

THE CONTEMPORARY FERTILITY EVALUATION

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Infertility is a complex medical, emotional and social condition that afflicts more than four million reproductive-age couples in the United States. Successful fertility treatment includes not only achieving pregnancy, but also achieving it in the most efficient and cost effective manner possible. The frequently ignored psychological toll of repeated treatment failures must also be considered. To achieve success, it is imperative that a timely and complete evaluation of both partners be performed. As our knowledge of reproductive physiology has expanded, the fertility workup has evolved as well. In this article, the contemporary fertility workup will be discussed. Attention will also be given to organizing the evaluation to prevent unnecessary testing.

Evaluation of the male

It is natural for the attention of the gynecologist and family practitioner to initially turn toward the female in cases of infertility. Although infertility is generally viewed a 'female problem', fully 45% of infertile couples have male factor as a contributing cause. It makes sense then to begin the fertility evaluation with a basic evaluation of the male partner. Because significant male factor is generally treated with in vitro fertilization, needless hysterosalpingograms, laparoscopies and clomiphene cycles can be avoided by early detection of significant dysfunction in the male partner. The savings of time and money can be tremendous. In vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI) has made it possible to successfully treat virtually all cases of male factor infertility, even with only a few moving sperm in the entire ejaculate.

The evaluation of the male partner starts with a competent semen analysis. Non-specialized laboratories, such as LabCorp and Unilab, perform a World Health Organization (WHO) semen analysis. This is a crude screening test and should be replaced by the strict semen analysis (Kruger) that is done by most fertility centers. The difference between the WHO and the Kruger test is that, with the Kruger test, sperm morphology is evaluated in a very stringent manner. The results of the Kruger test predict fertilization rates in vitro and presumably in vivo as well. The WHO does not predict outcome and will frequently miss subtle but clinically significant sperm abnormalities. The cost of the Kruger test is the same or less than a WHO analysis at our center.

When the male has abnormal semen parameters, the couple should be referred to a reproductive endocrinologist and/or urologist for further evaluation.

Conditions warranting referral are: a sperm concentration of less than 20 million per mL, motility less than 35%, and morphology less than 5% (Kruger) or 30% (WHO).

A direct antisperm antibody test should be done in cases where the male has a history of genital trauma, genital surgery or has never initiated a pregnancy. The

direct antibody test is done on a semen sample and detects whether antibodies are attached to the sperm themselves. The cutoff for a positive test varies between labs but is usually considered positive when greater than 10%-20% of sperm are bound. Couples with antisperm antibodies should be referred to a reproductive endocrinologist for further evaluation and treatment.

Genetic evaluation is indicated in males with a sperm concentration less than 5 million per milliliter. This evaluation should consist of a karyotype and a study to look for microdeletions on the long arm of the Y chromosome (Yq deletion study). An assay for DNA fragmentation in the sperm cells may also be helpful in select patients. If azoospermia is present, carrier status for one of the cystic fibrosis mutations should be ruled out. These men should, of course, be referred for a urological evaluation. If surgical treatment of the male is not indicated, a reproductive endocrinologist can then complete treatment.

Hormonal evaluation of the male is indicated when there is a history of sexual dysfunction, azoospermia or abnormal physical findings. This work-up, which consists of testosterone, FSH, LH and prolactin levels, should be accompanied by urological consultation.

Evaluation of the Female

The work-up of the female partner has undergone several changes over the years but the basics have remained the same. The well-orchestrated female work-up can be completed in a single menstrual cycle. At the end of this work-up, along with the male data, the clinician should be able to plot a definitive course of treatment. The work-up will be divided between female patients who are ovulatory by history and those that are not.

Ovulation is presumed if the female has had regular menses every 26-32 days for the last six months. It is important to organize the work-up to prevent unnecessary testing.

The female work-up should start with an initial intake that includes a thorough history, physical examination and a transvaginal pelvic ultrasound. Important historical details include those that might indicate previous exposure to STDs (such as a history of abnormal pap smears), recurrent pregnancy loss and the duration of infertility. Physical examination and pelvic ultrasound will identify patients that have gross pathology requiring surgical treatment prior to further fertility evaluation. For example, a dermoid cyst requiring surgery would allow the surgeon to evaluate tubal patency at the time of surgery rather than ordering an HSG.

Ovarian Reserve Testing

After the initial intake, the next step in the evaluation of the ovulatory female is the evaluation of ovarian reserve. The level of ovarian reserve and the age of

the female partner are the most important prognostic factors in the fertility work-up. Ovarian reserve is evaluated with a cycle day three FSH and estradiol level. On the third day of bleeding, a simple blood test yields a lot. An FSH level alone is never useful and should always be accompanied by an estradiol (E2) level. Normal ovarian function is indicated when the FSH is <10 mIU/mL and the estradiol is <65 pg/mL. If the FSH is >15 mIU/mL, the patient will require egg donation. If the FSH is 10-15 mIU/mL or the E2 is >65 pg/mL, the more sensitive clomiphene citrate challenge test (CCCT) should be performed to further define ovarian reserve. CCCT should also be routinely performed in all women aged 38 years and up regardless of how the cycle day 3 levels look. This will identify patients with incipient ovarian dysfunction. CCCT should also be considered in women of any age with otherwise unexplained infertility as approximately 30% will show abnormalities that adversely impact their prognosis with fertility treatment. A CCCT is performed as follows: After drawing a cycle day 3 FSH/E2, the patient begins taking 100 mg of clomiphene per day on cycle days 5 through 9. On cycle day 10, the FSH only is repeated. The patient's prognosis is only as good as her worst FSH level. A level less than 10 mIU/mL is normal. A level from 10-12.5 mIU/mL predicts resistance to fertility medications and a diminished prognosis. At 12.5-15 mIU/mL, the prognosis is poor but pregnancies do occur with aggressive treatment. Levels greater than 15 mIU/mL indicate that fertility treatment with the patient's own eggs is not likely to succeed and that egg donation should be offered. Patients with any FSH level greater than 10 mIU/mL should be referred to a reproductive endocrinologist for further evaluation.

Tubal Patency

The next step in the ovulatory patient is to confirm tubal patency. This has been done traditionally with the hysterosalpingogram (HSG) and nothing has really improved on this. This test should be done in the follicular phase of the cycle after bleeding has stopped and before possible ovulation. The ordering physician should personally review the films to confirm findings of the study. Loculation of spill and tubal phimosis indicate that laparoscopy may be helpful. If large hydrosalpinges are identified, they should be clipped or removed laparoscopically prior to in vitro fertilization. Several large studies as well as a recent meta-analysis, have confirmed the pregnancy rates with IVF are reduced by half in the presence of hydrosalpinges and that the rates are normalized with salpingectomy. The exact etiology of the phenomenon is not known.

Confirmation of Ovulation

Confirmation of ovulation is unlikely to be helpful in women when a careful history is consistent with ovulation. If there is doubt, a cycle day 21 progesterone with a level greater than 4 ng/mL is indicative of ovulation with most conceptions cycles having levels greater than 10 ng/mL. Alternately, sonographic confirmation of follicle rupture with serial ultrasound can be performed.

Anovulatory Patients

The apparently oligomenorrheic patient should have the cause of their anovulation evaluated thoroughly prior to the initiation of treatment. The initial physical examination should note the presence or absence of goiter, acanthosis nigricans, striae, normal secondary sexual characteristics, Turner's stigmata, galactorrhea, hirsutism and abnormalities of the reproductive tract. Ultrasound should note the thickness of the endometrial lining as well as whether the ovaries are polycystic in nature. An endometrial biopsy should be considered if the uterine lining measures greater than 15mm.

Endocrine Evaluation

In anovulatory patients, the initial laboratory evaluation should include random levels of FSH, LH, prolactin, TSH, DHEAS and testosterone. Insulin resistance should be considered in patients that have any of the following: obesity, hirsutism or acanthosis nigricans on physical exam; polycystic ovaries on ultrasound; inverted FSH/LH ratio or androgen excess on laboratory examination. Evaluation for insulin resistance can be accomplished simply with a 2 hour glucose tolerance test with insulin levels. A glucose to insulin ratio of >4.5 being normal. Routine testing of patients that don't meet these criteria is not useful. Patients with abnormal insulin to glucose ratio should be referred to a reproductive endocrinologist for further evaluation.

Summary:

In summary, the contemporary fertility evaluation should be both thorough and rapidly accomplished. All aspects of both the female and male reproductive systems should be considered. The work-up should be completed within a single menstrual cycle if at all possible. Referrals to sub-specialists should be made when appropriate. Some referral guidelines are listed below:

Factors Warranting Referral to REI Subspecialist

1. Female age greater than 37 years
2. Tubal occlusion
3. Abnormal semen parameters
4. Insulin resistance
5. Abnormal ovarian reserve testing
6. Clomid failure
7. Infertility for greater than 3 years

Factors Warranting Referral to a Urologist

1. Male sexual dysfunction
2. Abnormal male physical findings

3. Azoospermia