

Evaluating the Infertile Patient: An Evidence-Based Review

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The field of reproductive medicine continues to evolve rapidly by offering newer diagnostic modalities and therapeutic options to improve fertility. This article will provide an overview of the current infertility evaluation, as well as the potential impact of several common gynecologic diseases.

The natural peak monthly fecundity rate is 35%, while the cumulative peak pregnancy rate after one year of trying to conceive is 85%, rising to 92% after 2 years, and 93% following 3 years.^{1,2} Infertility affects 1 in 7 couples³ and is generally accepted to be defined by the absence of a live birth following 1 to 2 years of attempting pregnancy.

The basic infertility evaluation has remained constant and focused on the most common areas of abnormality: 40% female factor, subdivided into 40% ovulation dysfunction and 40% fallopian tube blockage; 40% male factor; and 20% unexplained. Because of unpredictable insurance coverage for infertility patients, clinicians should be especially conscious of a cost-effective, evidence-based approach to the evaluation.

While diagnostic testing prior to therapy is prudent in all areas of medicine, the em-

piric use of treatment in the field of infertility has gained increasing favor, given the strong desire of patients to conceive and the financial burden placed on patients. Within one menstrual cycle, the essentials of an infertility evaluation can be efficiently achieved by performing a hysterosalpingogram between cycle days 6 through 12, testing for presumptive ovulation by urine luteinizing hormone or midluteal serum progesterone, and obtaining a comprehensive semen analysis.

Nevertheless, a surprising but sobering study identified at least one abnormal diagnostic test in 69% of fertile and 84% of infertile couples with no significant differences between the 2 groups after excluding tubal disease and endometriosis.⁴ Consequently, discretion is clearly needed prior to offering a prognosis or planned treatment for a presumed "abnormal" finding.

HISTORY

Female age, a marker of oocyte competence, represents the predominant biologic statistic influencing the monthly fecundity of a couple.⁵ Additional important factors affecting prognosis include years of infertility and a prior live birth (Table). A full medical history, including chronic medical conditions and medications, should be taken, along with a complete gynecologic history. It is critical to gain insight into ovulation function using the menstrual interval; declining ovarian reserve (DOR) by lessening duration and intensity of menstrual flow, along with vasomotor symptoms and vaginal dryness; and severity of dysmenorrhea and dyspareunia as an association with endometriosis.

Other gynecologic factors to elicit are coital frequency and timing; sexual dysfunction; use of spermicidal lubricants; complications

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TABLE. Factors Affecting Fertility Prognosis

• Female age	• Complications during prior pregnancies
• Years of infertility	• Prior gynecologic surgeries, namely tubal and myomectomy
• Prior live birth	• History of pelvic infections
• Chronic medical conditions and medications	• History of salpingitis
• Coital frequency and timing	• Prior laparotomy due to pelvic adhesions
• Sexual dysfunction	• Tobacco use, including secondhand smoke
• Use of spermicidal lubricants	

during prior pregnancies; prior gynecologic surgeries, namely tubal and myomectomy; and prior pelvic infections. The risk of tubal factor infertility increases fivefold from one episode of salpingitis and also increases with prior laparotomy, which can cause pelvic adhesions.^{6,7}

Perhaps the most devastating environmental exposure to female and, to a lesser degree, male infertility is tobacco use, including secondhand smoke.⁸

The couple's prior medical records of diagnostic tests should be reviewed to prevent unnecessary redundancy and delay.

PHYSICAL EXAMINATION

All patients should undergo a complete physical exam with attention to body mass index (BMI) and evidence of hirsutism. Other areas of importance are endocrinologic abnormalities including galactorrhea, weight changes, acne, and frontal balding. The extremes of body weight have always posed reproductive challenges for women, usually by impairing ovulation function. Recently, multiple studies have demonstrated decreased fertility, increased miscarriage rates, and higher pregnancy complications in women with an elevated BMI.⁹

In reproductive medicine clinics, given the frequency of ovarian follicle monitoring, transvaginal ultrasound (TVUS) has become an extension of the traditional pelvic exam. TVUS allows assessment of the ovaries for polycystic ovary syndrome (PCOS) and masses suggestive of endometriomas, as well

as the uterus for leiomyomas. The advance of 3-D ultrasound allows a diagnosis of müllerian anomalies and possibly visualization for intrauterine pathology.

For many years, the postcoital test (PCT) was a routine part of the infertility evaluation. But a randomized trial comparing patients having a PCT versus not being tested revealed the former undergoing additional testing with no significant difference on pregnancy outcome.¹⁰ As a result, there is no compelling evidence supporting the inclusion of PCT in evaluating the infertile couple, except as a means to confirm appropriately timed coitus.

DIAGNOSTIC TESTING

Ovarian Age Testing

Arguably, the most nebulous concept for clinicians to counsel and patients to comprehend is ovarian reserve, ie, the quantity and quality of the oocyte pool. Born with a finite number of 1 million to 2 million oocytes, which is reduced by apoptosis to 300,000 to 500,000 at puberty, a woman ovulates from 300 to 500 follicles during her reproductive life span.¹¹ Pregnancy rates begin a steady decline after the female ages of 32 to 33, according to in vitro fertilization (IVF) data presented annually by the CDC. Some women experience DOR at an earlier age, varying from mild DOR to frank premature ovarian failure (POF).

For decades, early follicular phase follicle-stimulating hormone (FSH) and, more recently, estradiol, inhibin-B, and ovarian an-

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Hysterosalpingography is the gold standard screening test for fallopian tube assessment.

tral follicle count by TVUS were used to measure the oocyte pool. FSH acts through feedback inhibition from ovarian estradiol and, more profoundly, inhibin-B. However, as a means of diagnosing ovarian aging, FSH is only a valuable tool if the result is abnormal, ie, elevated. Because of unexplained monthly variations, a “normal” FSH level is a negligible contributor to an infertility evaluation, other than excluding POF—a moot point in a woman with regular menstrual cycles.

Over the past few years, antimüllerian hormone (AMH), produced by the granulosa cells of the ovary, is rapidly surpassing FSH as the more reliable and valid tool to measure DOR. Not requiring a feedback mechanism, AMH’s other distinction from FSH is the ability to be measured any day in a woman’s menstrual cycle, even while on combined oral contraceptive pills, and it is an earlier predictor of DOR.¹² Still, the holy grail of tests to predict the age of menopause remains elusive.

Genetic

In patients with recurrent pregnancy loss (a topic beyond the scope of this article), 5% of causes have been attributed to balanced translocations in one or both partners. While karyotype testing is probably not cost-effective in the basic fertility evaluation, of concern is that women who underwent IVF with intracytoplasmic sperm injection displayed higher rates of chromosomal abnormalities.¹³

Male Infertility

As in their female counterparts, men appear to have biologic testicular aging with possible negative consequences on fertility. The male infertility literature is increasingly exploring the reproductive associations of advancing paternal age (>40) to include declining semen parameters, higher pregnancy complications (miscarriage, preeclampsia, and preterm births), and increases in poor outcome of offspring.¹⁴ Historical risk factors for infertility include cryptorchidism, unilateral orchiectomy, chemotherapy, and radiation.

If the semen analysis reveals persistent abnormalities, the man’s external genitalia should also be examined, along with a hormonal evaluation, to exclude serious pathology.

Despite the beneficence of intention to assist a male who complains of decreased libido/energy and is found to be hypogonadal, testosterone therapy is not recommended. This is because it has returned inconsistent results to improve fertility and may suppress gonadotropins and reduce spermatogenesis, even to azospermia.¹⁵

ANATOMICAL EVALUATION

Hysterosalpingography is the gold standard screening test for fallopian tube assessment, though other methods have been utilized: saline infusion sonogram, TVUS, and laparoscopy. Another possible screen, *Chlamydia trachomatis* immunoglobulin G serology, has been evaluated to discern high- versus low-risk patients for tubal pathology.¹⁶ Hydrosalpinges, particularly when visible by ultrasound, have been shown to decrease implantation, and many studies have supported tubal interruption or salpingectomy to improve outcome prior to IVF.^{17,18} Several case reports have demonstrated efficacy in treating hydrosalpinges by the non-FDA-approved use of hysteroscopic tubal occlusion using the Essure® device.

Endometriosis

Defined as the presence of ectopic endometrial glands and stroma outside the uterine cavity, endometriosis is prevalent in 20% to 50% of infertile women, yet it remains an enigma as to the definitive mechanism affecting reproduction. Currently, there is no consensus on a negative impact of stage I and II disease on infertility or any benefit following surgery. Adding to the confusion, surgery appears to demonstrate only a modest increase in fertility and only in stage III disease (44% pregnancy rate), with less of an effect in stage IV (16.7% pregnancy rate).¹⁹

Questions also continue on the management of asymptomatic ovarian endometriomas. Their presence reduces ovarian follicle response to gonadotropin stimulation, but their removal diminishes ovarian reserve contributed by sacrificing portions of ovarian tissue during cystectomy.^{20,21}

IVF pregnancy rates may be slightly lower in patients with endometriosis, though this is a matter of debate.²² A possible contributor to decreased implantation in endometri-

osis patients may be the aberrant expression of an important implantation protein called alpha v beta 3 integrin.²³ A simple office endometrial biopsy can assess for this protein.

Fibroids

Fairly ubiquitous in the reproductive years, with an accumulative incidence above 80% in African Americans and nearly 70% in Caucasians, leiomyomas join endometriosis in the association with pain and infertility.²⁴ Also similar to endometriosis, the management of leiomyomas is controversial. A comprehensive review of the topic concluded submucous fibroids decrease fertility and increase miscarriage, while intramural fibroids have not been definitely shown to impair fertility.²⁵ Though an intramural myoma greater than 4 cm may impair reproduction, current evidence supports myomectomy, and only with submucous location and not conclusively with intramural. Subserosal fibroids unlikely affects fertility, though all fibroids may increase obstetric complications.

Polycystic Ovary Syndrome

Despite being the most prevalent reproductive endocrinopathy, affecting 5% to 10% of all women, PCOS and its management continues to be evasive. In addition to having the reproductive health risks of abnormal uterine bleeding, anovulation, infertility, and endometrial hyperplasia, PCOS patients are at higher prevalence for the metabolic syndrome, namely abdominal obesity, dyslipidemia, hypertension, and prediabetes.

Many studies have suggested the non-FDA-approved usage of metformin will improve ovulation function in PCOS patients, along with decreasing the miscarriage rate and the development of gestational diabetes. Initial enthusiasm for metformin in infertility PCOS patients has waned as the available evidence is inconsistent regarding its beneficence, particularly in those trying to conceive and in adolescence.^{26,27} As with many medical therapies, “one size does not fit all,” and there appears to be a more selective patient population that may benefit from metformin. Letrozole, though an off-label indication, has also been used as a second-line therapy for ovulation induction.

The second ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group in 2007 concluded that clomiphene citrate is the first-line agent for ovulation induction, followed by gonadotropins or laparoscopic ovarian diathermy.²⁸ The expert panel said metformin should be limited to PCOS patients with glucose intolerance, as current evidence does not support the routine use of metformin in ovulation induction. Metformin may benefit women with prediabetes, clomiphene resistance, or prior miscarriage, and those undergoing IVF. Unfortunately, debate continues as to which infertility PCOS patients, if any, truly will gain from metformin.

CONCLUSION

It is important to provide appropriate education to assist the infertile couple in understanding the problem, evaluation, and treatment proposed. Ultimately, earlier referral to a reproductive endocrinology and infertility specialist, particularly in women older than 35 or with other high-risk factors, will alleviate patient anxiety and potentially expedite success with fertility treatment.

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