, unprotected intercourse: – 50-60% will conceive in 3 months – 70% will conceive in 6 months – 85% will conceive in 1 year – 90% will conceive in 2 years • Infertility is defined as the failure to conceive after one year of regular unprotected intercourse • Affects 10-15% of couples • Infertility further defined as: – Primary infertility when the female partner has not had a prior pregnancy – Secondary infertility when the female partner has had a prior pregnancy Fertil Steril 2008;89:1603	Of couples having regular unprotected intercourse, 50-60% will conceive in 3 months, 70% will conceive in 6 months, 85% will conceive in 1 year and 90% will conceive in 2 years. Infertility is defined as the failure to conceive after one year of regular unprotected intercourse and affects 10-15% of couples. Infertility is further defined as primary infertility when it occurs in a female partner who has not had a prior pregnancy and secondary infertility when the female partner has had a prior pregnancy.
5.IV. A.1. Definition of Infertility: Special Cases • Earlier evaluation and treatment is indicated for women > 35 years old who have not conceived after 6 months of unprotected intercourse • Evaluation and treatment prior to 1 year is also appropriate for women with a history of: – Oligo- or amenorrhea – Known or suspected uterine or tubal disease – Male partner with known or suspected subfertility Fertil Steril 2013;99:63	Earlier evaluation and treatment is indicated for women over age 35 years who have not conceived after 6 months of unprotected intercourse. Evaluation and treatment prior to one year is also appropriate in women who have a history of oligo- or amenorrhea, known or suspected uterine or tubal disease, or a male partner with known or suspected subfertility.
5.IV.A.2. Female Anatomy  © 2011 ASRM	Familiarity with female pelvic anatomy and the steps required to establish a normal pregnancy is key to understanding the components of a fertility evaluation. For a pregnancy to occur, an oocyte must be released from the ovary and picked up by a patent and functional fallopian tube. Sperm must be deposited in the upper vagina and be of sufficient number and motility to swim through the cervical mucus and endometrial cavity to meet and fertilize the egg in the fallopian tube. The fertilized oocyte must then be transported to the uterine cavity to implant in a receptive endometrium. The uterine cavity should be free of structural defects that would interfere with implantation.

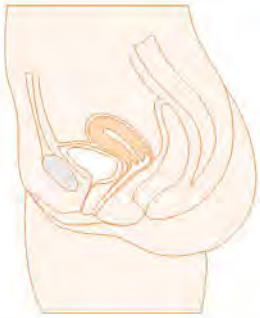
5.IV.A.2. Causes of Infertility • Ovulatory dysfunction – Primary ovarian insufficiency (premature ovarian failure) – Hypogonadotropic hypogonadism – Polycystic ovary syndrome (PCOS) – Prolactin disorders • Endometrial/uterine abnormalities • Tubal obstruction • Cervical stenosis • Male factor – Azoospermia: zero sperm count – Oligospermia: low sperm count – Asthenospermia: low sperm motility – Teratozoospermia–abnormal sperm morphology • Unexplained infertility	Given the number of steps required for a normal pregnancy to develop, there are many potential causes of infertility. They include ovulatory dysfunction, such as primary ovarian insufficiency (*also known as premature ovarian failure)*, hypogonadotropic hypogonadism, polycystic ovary syndrome and prolactin disorders; abnormalities of the endometrium or uterine structure; tubal obstruction or dysfunction; cervical stenosis; and male factors such as azoospermia (zero sperm count), oligospermia (low sperm count), asthenospermia (low sperm motility) and teratozoospermia (abnormal sperm morphology). Occasionally, there is no evident explanation for a couple's infertility.
5.IV.A.2. Frequency of Infertility Diagnoses  	This chart from the Centers for Disease Control and Prevention describes the types of infertility among couples who had assisted reproductive technology cycles with fresh, nondonor eggs or embryos. The data reveal that 30% of couples undergoing this most advanced fertility treatment have multiple factors contributing to their infertility, and that male factor, tubal factor and diminished ovarian reserve are also common causes of infertility at 18.4%, 8.4%, and 11.0%, respectively. Unexplained infertility is also relatively common at 12.8%. Infertility solely attributed to endometriosis or uterine factors is less common.
5.IV.A.3. Basic Infertility Evaluation • Medical history of female and male partners • Focused physical examination • Semen analysis • Detection of ovulation • Ovarian reserve (if indicated) • Patency of fallopian tubes • Uterine evaluation • Semen analysis • Preconception counseling and laboratory testing	A basic evaluation for infertility should include a medical history of the female and male partners, a semen analysis, a focused physical examination of both partners, testing to detect ovulation, assessment of ovarian reserve (if indicated), evaluation of tubal patency and a uterine evaluation. Preconception counseling and some specific laboratory testing, while not strictly part of the infertility evaluation, should be considered at the time of the initial work-up.



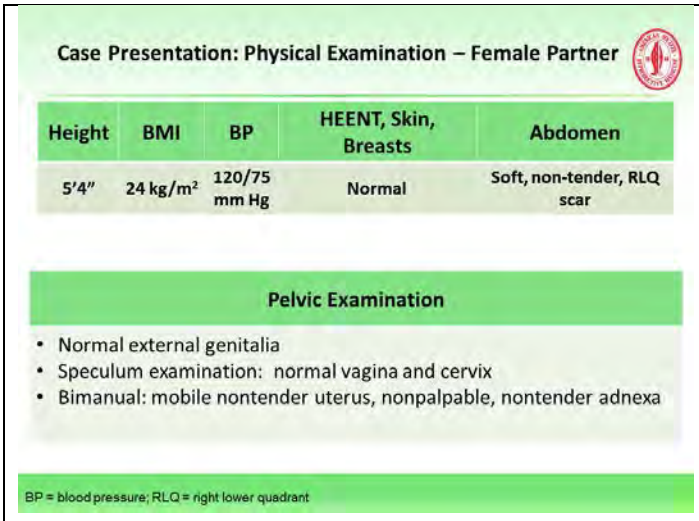
An infertility evaluation typically begins with a medical history of the female and male partners. History from the female partner includes the duration of infertility and a careful sexual history, noting the frequency and timing of sexual intercourse. Prior infertility evaluation and treatment is noted, as well as a pregnancy history recording the time to conception and pregnancy outcome for each past pregnancy. A careful gynecologic history is important, including a menstrual history, history of any sexually transmitted infections, and any prior pelvic surgery involving the cervix, uterus, adnexa or appendix. Other details include current medical conditions, prior surgeries, current medications and social habits such as tobacco and alcohol use**,** as well as a family history including any history of infertility, the age of menopause of the patient's mother, if known, and any genetic diseases.



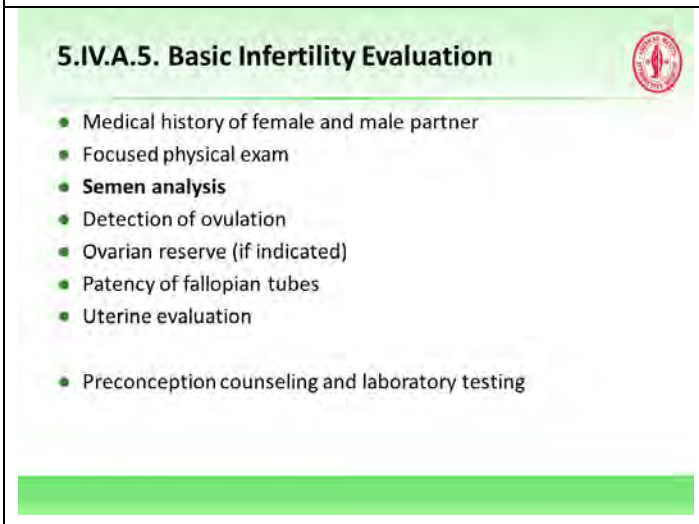
The history of the male partner includes any prior infertility or urologic evaluation, noting any prior paternity. A complete genitourinary history includes assessment of sexual function including the ability to achieve erection and ejaculation, history of groin injury or infections, undescended testes, varicocele or surgery to the area, including inguinal hernia repair. Other details include current medical conditions, prior surgeries, current medications, and social habits such as tobacco and alcohol use, as well as a family history, including any history of infertility or any genetic diseases.

5.IV.A.4. Focused Female Physical Examination • Weight and height, body mass index (BMI) – Underweight: BMI <18 kg/m^2 – Overweight: BMI 25-29 kg/m^2 – Obese: BMI ≥30 kg/m^2 • HEENT – Thyroid • Breast – Assess development, masses, nipple discharge • Skin – Acne, hirsutism, acanthosis nigricans HEENT = Exam of head, eyes, ears, nose and throat	A focused physical examination is also an important part of the infertility evaluation. For the female this includes assessment of height and weight commonly summarized using a body mass index, as both extremes of weight – underweight and overweight – can be associated with infertility. As thyroid disease is common in reproductive-aged women, a thyroid examination should also be performed, and a breast examination should assess for normal development and the presence of any masses or nipple discharge. Examination of the skin can reveal signs of endocrine disorders; the presence of acne, hirsutism, or acanthosis nigricans should be noted. As many women will use methods of mechanical hair removal to manage hirsutism, the patient should be asked if she has problems with excess hair growth.
5.IV.A.4. Focused Female Physical Examination • Pelvic examination – Appearance of external genitalia – Speculum to examine vagina and cervix – Bimanual examination to evaluate size and contour of uterus, palpate for adnexal masses or tenderness – Rectovaginal examination may detect nodules characteristics of endometriosis. 	A pelvic examination is an important part of the infertility evaluation. The appearance of external genitalia should be noted, and a speculum should be inserted to examine the vagina and cervix. A bimanual examination should be performed to assess the size and contour of the uterus and adnexal masses masses or tenderness. A rectovaginal examination may detect nodules characteristic of endometriosis.

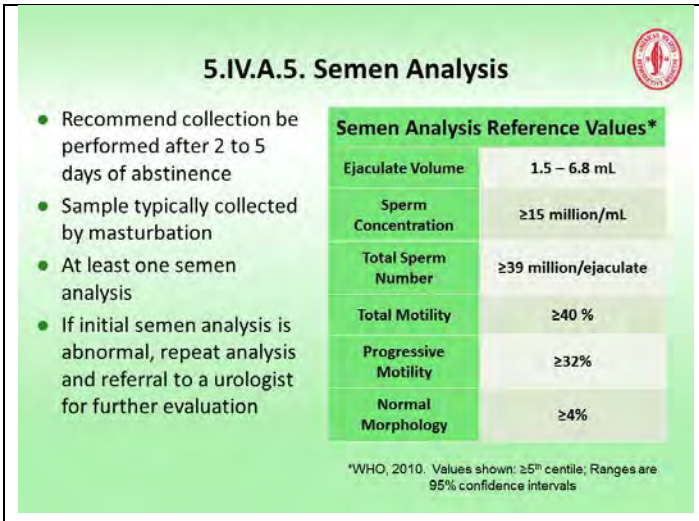
5.IV.A.4. Focused Male Physical Examination • Typically performed by a urologist • Indicated for scrotal symptoms, symptoms of androgen insufficiency or abnormal semen analysis • Assessment/examination: – General appearance – Penis – Testicular volume and consistency – Vas deferens – present or absent – Epididymal induration – Varicocele – Hernia 	The male infertility exam is typically performed by a urologist. This is indicated if the man's medical history reveals symptoms of a genitourinary abnormality, symptoms of androgen insufficiency, or if a semen analysis is abnormal. The male exam typically includes assessments of general appearance, the skin for hair distribution, penis, evaluation of testicular volume and consistency, presence or absence of vas deferens, and detection of epididymal induration, varicocele or hernia.
Case Presentation **27-year-old woman** • Chief complaint: primary infertility • Stopped birth control pills last year; intercourse 2-3 times/week with husband. • Gravida 0; menstrual cycles every 28-30 days; no cervical dysplasia, no known STIs • No past medical problems • Appendectomy, ruptured • Daily prenatal vitamin • Married, no alcohol/tobacco **31-year-old man** • Chief complaint: infertility • Presents with wife; no prior paternity; no history of groin injury/infection; normal sexual function. • No past medical problems • No prior surgeries • No medications • Married, occasional alcohol, no tobacco	Let's return to our case. The patient is a 27-year-old woman with primary infertility. She has had one year off contraception and has unprotected intercourse 2 to 3 times per week with her husband. She has never been pregnant and reports that her periods begin every 28-30 days. She reports no history of cervical dysplasia and no known sexually transmitted infections. She has no past medical problems, but had an appendectomy following a rupture 5 years ago. She takes a prenatal vitamin daily. She does not smoke or drink alcohol. Her partner is a 31-year-old man who has no prior paternity. He has no history of groin injury or infection, and reports normal sexual function. He has no past medical problems and no past surgeries. He takes no medications, occasionally drinks alcohol, and does not smoke.



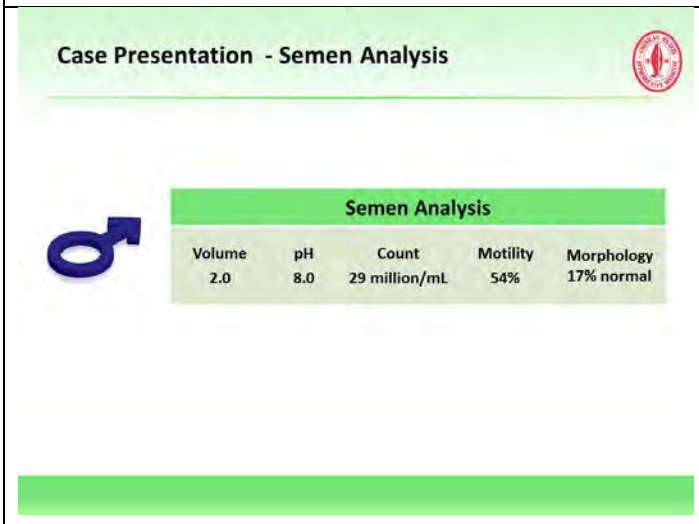
On examination, the patient's weight, BMI and blood pressure are normal. She is well-appearing with normal affect. Her thyroid, skin and breast exams are normal. Her abdomen is soft, nontender and has a well-healed surgical scar in the right lower quadrant. On pelvic examination, she has normal external genitalia. The speculum examination reveals a normal vagina and cervix, and on bimanual examination she has a mobile, nontender uterus and nonpalpable, nontender adnexa.



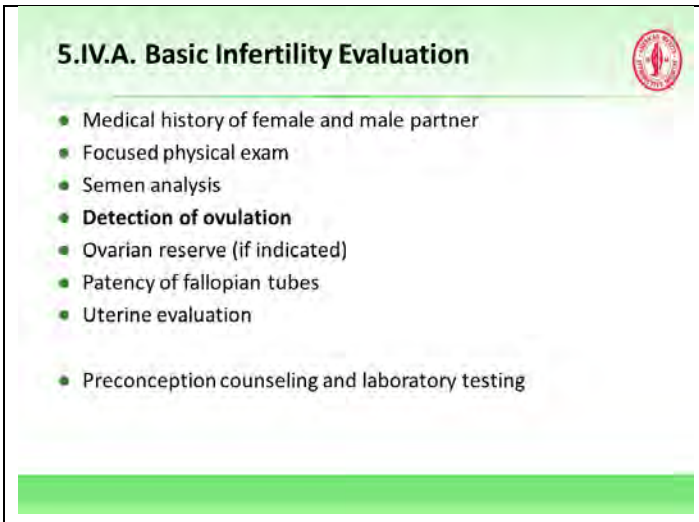
Let's review again the elements of the basic infertility evaluation. The focused medical history and physical examination of each partner may reveal a likely etiology for their infertility. Thus the evaluation can begin in that area and be broadened as indicated. A critical step in the infertility evaluation is the semen analysis.



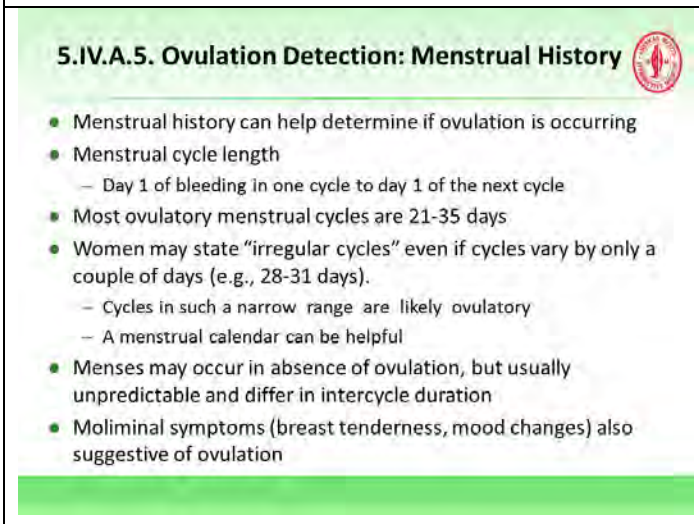
Collection for a semen analysis is recommended after a 2 to 5 day period of abstinence. The sample is typically collected by masturbation. This table provides reference values for a semen analysis from the 2010 World Health Organization report. The ejaculate volume should fall between 1.5 and 6.8 mL. The sperm concentration should be at least 15 million per mL, with a total sperm count per ejaculate of 39 million or more. Total sperm motility should be 40% or higher, with at least 32% progressive motility. The sample should have greater than 4% normal forms. Also, the presence of sperm agglutination and ejaculate viscosity should be noted, as well as the pH. The evaluation of the male partner should include a reproductive history and at least one semen analysis. If this initial semen analysis is abnormal, additional evaluation of the male partner is recommended. This should include a repeat semen analysis and a urologic examination. Based upon these results, further testing for anatomic, endocrine, or genetic abnormalities may be warranted.



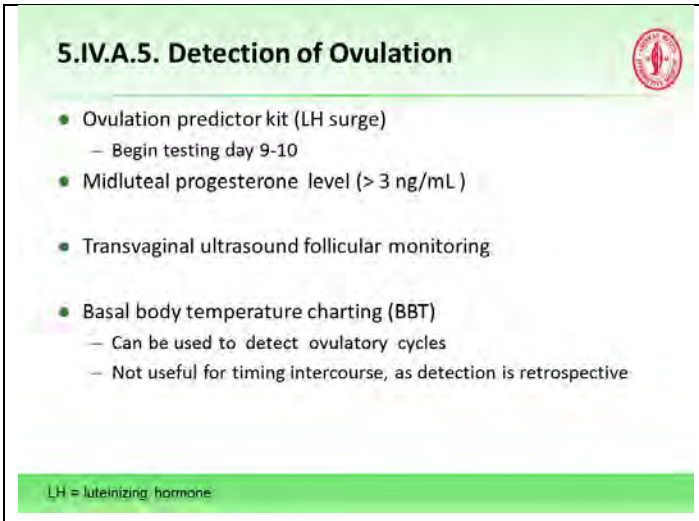
Her husband's semen analysis is normal, with a volume of 2.0 mL, pH of 8.0, count of 29 million per mL, motility of 54% and 17% normal forms by Kruger morphology.



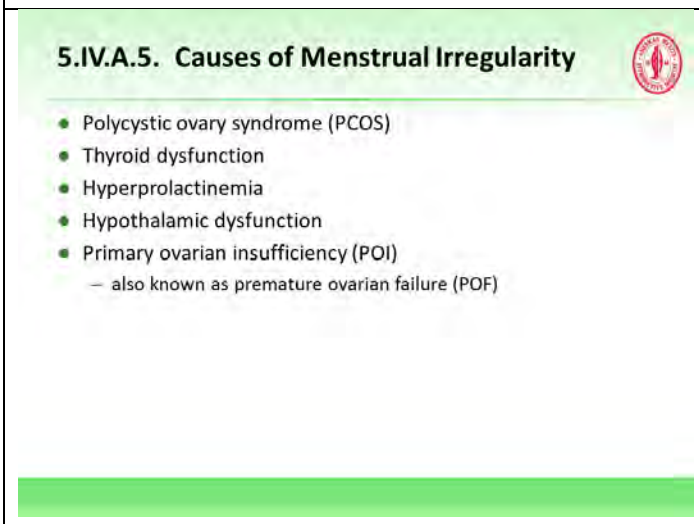
If the history, examination and semen analysis reveal no apparent cause, or the woman is over age 30, a more detailed evaluation may be appropriate. We will now discuss detection of ovulation.



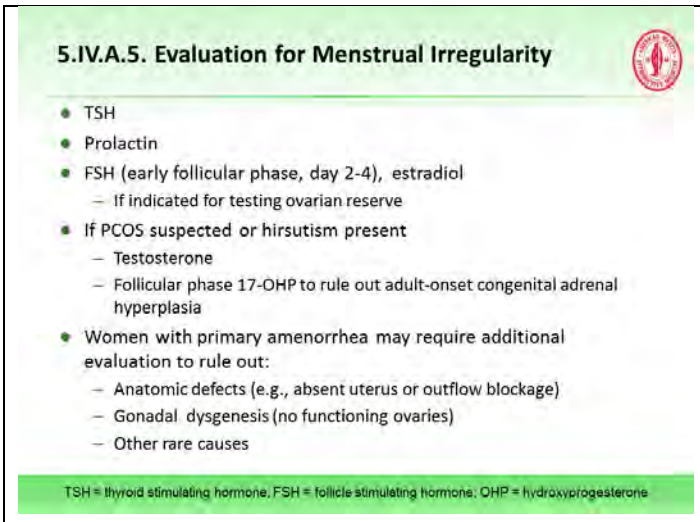
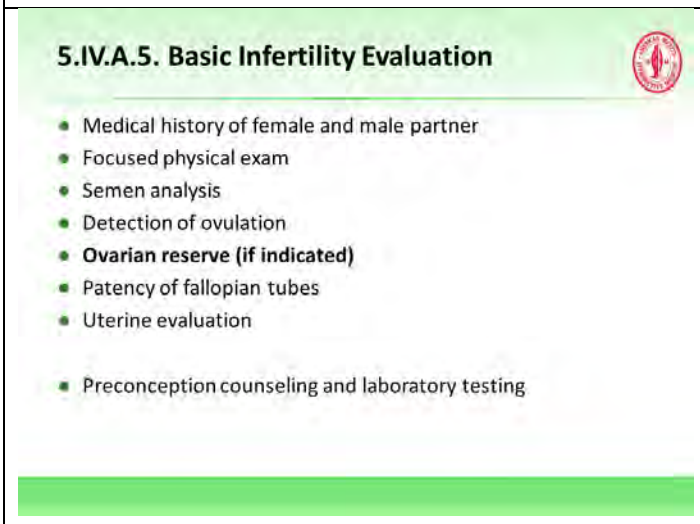
A menstrual history can help determine if ovulation is occurring. Menstrual cycle length is measured from day 1 of bleeding in one cycle to day 1 of the next cycle. Most ovulatory menstrual cycles are every 21-35 days. Women may state they have irregular cycles even if their cycles only vary by a few days, such as ranging between 28 and 31 days. Cycles in such a narrow range are likely ovulatory, and a menstrual calendar can be helpful to determine the menstrual pattern. Menses can occur in the absence of ovulation, but typically are unpredictable and differ in intercycle duration. Moliminal symptoms, such as breast tenderness and mood changes, are suggestive of ovulation.



In addition to menstrual history, other tests can help detect ovulation. Ovulation predictor kits measure urinary LH and are sold over the counter. Testing is typically started on day 9 or 10 of a cycle and performed daily to detect the LH surge leading to ovulation. Another test is a midluteal (typically day 21) progesterone level; a value greater than 3 ng/mL suggests a functional corpus luteum, indicating that ovulation occurred. Progesterone levels are typically greatest (but fluctuate markedly because of pulsatile secretion) 6 to 8 days prior to menses in an ovulatory cycle. Finally, serial transvaginal ultrasound exams can be performed if other tests are not definitive or if the patient is undergoing treatment. Collapse of a developing follicle and formation of a corpus luteum cyst indicate ovulation. An additional method to detect ovulation is basal body temperature charting, where the patient charts her temperature taken first thing in the morning. A 1-degree increase in the temperature is seen following ovulation, but does not occur reliably in all ovulatory women. This test can be used to document ovulatory cycles. However, as the temperature increase occurs after ovulation, it is not useful for timing intercourse as the ovulation detection is retrospective.



There are a number of endocrine disorders that result in oligo- or anovulation and thus menstrual irregularity. These include polycystic ovary syndrome, thyroid dysfunction, hyperprolactinemia, hypothalamic dysfunction, and primary ovarian insufficiency, also known as premature ovarian failure.

	Laboratory testing for common endocrine disorders includes measurement of serum levels of thyroid stimulating hormone and prolactin. An early follicular phase FSH level may be considered in women in whom diminished ovarian reserve is likely. Measurement of estradiol is generally not needed in the initial evaluation of a young, infertile woman, but is warranted when ovarian reserve is being assessed. If PCOS is suspected, or if hirsutism is present, total testosterone should be measured to evaluate for PCOS or rule out an androgen-secreting neoplasm and 17-hydroxyprogesterone should be measured to assess for congenital adrenal hyperplasia. Women with primary amenorrhea may require additional evaluation to rule out anatomic defects, gonadal dysgenesis, and other rare causes.
	The next test for review is measurement of ovarian reserve.

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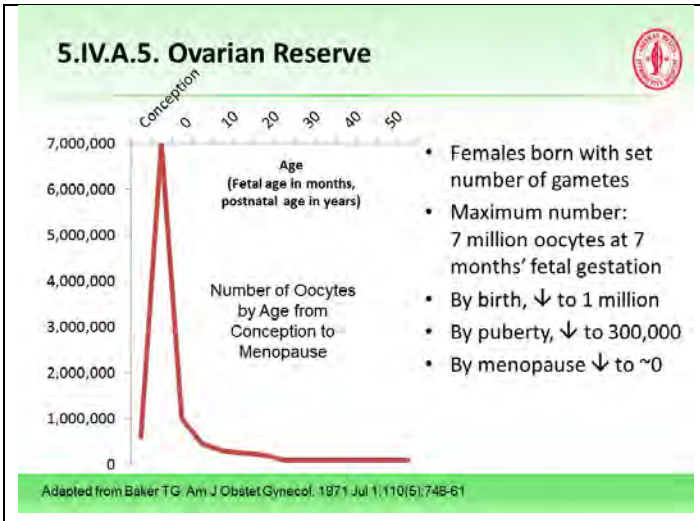
<td> 
</td>
<td>Unlike men, women are born with a set number of gametes, and fertility declines as the number of available oocytes decrease. For this reason ovarian reserve may provide important prognostic information in women who are over age 35 years; have a family history of early menopause; have a single ovary or history of previous ovarian surgery, chemotherapy, or pelvic radiation therapy; have unexplained infertility; or are planning treatment with assisted reproductive technology (ART).</td>
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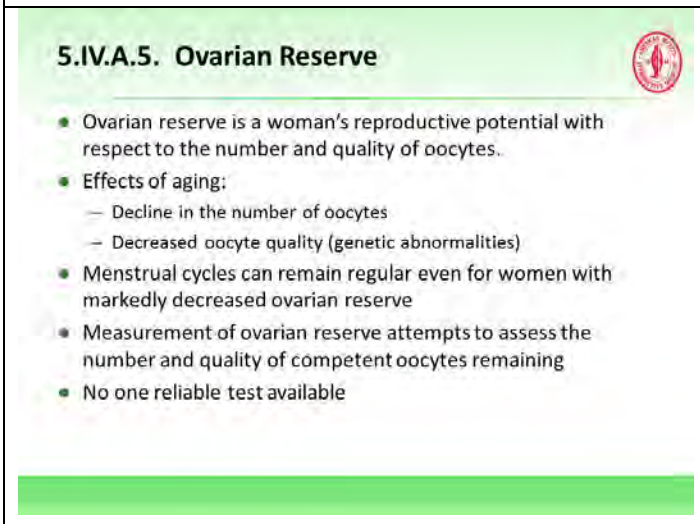
<td> 
</td>
<td>Ovarian reserve is best defined as a woman's reproductive potential with respect to number and quality of ovarian oocytes. As we have seen, aging results in a decline in the number of available oocytes. Aging also affects the quality of the remaining oocytes, and older women have a higher percentage of genetically abnormal oocytes, demonstrated by the higher incidence of aneuploidy in older women, likely due to meiotic spindle abnormalities. Menstrual cycles can remain regular in women with markedly decreased ovarian reserve. A measurement of ovarian reserve attempts to assess the number and quality of competent oocytes remaining. Unfortunately, there is no one reliable test available to accomplish this and virtually all tests assess oocyte number only.</td>
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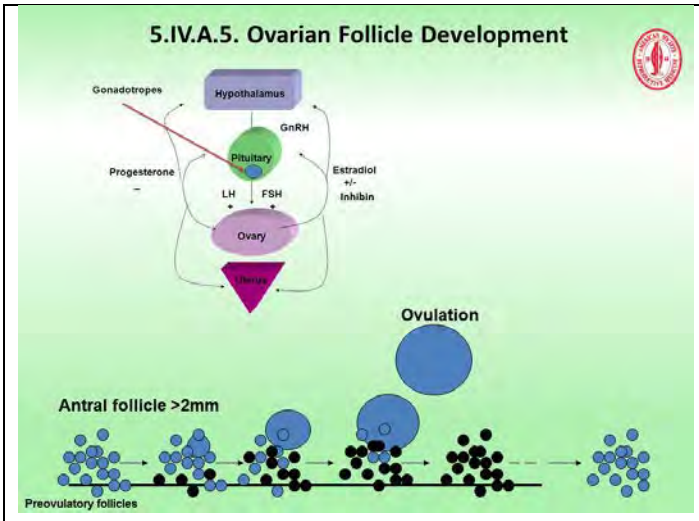
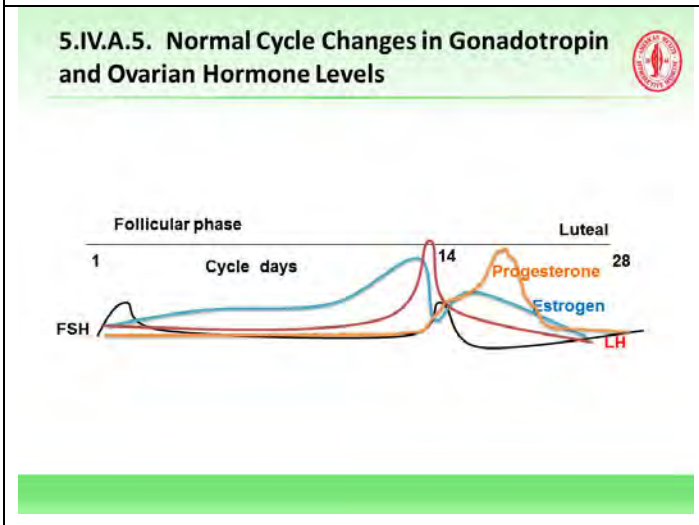
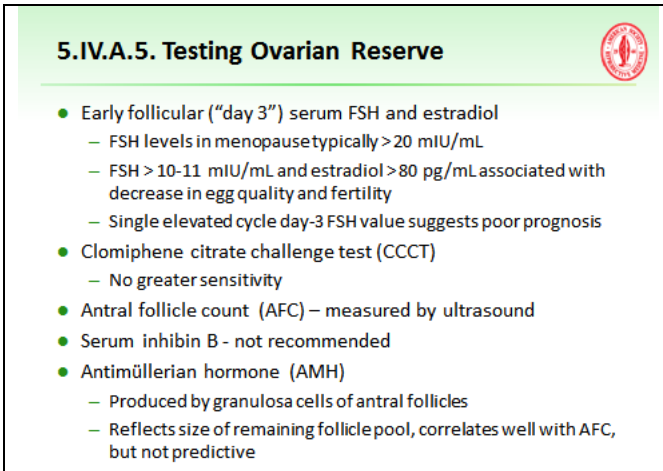


It is helpful to review the hormones involved in the development of an ovarian follicle to understand the tests used to measure ovarian reserve. Gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile fashion by the hypothalamus. GnRH stimulates the pituitary gland to release the gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH). Gonadotropins promote follicular growth, stimulating division of the granulosa and theca cells surrounding the oocyte and growth of the oocyte itself. This results in the eventual selection of a single dominant follicle from the pool of available follicles. Estradiol is a hormone produced by the developing granulosa cells and functions to develop the endometrium of the uterus. It also provides negative feedback to the pituitary to reduce gonadotropin levels. Inhibin is another hormone released by the granulosa cells that functions to provide negative feedback to the hypothalamus and pituitary to reduce gonadotropin levels. When a follicle is mature, the pituitary gland releases a surge of LH, which stimulates the final maturation and release of the oocyte from the dominant follicle.



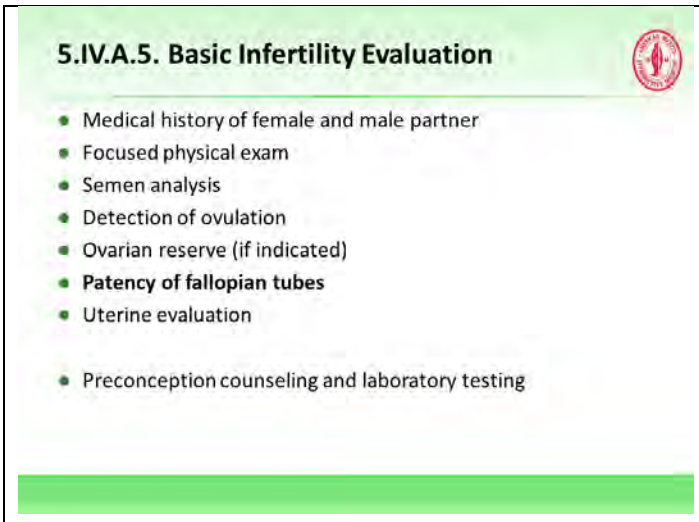
This graph shows the changes in gonadotropin levels and ovarian hormone levels over the menstrual cycle. Focusing on the follicular phase, note that FSH levels drop as estrogen levels rise due to the negative feedback of estrogen on the hypothalamus and pituitary.



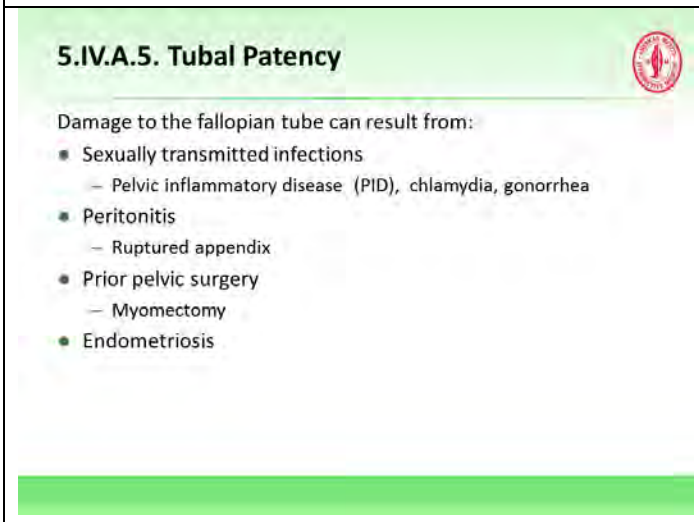
- An antral follicle count is the number of antral follicles measuring 2 to 10 mm in both ovaries seen on transvaginal ultrasound in the early follicular phase. The antral follicle count has been shown to correlate with age and can be used to predict a patient's response to gonadotropin therapy.
- Inhibin B, like estradiol, is an ovarian hormone that provides negative feedback to the hypothalamus and pituitary during folliculogenesis. It has not, however, been found to be predictive of ovarian reserve and is not recommended.
- Antimüllerian hormone (AMH) is a hormone produced by the granulosa cells of antral follicles that appears to function as a cycle-independent assessment of ovarian reserve. Like the antral follicle count, AMH reflects the size of the remaining follicle pool and these two markers of ovarian reserve are highly correlated, but are not predictive. Low AMH has also been associated with poor response to ovarian stimulation and poor pregnancy outcomes. One benefit of AMH over FSH for ovarian reserve testing is that it can be drawn on any day of the menstrual cycle.

A number of tests exist to assess ovarian reserve. None is ideal, so they are often used in combination.

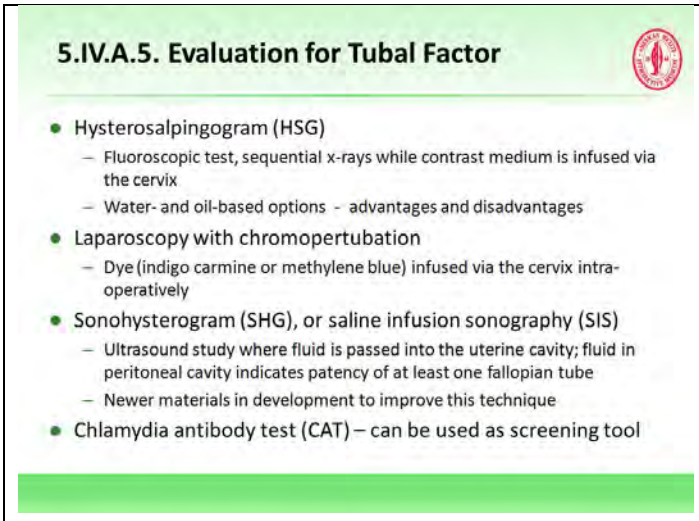
- Early follicular, or "day 3," FSH and estradiol levels together constitute one test for ovarian reserve. Alternately, FSH can be measured without estradiol as an initial assessment of ovarian reserve. FSH levels are higher when the available oocyte pool is smaller, and levels in menopause are typically >20 mIU/mL. A serum FSH obtained on cycle day 2, 3, or 4, that is greater than 10-15 mIU/mL is indicative of diminished ovarian reserve. Each laboratory must establish its own normal range. Elevated estradiol levels (greater than 80 pg/mL) in the early follicular phase also indicates early recruitment of follicles, another hallmark of diminished ovarian reserve. FSH and estradiol levels can fluctuate with each menstrual cycle, but a single elevated FSH confers a poor prognosis, even if subsequent levels are normal.
- A variation of early follicular FSH and estradiol testing is the clomiphene challenge test. This involves testing FSH and estradiol levels on cycle day 3, administering the anti-estrogen clomiphene citrate 100 mg on cycle days 5 to 9, and then repeating the FSH and estradiol levels on day 10. The test is considered abnormal if the FSH is elevated on either day 3 or day 10. As noted, an FSH level indicating diminished ovarian reserve is typically >10-15 mIU/mL, but varies among laboratories due to the variability of different FSH assays. The clomiphene challenge test has not been shown to be more sensitive than the simpler single measurement on day 2 to 4, so it is no longer routinely performed.



Next to consider in the infertility evaluation is the assessment of fallopian tube patency.



For conception to occur, the fallopian tubes must be patent and function to transport the oocyte, sperm, and the fertilized embryo. Damage to the fallopian tube can result from a number of different insults, including sexually transmitted infections such as chlamydia, gonorrhea, or pelvic inflammatory disease. Chlamydial infections are not always symptomatic, so a woman may not know she has been exposed. Other infections in the area, such as peritonitis from a ruptured appendix, can also damage the tubes. Furthermore, pelvic surgery can result in adhesions involving the fallopian tubes. Myomectomies, frequently done in women with infertility, are known to result in adhesions. Endometriosis is also commonly found in women with infertility, and can affect the function of the fallopian tubes.

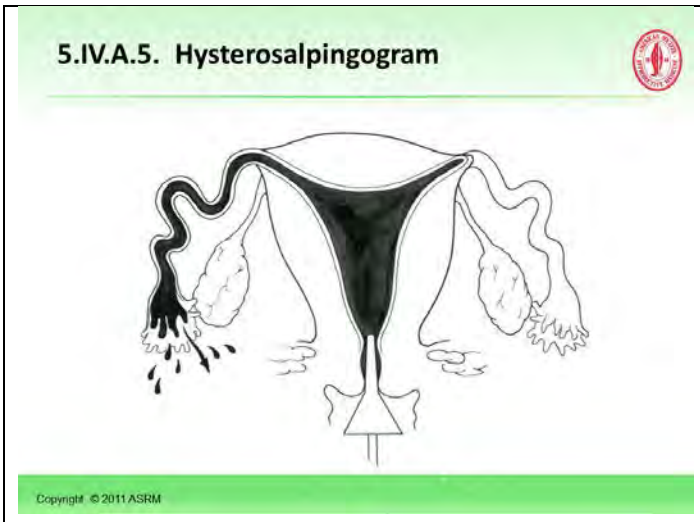


Accumulation of fluid in the peritoneal cavity indicates patency of at least one fallopian tube. The sonohysterogram is inferior to the HSG in that the tubal structure cannot be visualized; newer fluid materials containing bubbles are in development that may improve this technique.

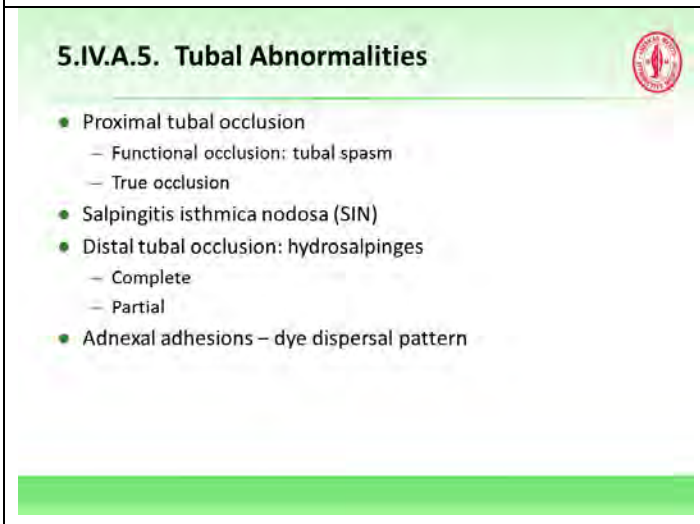
Although not commonly used in the U.S., a serum chlamydia antibody test can be used to screen for tubal disease. In women without known pelvic infection, a negative chlamydia antibody test provides evidence against an asymptomatic *Chlamydia trachomatis* infection, and an HSG can be deferred from the initial infertility work-up. If positive, further tubal assessment would be warranted.

There are a few options for evaluating the patency of the fallopian tubes. The standard test is the hysterosalpingogram, (HSG). This is a fluoroscopic test where sequential x-rays are taken while contrast medium is infused via the cervix. Water- and oil-based contrast media exist; proponents of the oil-based media argue pregnancy rates are higher with oil-based compared to water-based media. Studies comparing the two have had conflicting results. The oil-based medium is more viscous and disperses poorly, while the water-based provides better detail about tubal architecture and pelvic adhesions. There have been reports of a granulomatous response following use of the oil-based medium, as well as concern for intravasation and embolism; however these events are exceedingly rare. Both oil- and water-based media are acceptable options. To perform the HSG, the medium is infused through the cervix and fills and outlines the endometrial cavity, then fills and spills out the fallopian tubes. Women with high suspicion for salpingitis are given prophylactic antibiotics to prevent an infection from this procedure.

Other options for evaluating the fallopian tubes include chromopertubation during laparoscopy, where blue dye, either indigo carmine or methylene blue, is infused via the cervix intra-operatively and seen to pass through the tubes under direct visualization. Indigo carmine is the dye typically used, since methylene blue, in rare instances, induces methemoglobinemia, especially in individuals with glucose-6-dehydrogenase deficiency. A laparoscopy with chromopertubation is the method of choice in women already undergoing a laparoscopy for other reasons or who have a history of endometriosis. A final option is evaluation by sonohysterogram (SHG), an ultrasound study where fluid is passed through the cervix via a catheter.

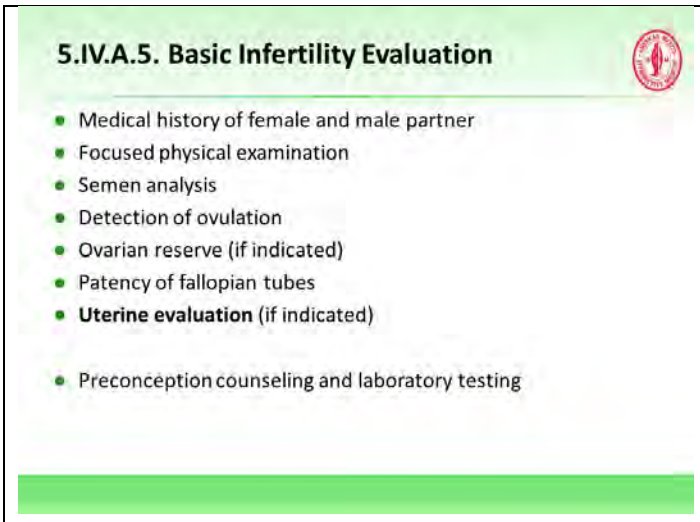


This diagram illustrates a hysterosalpingogram. As the uterine cavity fills, there is passage and free spill of dye from the patient's right fallopian tube. The left fallopian tube does not fill, indicating a proximal obstruction.

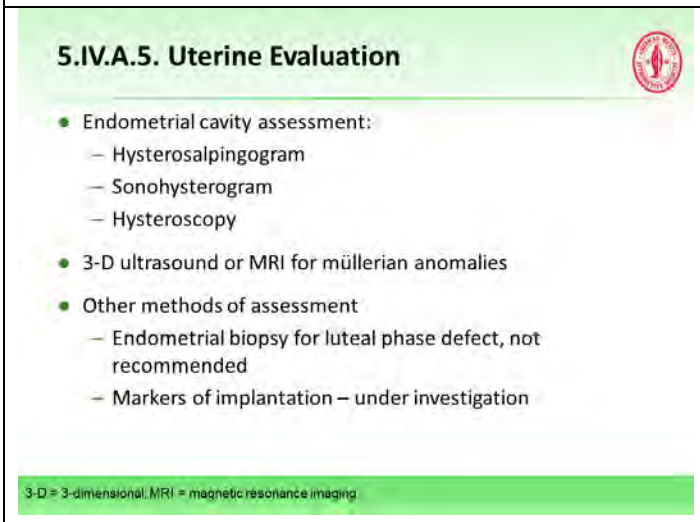


Tubal evaluation can reveal a number of different abnormalities. Occlusion can occur at the proximal or distal end of the fallopian tube. Proximal tubal occlusion can be a false-positive finding, sometimes due to muscle spasm when the dye is injected too quickly. True proximal occlusion can result from scarring from an ascending infection or a prior procedure. Salpingitis isthmica nodosa (SIN) is a finding indicating prior infection of the tubes. In SIN there are small, characteristic outpouchings of contrast along the isthmic portion of the tubes and **this** is associated with tubal infertility and ectopic pregnancy.

Distal occlusion is typically a result of ascending infection. Distal occlusion can be complete, with fimbrial fusion, resulting in a large sac-like appearance to the tube, or partial, with varying degrees of fimbrial adhesion. Delayed filling of the tube may indicate partial obstruction and is a risk factor for ectopic pregnancy. The distribution of dye on HSG once it exits the tubes can also be informative; uniform dispersion of the dye suggests no pelvic adhesions, and loculation of dye is suggestive of adhesive disease.



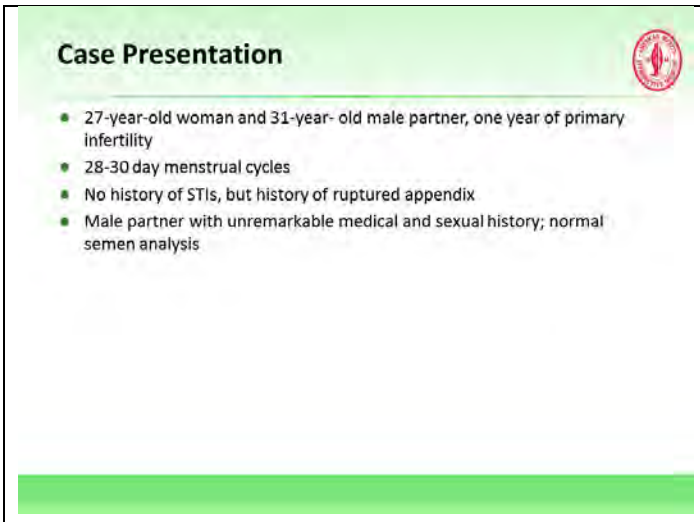
The uterine evaluation is another important part of the infertility evaluation.



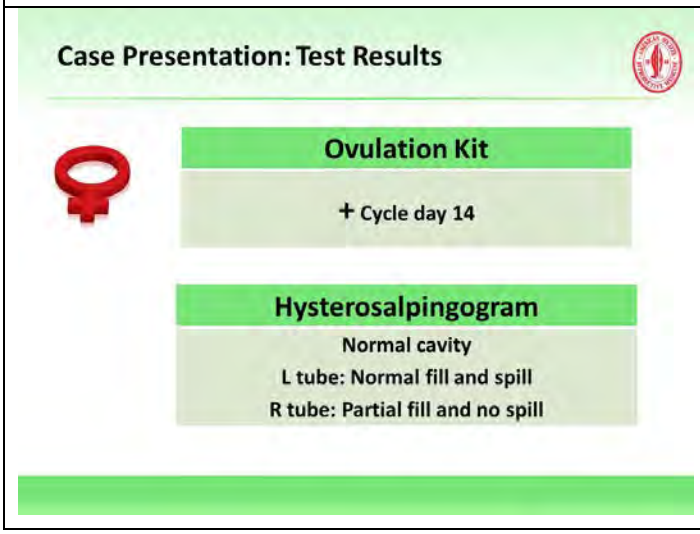
A normal uterine cavity and endometrial lining are essential for implantation of the developing embryo. A number of imaging studies can be used to evaluate the endometrial cavity. The HSG previously discussed as a means to assess tubal patency also shows the shape and contour of the endometrial cavity. A sonohysterogram is the preferred test for uterine evaluation, as this ultrasound can evaluate the endometrial cavity, check for fibroids and assess uterine contour at the same time. A hysteroscopy also provides uterine assessment, and can be performed in either an office or surgical setting.

When there is concern for a müllerian anomaly, 3-D ultrasound and magnetic resonance imaging are options for better delineation of uterine structure.

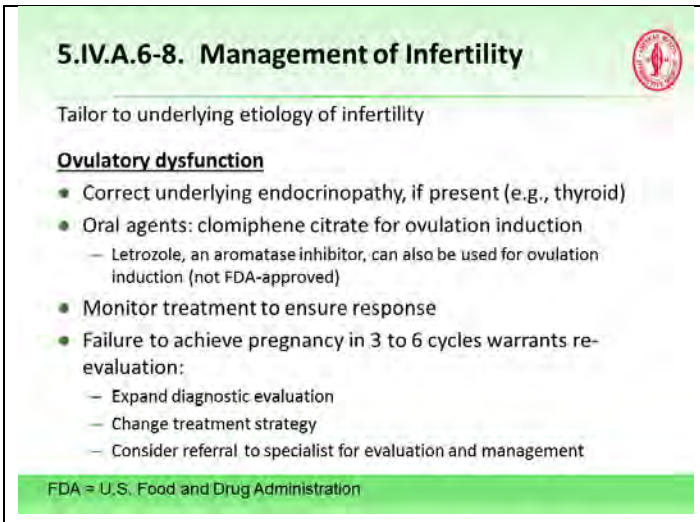
Other tests have been proposed to test the receptivity of the endometrial tissue itself. An endometrial biopsy to test for luteal-phase defect was routinely performed in the past; this test is no longer recommended. There are also endometrial markers of implantation under investigation; an endometrial biopsy to test for these is also not recommended at this time.



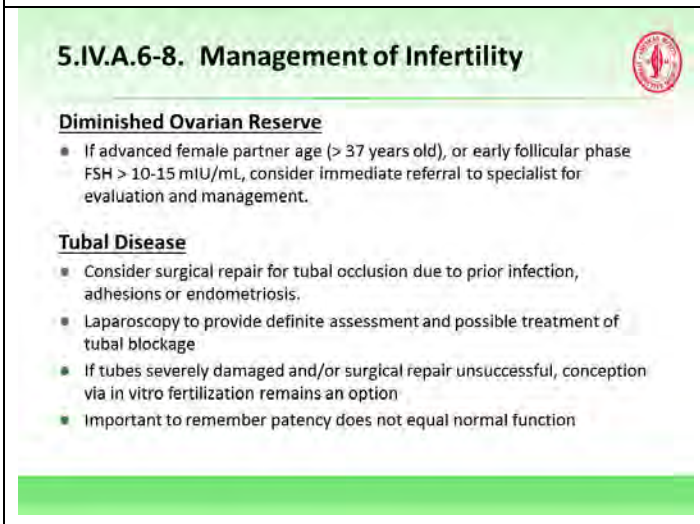
Now let's return to the case presentation. Recall that the couple is a 27-year-old woman and her 31-year-old male partner with one year of primary infertility. She has regular, 28-30 day menstrual cycles, which suggests normal ovulation. She has no known history of STIs, but does have a history of a ruptured appendix, making tubal patency a concern. Her partner has an unremarkable medical history and a normal semen analysis.



The couple returns one month later to review their test results. The patient states she was able to detect ovulation using the ovulation predictor kit and had a positive result on cycle day 14. Her HSG images are reviewed and reveal a normal uterine cavity, with normal fill and spill of the left fallopian tube, but partial fill and no spill of the right fallopian tube.

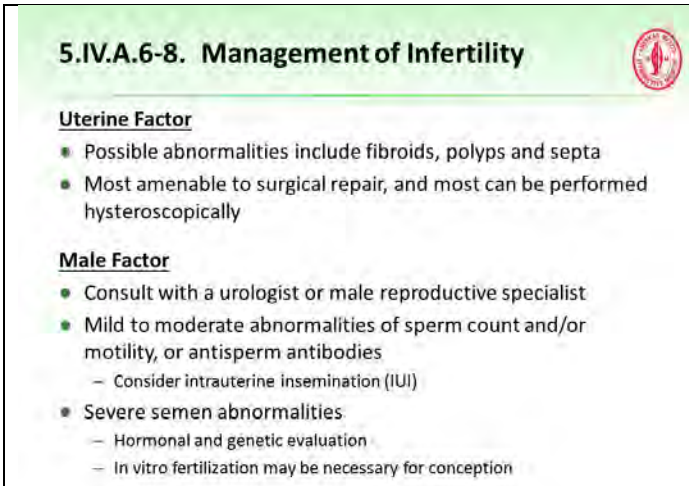


The management of each infertility case must be tailored to the underlying etiology of the infertility. For cases where ovulatory dysfunction is involved, the first step is to correct any underlying endocrinopathies, such as thyroid or prolactin abnormalities. Oral agents such as clomiphene citrate can be used for ovulation induction. Alternatively, an aromatase inhibitor can be used, with the understanding that these agents have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of infertility. This treatment should be monitored to ensure response to therapy, and failure to achieve pregnancy in 3 to 6 cycles warrants re-evaluation. At that time expanding the diagnostic evaluation, if initially limited, or changing the treatment strategy should be considered. Referral to a board-certified reproductive endocrinologist for evaluation and management should also be considered.



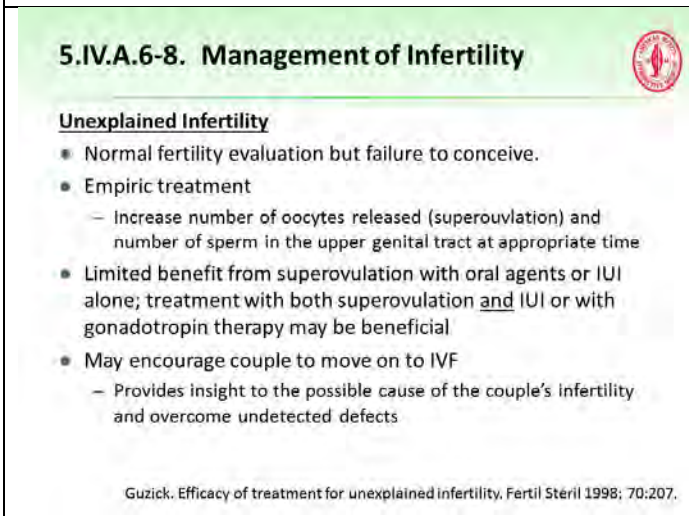
For patients with diminished ovarian reserve, there is no therapy to correct the underlying abnormality. For this reason women of advanced reproductive age (> 37 years old) and women with an early follicular phase FSH greater than 10-15 mIU/mL should be immediately referred to a specialist for evaluation and management.

For women with tubal disease, surgical repair can be considered for tubal occlusion due to prior infection, adhesions or endometriosis. In these cases, it is reasonable to proceed with laparoscopy for definitive diagnosis and possible treatment of the tubal blockage. If the tubes are severely damaged and/or surgical repair is unsuccessful, conception via in vitro fertilization remains an option. It is important to remember that tubal patency does not always equal normal function.

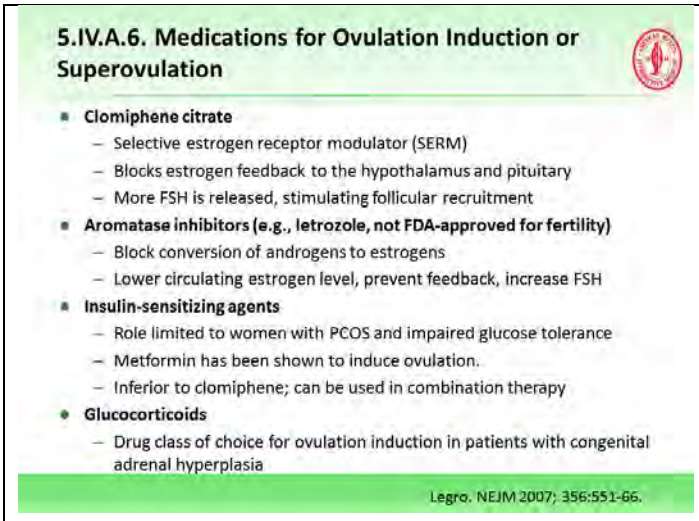


In cases where a uterine factor is involved, the abnormality is typically a submucosal fibroid, endometrial polyp, or uterine septum. These etiologies are usually amenable to surgical repair, and most can be performed hysteroscopically.

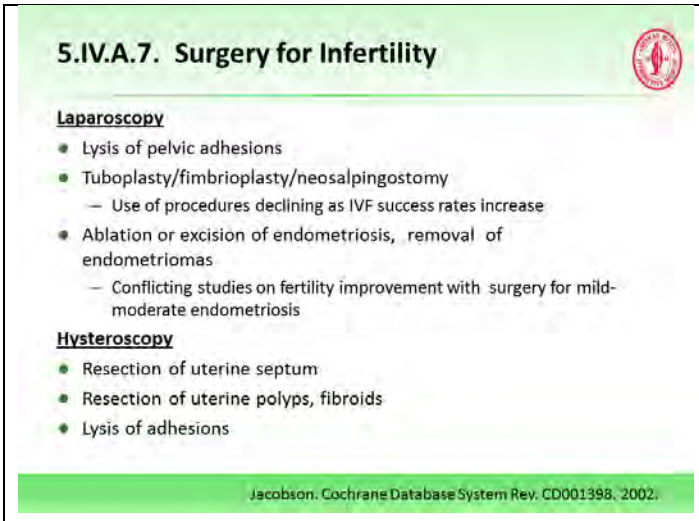
Management of male factor infertility should be performed in consultation with a urologist or male reproductive specialist. Intrauterine insemination (IUI) may be effective for men with mild to moderate abnormalities of sperm count and/or motility, and for those with antisperm antibodies. Severe semen abnormalities warrant hormonal and genetic evaluation, and in these cases in vitro fertilization may be necessary for conception.



When a couple has a normal fertility evaluation but fails to conceive, they are given the diagnosis of "unexplained" infertility. Treatment is empiric, with the goal of increasing the number of oocytes released and the number of sperm in the upper genital tract at the appropriate time. Studies have revealed limited benefit from superovulation using oral agents or intrauterine insemination alone; treatment with both or gonadotropin therapy may be beneficial. Couples with unexplained infertility may be encouraged to move on to in vitro fertilization, which can provide insight into the possible cause of the couple's infertility and overcome undetected defects.



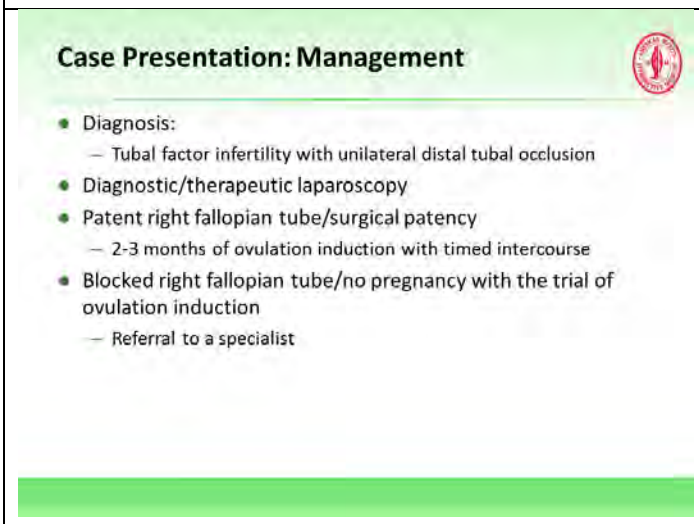
A number of medications can be used to induce ovulation in an anovulatory patient, or induce superovulation in an ovulatory patient. The two most commonly used drugs, clomiphene citrate and aromatase inhibitors, were noted in the discussion of ovulatory dysfunction. Clomiphene is a selective estrogen-receptor modulator, which works by blocking estrogen feedback to the hypothalamus and pituitary. The hypothalamus and pituitary respond by increasing FSH release, stimulating follicular recruitment. The aromatase inhibitors (such as letrozole) block the conversion of androgens to estrogens and function by reducing circulating estrogen levels. This also blocks estrogen feedback to the hypothalamic-pituitary-ovarian (HPO) axis and increases the release of FSH, providing additional stimulation for follicular development. As mentioned previously, the use of aromatase inhibitors for fertility treatment is not FDA-approved. The insulin-sensitizing agent metformin may also have a role in ovulation induction; for women with PCOS and impaired glucose tolerance, use of an insulin-sensitizing agent has been shown to stimulate ovulation. A head-to-head study of clomiphene and metformin demonstrated that metformin was inferior to clomiphene for inducing ovulation and conception; however, it may provide some benefit when used in combination with clomiphene. A final class of drugs used for ovulation induction is the glucocorticoids. Use of these medications for ovulation induction is limited to patients with congenital adrenal hyperplasia, an androgen excess disorder than can mimic PCOS. Treatment with glucocorticoids corrects the deficiency, normalizes androgen levels and often results in resumption of ovulation.



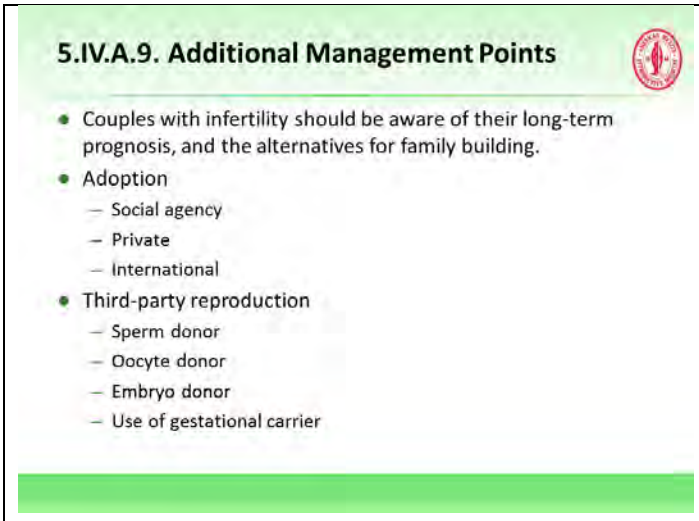
There are occasions when surgical intervention is indicated in infertility management. When a hysterosalpingogram indicates tubal blockage or dilation, or a patient's history is highly suspicious for pelvic adhesions, laparoscopy with lysis of adhesions and chromopertubation is appropriate to address the tubal factor. Surgery on the tube itself, such as re-opening an agglutinated end (neosalpingostomy) has been performed with varying success; best post-procedure pregnancy rates approach 50%, and success depends on the degree of tubal damage. In the era of continually improving IVF success rates, the use of surgery to correct tubal factor has decreased.

If a patient has symptoms suggesting endometriosis or an endometrioma is seen on ultrasound, laparoscopy to ablate or excise any endometriotic implants and remove the endometriotic cysts can be considered. Studies have shown conflicting results on whether surgery for mild or moderate endometriosis improves fertility.

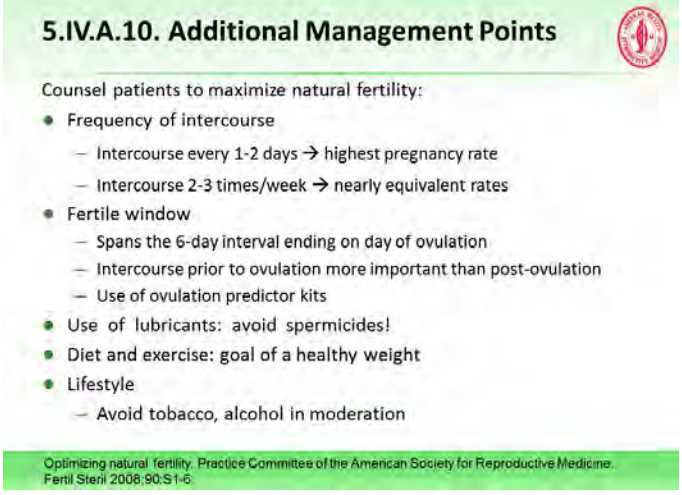
With respect to the uterus, recall that hysteroscopy can be used to enter the uterine cavity via the cervix to resect a septum, polyps or fibroids. The hysteroscope can also be used to lyse adhesions from prior uterine procedures.



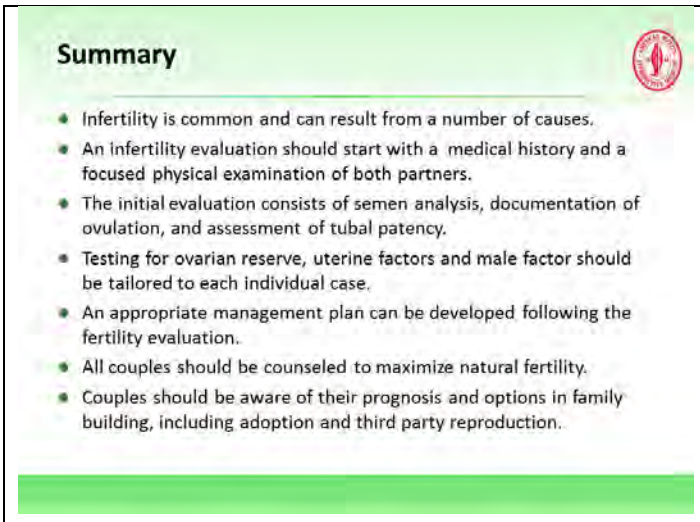
For this patient, diagnostic, and possibly therapeutic, laparoscopy is a reasonable approach to address the abnormal HSG finding. If her right fallopian tube is found to be patent, or can be made patent by the surgery, two to three months of ovulation induction with timed intercourse would be reasonable. If the right fallopian tube is blocked, or if pregnancy does not occur with the trial of ovulation induction, referral to a specialist should be considered for more intensive therapy.



Couples with infertility should be aware of their long-term prognosis and of the alternatives for family building. Couples considering adoption have a few options, including social agency adoptions, private adoptions, and international adoptions. For some couples, the use of donor gametes (sperm or oocytes) or donor embryos may be an appropriate option. Similarly, for women with uterine disease or medical problems prohibiting them from carrying a pregnancy, use of a gestational carrier may be considered. Complete infertility care should include resources for these third-party reproduction options.



It is important to counsel patients trying to conceive to maximize natural fertility. This includes reviewing their sexual practices and informing them that intercourse frequency of every 1-2 days provides the highest pregnancy rates, although intercourse 2 to 3 times per week provides nearly equivalent rates. So that couples can best time intercourse, the fertile window should be explained; this spans the 6-day interval ending on the day of ovulation. For this reason, intercourse prior to ovulation is more important than post-ovulation. Couples using an ovulation predictor kit sometimes withhold intercourse until they have a positive result, which can actually harm their chances of conceiving. An additional point to review is the selective use of lubricants and avoidance of those with spermicides. Finally, an important part of maximizing natural fertility is living a healthy lifestyle. Obesity has been shown to impair fertility, so efforts should be made to maintain a healthy weight. Tobacco use is also known to decrease fertility. Alcohol should only be consumed in moderation, and women should avoid it completely in the luteal phase when pregnancy may have occurred.

	Infertility is common and can result from a number of causes. An infertility evaluation should start with a medical history and a focused physical examination of both partners. The initial evaluation consists of semen analysis, documentation of ovulation, and assessment of tubal patency. Testing for ovarian reserve, uterine factors and male factor should be tailored to each individual case. An appropriate management plan can be developed following the fertility evaluation. All couples should be counseled to maximize natural fertility. Couples should be aware of their prognosis, and of family building options including adoption and third-party reproduction.
	Thank you for participating in this educational activity.

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