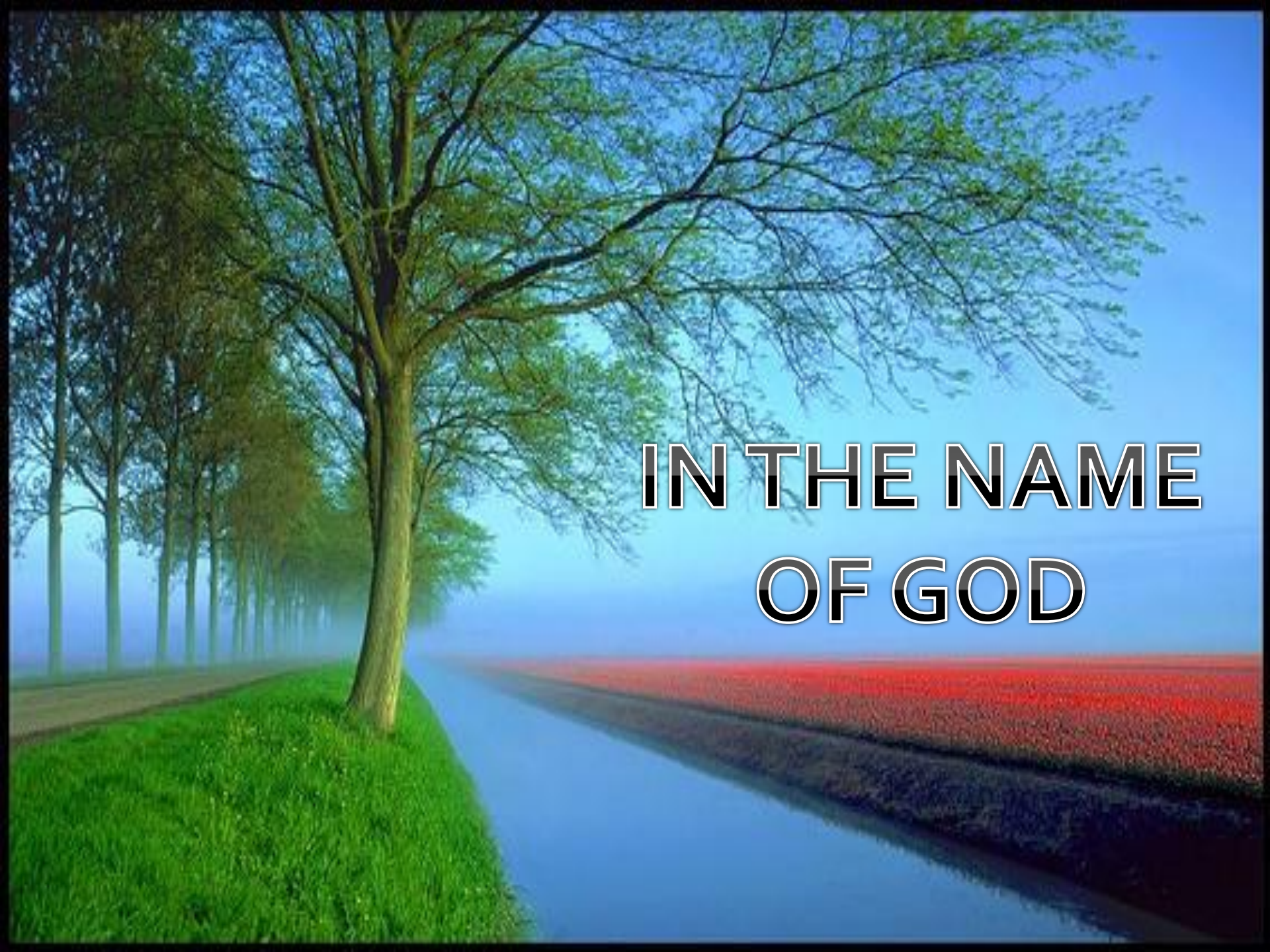
IN THE NAME
OF GOD

Evaluation of female infertility

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INTRODUCTION

- in women under age 35 years
- in women age 35 years and older.
- in women with irregular menstrual cycles or known risk factors for infertility, such as endometriosis, a history of PID, or reproductive tract malformations.

Infertility evaluation: History

Duration of infertility
Obstetric history
Gyn history
Menstrual history
Changes in hair growth, body weight, or breast discharge
Other medical and surgical history
Medications
History of chemotherapy or radiation
Cigarette smoking, alcohol, drug use; environmental and occupational exposures
Exercise and dietary history, age, occupation
Sexual history
Previous infertility testing and therapies
Family history
Pelvic or abdominal pain, symptoms of thyroid disease

Physical examination

- BMI and fat distribution
- In the setting of primary amenorrhea, incomplete development of secondary sexual characteristics .
- A body habitus that is short and stocky, with a squarely shaped chest, suggests Turner syndrome in patients with absent periods.

Physical examination

- Abnormalities of the thyroid gland, galactorrhea, or signs of androgen excess suggest the presence of an endocrinopathy

- Tenderness or masses in the adnexae or posterior cul-de-sac are consistent with chronic PID or endometriosis. Palpable tender nodules in the posterior cul-de-sac, uterosacral ligaments, or rectovaginal septum are additional signs of endometriosis.

Physical examination

- Vaginal/cervical structural abnormalities or discharge suggest the presence of a müllerian anomaly, infection, or cervical factor.

- Uterine enlargement, irregularity, or lack of mobility are signs of a uterine anomaly, leiomyoma, endometriosis, or pelvic adhesive disease.

Diagnostic tests

- Semen analysiS
- Documentation of normal ovulatory function.
- A test to rule out tubal occlusion and assess the uterine cavity.
- A test or tests of ovarian reserve such as cycle day 3 FSH or estradiol, clomiphene citrate challenge test, AMH, or antral follicle count.
- Risk factors noted from the couple's history may indicate the need for additional testing after the initial infertility evaluation.
- Preconceptional laboratory screening .
- Genetic screening

Semen analysis

- The semen analysis is the cornerstone of the assessment of the male partner of an infertile couple.

1- It should be collected after two to seven days of abstinence
2-It should be submitted to the laboratory within one hour of collection .

- It is difficult to predict the likelihood of pregnancy based upon the results of semen analysis alone, as there is extensive overlap between the semen parameters of fertile and infertile men.
- If the semen analysis is abnormal:

1- the clinician should review details of specimen collection and transport with the patient
2- repeat the test due to the marked inherent variability of semen analyses
3- consider referral to a urologist or other specialist in male reproduction

Assessment of ovulatory function

- Regular menses with molimina symptoms .
- mid-luteal phase serum progesterone level, A progesterone level >3 ng/mL is evidence of recent ovulation
- The urinary ovulation prediction kit. These kits detect (LH) and are highly effective for predicting the timing of the LH surge that reliably indicates ovulation. Home kits have a 5 to 10 percent false positive and false negative rate.
- Daily ultrasounds to follow the development and ultimately the disappearance of a follicle (the most accurate method of documenting ovulation) and endometrial biopsy to document secretory changes in the endometrium are too expensive or invasive for routine diagnostic assessment of ovulation.
- If the mid-luteal progesterone concentration is <3 ng/mL, the patient is evaluated for causes of anovulation. The minimal work-up includes serum prolactin, TSH, FSH, and assessment for (PCOS).

Assessment of ovarian reserve

- Diminished ovarian reserve can refer to diminished oocyte quality, oocyte quantity, or reproductive potential . There is no ideal test for assessing ovarian reserve. Therefore, coordination of tests provides the best assessment.

- We test ovarian reserve with an AMH level and a day 3 FSH and **estradiol** levels. Other tests such as the clomiphene citrate challenge test (**CCCT**) and **antral follicle count** are utilized by some specialists and in special circumstances. These tests have good specificity for predicting a poor response in IVF cycles, but have more limited value for predicting IVF outcome.

Day 3 FSH and CCCT

- The CCCT involves oral administration of 100 mg clomiphene citrate on cycle days 5 through 9 with measurement of day 3 and day 10 FSH levels and day 3 estradiol level.
- The premise of these tests is that women with good ovarian reserve have sufficient production of ovarian hormones from small follicles early in the menstrual cycle to maintain FSH at a low level. In contrast, women with a reduced pool of follicles and oocytes have insufficient production of ovarian hormones to provide normal inhibition of pituitary secretion of FSH, so FSH rises early in the cycle .
- With either test, a normal result is not useful in predicting fertility, but a highly abnormal result (we use FSH >15 milli-international units/mL) suggests that pregnancy is unlikely with treatment involving the woman's own oocytes, particularly in women of more advanced reproductive age.
- Based on these findings and the cost advantage and simplicity of the day 3 FSH, we obtain a day 3 FSH concentration and consider a value less than 10 milli-international units/mL suggestive of adequate ovarian reserve, and levels of 10 to 15 milli-international units/mL borderline. The upper threshold for a **normal FSH** concentration is **laboratory dependent**; cutoff values of **10 to 25** milli-international units/mL have been reported because of use of different FSH assay reference standards and assay methodologies.

Day 3 FSH and CCCT

- We also check a cycle day 3 estradiol level, although there are conflicting data as to whether it is predictive of ovarian reserve and the response to ovarian stimulation (as in IVF) . We consider a value <80 pg/mL suggestive of adequate ovarian reserve, but other cutoffs are also utilized. In one prospective study of women undergoing IVF, day 3 estradiol levels >80 pg/mL resulted in higher cycle cancellation rates and lower pregnancy rates, and estradiol levels >100 pg/mL were associated with a 0 percent pregnancy rate .

- Elevated basal estradiol levels are due to advanced premature follicle recruitment that occurs in women with poor ovarian reserve. **High estradiol** levels can **inhibit pituitary FSH** production and thus **mask** one of the signs of decreased ovarian reserve **in perimenopausal** women. Thus, **measurement of both FSH and estradiol** levels helps to avoid false-negative FSH testing.

Day 3 FSH and CCCT

- If CCCT is performed, we consider FSH less than 10 milli-international units/mL on both day 3 and day 10 suggestive of adequate ovarian reserve; a borderline FSH of 10 to 15 milli-international units/mL and an elevated FSH level on either day 3 or day 10 suggests decreased ovarian reserve. Estradiol can be measured on day 3, but a cycle day 10 estradiol is not part of the standard CCCT as it reflects the magnitude of the ovarian follicular response to clomiphene 100 mg daily for five days, not ovarian reserve.

- If the day 3 FSH or **CCCT is abnormal**, the patient should be **referred** to a reproductive endocrinologist to discuss further diagnostic and treatment options. These options **depend on the results of other diagnostic tests**, the patient's **age** , and other factors and may include aggressive ovulation induction, IVF, or use of donor oocytes. However, patients with markedly **diminished ovarian reserve rarely conceive without the use of donor eggs.**

Anti-müllerian hormone

- In adult women, AMH levels gradually decline as the primordial follicle pool declines with age ; **AMH is undetectable at menopause** .

- The AMH level appears to be an **early, reliable, direct indicator** of **declining ovarian function**.
- In patients **planning IVF**, AMH level correlates with the number of oocytes retrieved after stimulation and is the best biomarker for **predicting poor and excessive ovarian response** . However, its diagnostic accuracy for **predicting live birth** is poor, so it should not be used to **exclude couples** from IVF/intracytoplasmic sperm injection (ICSI) . It may also play a useful role in identifying reduced ovarian follicle pool in certain types of patients, such as women with demonstrated infertility, cancer patients, and patients who have had significant ovarian injury from radiation or surgery .
- In contrast to women with infertility, **AMH levels in women without infertility** do not correlate with **future fertility** potential or the time to pregnancy and should not be used to predict reproductive status or **onset of menopause .**

Anti-müllerian hormone

- For women with demonstrated infertility, there is no consensus on the threshold value suggestive of reduced fertility potential **. In general, a level well above the laboratory's lower threshold for normal suggests adequate ovarian reserve**. As the level falls below the lower limit of normal, the probability of diminished ovarian reserve progressively increases, with very low levels suggesting pregnancy is less likely to occur and the patient will have a poor response to IVF .
- Unlike the day 3 FSH, AMH can be measured anytime during the menstrual cycle and typically demonstrates minimal intercycle and intracycle variability since the **growth of small preantral follicles** that express it is **continuous**, not cyclical.

Anti-müllerian hormone

- One review suggested the following general guidelines :
- ●AMH <0.5 ng/mL predicts reduced ovarian reserve with less than three follicles in an IVF cycle.
- ●AMH **<1.0** ng/mL predicts baseline ovarian reserve with a likelihood of **limited eggs** at retrieval.
- ●AMH >1.0 ng/mL but <3.5 ng/mL suggests a good response to stimulation.
- ●AMH **>3.5** ng/mL predicts a vigorous response to ovarian stimulation and caution should be exercised in order to avoid ovarian **hyperstimulation syndrome**.

Assessment of fallopian tube patency

- We perform HSG as the first-line test for evaluation of tubal patency because of therapeutic, as well as diagnostic, benefits . HyCoSy is a reasonable alternative; the choice of test is determined by availability.

- When the diagnosis is in doubt, more invasive tests can be used to confirm the diagnosis and provide an opportunity for concurrent therapeutic intervention. These tests include laparoscopy with chromotubation and fluoroscopic/hysteroscopic selective tubal cannulation

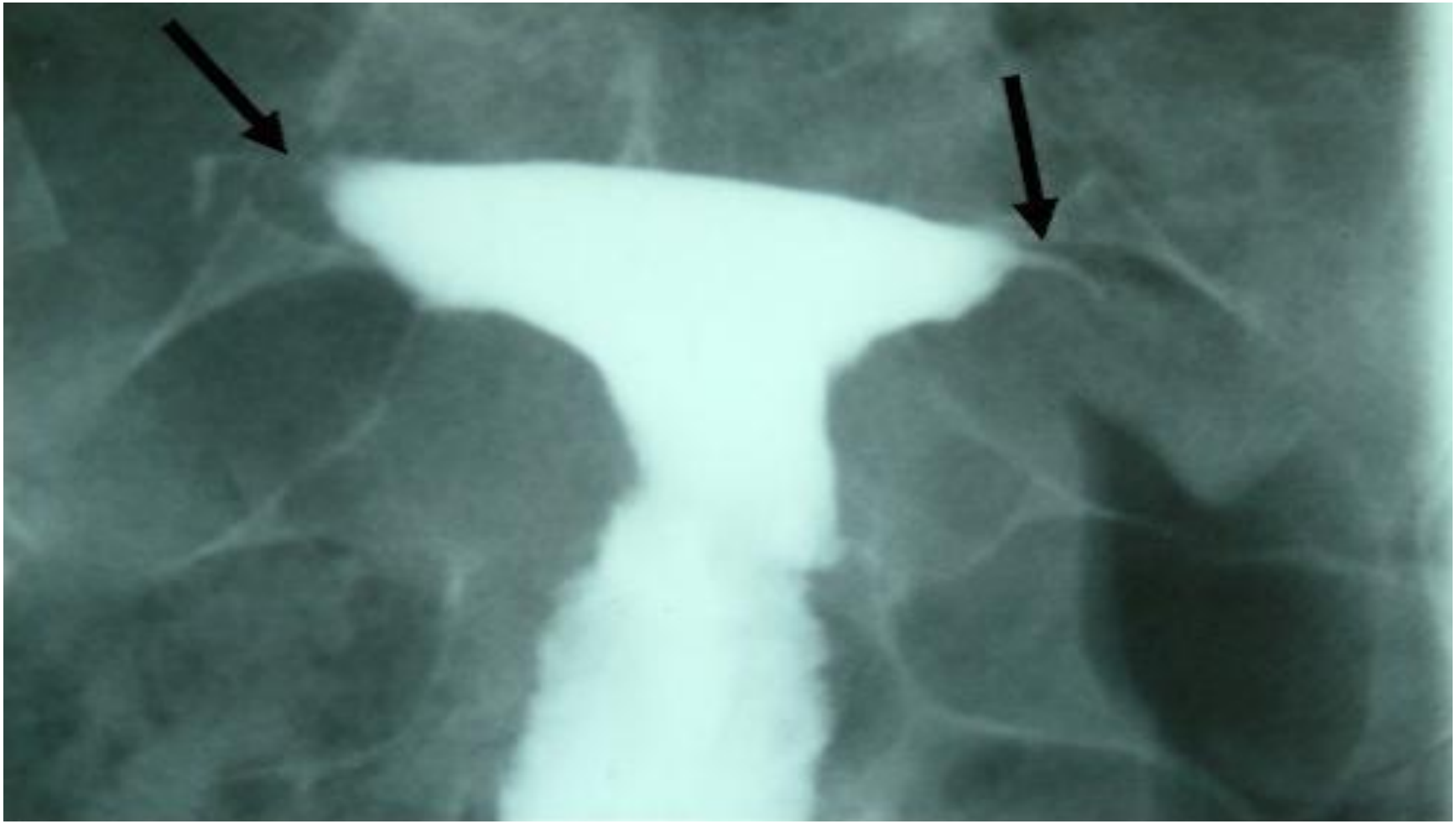
Hysterosalpingogram

- HSG is the standard of care to look for tubal occlusion in all patients , unless laparoscopy is planned .
- HSG(water- or lipid-soluble contrast)
- The uterine cavity

- Peritubal adhesions or endometriosis (laparoscopy and chromotubation)
- Distal tubal occlusion or major distal tubal adhesions
- Proximal tubal occlusion

- Therapeutic effects. pregnancy rates were similar whether oil or water soluble media were used .

Hysterosalpingogram



Hysterosalpingo-contrast sonography

- Ultrasound before and after transcervical injection of echogenic contrast media (either microbubble contrast or agitated saline).
- Safe, well tolerated, quick and easy method for obtaining information on tubal status, the uterine cavity, the ovaries, and the myometrium using conventional ultrasound.
- Tubal spasm and tubal fistula, as well as operator error could account for misdiagnoses
- atients tolerate HyCoSy better than HSG

Assessment of the uterine cavity

- Saline infusion sonohysterography, three-dimensional sonography, (HSG), and hysteroscopy.
- saline infusion sonohysterography is much better than routine ultrasonography for diagnosis of intrauterine adhesions, polyps, and congenital uterine anomalies and performs similarly to hysteroscopy at detecting intrauterine pathology .

Assessment of the uterine cavity

- HSG can also identify developmental or acquired abnormalities of the uterine cavity : submucous fibroids, a T-shaped cavity (associated with DES exposure), polyps, synechiae, and congenital müllerian anomalies.
- HSG to assess both fallopian tube patency and uterine cavity anatomy.
- Abnormalities found on HSG generally require further evaluation by other imaging modalities (three-dimensional sonography, sonohysterography, or MRI), hysteroscopy, or laparoscopy and referral to a reproductive endocrinologist

Assessment of the uterine cavity

- Hysteroscopy:(evaluation and treatment at the time of diagnosis)
- Limitations : lack of information about the myometrium, fallopian tubes, and adnexal structures.
- Hysteroscopy with laparoscopy: the endometrial cavity and pelvic structures can be evaluated simultaneously
- If the endometrial cavity is assessed by another modality, routine use of hysteroscopy may not be necessary.
- HSG or HyCoSy in infertile patients requiring assessment of tubal patency and uterine cavity evaluation. In women requiring only uterine cavity evaluation and no information on tubal status (eg, patients going directly to IVF for severe male factor), we perform either saline infusion sonohysterography or flexible hysteroscopy in the office to assess the uterine cavity.

ROLE OF LAPAROSCOPY

- The role of laparoscopy in the evaluation of infertility is controversial. invasive and expensive. do not alter the initial treatment . The clinician must decide about laparoscopy for endometriosis and other pathology as part of their workup(dysmenorrhea, pelvic pain, or deep dyspareunia; previous complicated appendicitis, pelvic infection, pelvic surgery, or EP)
- . When we perform laparoscopy, we also perform chromotubation to assess tubal patency and hysteroscopy to evaluate the uterine cavity. For this reason, if laparoscopy is planned, then HSG can be omitted .

- Normal infertility evaluation (unexplained infertility) undergo ovarian stimulation with or without IUI, and many will conceive without further intervention. No diagnostic laparoscopy prior to ovulation induction .
- Tubal or male factor infertility are offered IVF and bypass laparoscopy.

- The advantage of performing laparoscopy early in the evaluation of women suspected of having endometriosis or pelvic adhesions is that surgical therapy can be initiated, while avoiding potentially ineffective or unnecessary empiric medical treatment such as ovulation induction. Endometriosis, if identified, can be excised/ablated at the time of the diagnostic procedure, and pelvic adhesions can be lysed.

TESTS OF LIMITED CLINICAL UTILITY

- Postcoital test
- Endometrial biopsy
- Basal body temperature records
- Zona-free hamster oocyte penetration test
- Mycoplasma cultures
- Testing for antibodies
- Karyotype

Postcoital test

- Not recommend postcoital testing as neither test helps guide treatment selection.

- Poor diagnostic potential , the lack of consensus on a normal versus abnormal test result , interventions designed to improve cervical factor infertility have not been effective, while widely used infertility therapies, such as IUI and IVF, bypass the cervix.The outcome of infertility investigations with and without the postcoital test no difference in pregnancy rate.
- Incorporation of the postcoital test in standard infertility evaluations increases the number of tests and treatments but has no effect on the pregnancy rate.

Endometrial biopsy

- The American Society of Reproductive Medicine highlights the lack of benefit of the endometrial biopsy in the evaluation of the infertile female and does not recommend use of this test unless endometrial pathology is strongly suspected
- Endometrial biopsy has been performed for two reasons: (1) ovulation and (2) luteal phase defect.
- It is not a good test for either indication because it is invasive, expensive, uncomfortable

- As discussed above, ovulation is optimally assessed using serum progesterone level >3 ng/mL obtained in the late luteal phase.

- As the treatment of luteal phase defect does not improve pregnancy outcome in infertile women, luteal phase evaluation by histological dating of the endometrium is not recommended

Basal body temperature records

- Basal body temperature charts are the least expensive method for detecting ovulation, although interpretation of the charts can be difficult. We prefer serum or urine testing for assessment of ovulatory status in women with irregular cycles.

- Progesterone released from the corpus luteum at the time of ovulation has potent effects on the hypothalamus, one of which is to increase body temperature. (0.5ºF rise)
- In a normal cycle, the temperature rise begins one or two days after the LH surge and persists for at least 10 days. Thus, it occur too late to be useful for timing intercourse

Zona-free hamster oocyte penetration test

- This test is also known as the sperm penetration assay.
- predicts human oocyte fertilization .
- The experience of the laboratory performing the assay.
- The results would not influence our clinical management.

Mycoplasma cultures

- Do not suggest obtaining routine
- There is minimal evidence for a role of these organisms in female infertility

Testing for antibodies

- Routine testing for antiphospholipid, antisperm, antinuclear, and antithyroid antibodies is not supported by existing data .
- An association between antiphospholipid antibodies and recurrent pregnancy loss has been established.

Karyotype

- karyotype the male partner if there is severe oligospermia, as these men are at higher risk of karyotypic abnormalities.
- Separate testing for Y chromosome microdeletions may also be offered.
- karyotype women with premature ovarian insufficiency or a family history of early ovarian insufficiency (prior to age 40)
- Both partners if there have been recurrent pregnancy losses.
- In most other circumstances, karyotyping is not indicated as part of the initial evaluation because of the low incidence of abnormalities in women with unexplained infertility, endometriosis, or tubal factor infertility .
- Karyotype may be useful in patients with these conditions who have failed initial treatment approaches and plan to undergo IVF, although the cost-effectiveness of universal karyotype screening prior to IVF has not been established

INFORMATION FOR PATIENTS

- Basics topics :The Basics patient education pieces are written in plain language and they answer the four or five key questions a patient might have about a given condition
- Beyond the Basics topics: Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed and are best for patients who want in-depth information and are comfortable with some medical jargon.

SUMMARY AND RECOMMENDATIONS

- We suggest that an infertility evaluation be offered to couples who have not been able to conceive after 12 months of unprotected and frequent intercourse (Grade 2C). Earlier evaluation (eg, after six months) is indicated in some couples, such as those in whom the female partner is over 35 years of age or has a history of oligo/amenorrhea, known or suspected tubal disease or endometriosis. Immediate evaluation may be undertaken in patients with a history of chemotherapy or radiation therapy, and those in whom the male partner is known to be subfertile

SUMMARY AND RECOMMENDATIONS

- The history and physical examination are directed at identifying signs and symptoms suggestive of the etiology of the infertility.

The basic infertility evaluation of all couples

- Semen analysis.
- Assessment of ovulatory status by history or laboratory testing.
- Determination of tubal patency and presence or absence of abnormalities of the uterine cavity, usually by hysterosalpingogram.
- For the evaluation of women with infertility, ovarian reserve is assessed with an anti-müllerian hormone (AMH) level, and day 3 follicle-stimulating hormone (FSH) and estradiol levels. Other tests such as the clomiphene citrate challenge test (CCCT) and antral follicle count may be utilized in special circumstances.
- Diagnostic laparoscopy may be indicated for women with suspected endometriosis or pelvic adhesions. When we perform laparoscopy, we also perform chromotubation to assess tubal patency and hysteroscopy to evaluate the uterine cavity.