INFERTILITY

A Guide to Evaluation, Treatment, and Counseling®
The goal of this guide is to provide physicians with clear clinical pathways to identify and treat infertility. The recommendations presented in this guide are designed to provide women with optimal and personalized care. They are based on a comprehensive review of recent medical literature and reflect the expertise of leading clinicians at Brigham and Women’s Hospital.

This guide is not intended to convey rigid standards, but instead, provide the primary care physician an algorithm for thinking through the identification and management of infertility problems. Treatment should be tailored to the needs of the individual woman.

The Women’s Health Guidelines are now available on Partner’s Handbook (Partners Applications/Clinical References/Partner’s Handbook/Guidelines). Please consult Partners Handbook for revisions and updates of this and other Women’s Health Guidelines.
Epidemiology and Causes of Infertility

Infertility is a unique medical condition, in that it is a disorder that often involves a couple, not an individual. An infertile couple is one that has been unable to conceive a pregnancy in one year of unprotected intercourse. Of couples without fertility problems (who ultimately conceive), about 20 percent will conceive per cycle, 50 percent will have conceived after three cycles, 75 percent will have conceived by six cycles, and 85-90 percent will conceive after 12 months. About 10-13 percent of couples are infertile. As women delay childbearing, the rate of infertility is increasing.

Timely referrals to infertility specialists (reproductive endocrinologists with specialized training in assisted reproductive technology) are critical to successful outcomes. Unfortunately, referral to infertility specialists is delayed for many women, either because of lack of awareness on the part of the couple, or because the patient’s physician (either primary care physician or gynecologist) does not refer in a timely fashion. An infertility evaluation should be initiated for:

Women < 35 years old—begin evaluation after 12 months
Women 35-40 years old—offer evaluation after six months
Women > 40 years old—begin evaluation immediately

Causes of infertility include:

- Male factor 25-40 %
- Ovulatory defect 20-30 %
- Tubal defect 20-30 %
- Unexplained 10-20 %
- Endometriosis 5-10 %
- Other 4 %

Table 1. Effects of Maternal Age on Pregnancy Rates

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Conceiving in 12 Months</th>
</tr>
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<tbody>
<tr>
<td>20-24</td>
<td>86 percent</td>
</tr>
<tr>
<td>25-29</td>
<td>78 percent</td>
</tr>
<tr>
<td>30-34</td>
<td>63 percent</td>
</tr>
<tr>
<td>35-39</td>
<td>52 percent</td>
</tr>
</tbody>
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Evaluation of the Infertile Couple

The goal of the initial evaluation of the couple is to determine the likely cause of the infertility, and to determine the most logical approach to treatment. The primary care physician or general gynecologist can play a critical role by taking a detailed history and ordering the initial testing so that the first appointment with an infertility specialist can be spent on planning appropriate additional testing and discussing therapeutic options.

**History**

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infertility</td>
<td>Duration of infertility</td>
</tr>
<tr>
<td>Fertility in other relationships</td>
<td>Prior pregnancies, fertility in other relationships</td>
</tr>
<tr>
<td>Medical, surgical history</td>
<td>Gynecologic history (PID; endometriosis; fibroids; cervical dysplasia; IUD use; DES exposure; previous pelvic or abdominal surgery)</td>
</tr>
<tr>
<td>Medications</td>
<td>Medications, including prior contraceptive use (oral contraceptives, IUDs)</td>
</tr>
<tr>
<td>Alcohol, marijuana use, cigarette smoking</td>
<td>Menstrual history (age at menarche, cycle length and regularity); presence of hot flashes</td>
</tr>
<tr>
<td>Environmental exposure (heat [e.g., saunas, hot tubs], chemical, radiation exposures)</td>
<td>Diethylstilbestrol exposure, cigarette smoking</td>
</tr>
<tr>
<td>Sexual dysfunction/frequency of intercourse</td>
<td>Frequency of intercourse</td>
</tr>
<tr>
<td>Previous infertility testing and/or therapies</td>
<td>Previous infertility testing and/or therapies</td>
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</tbody>
</table>

Tests to order prior to the initial visit with the infertility specialist

**Male Partner**

- **Semen analysis:** The male partner should provide a semen sample for semen analysis. In general, most laboratories have a private facility where the male partner can produce the sample. He should abstain from ejaculation for 48 hours but no more than six days prior to providing the sample. Alternatively, he may bring in the specimen from home in a sterile plastic container, but the sample cannot be more than 1.5 hours old, should not have been exposed to soaps, lubricants, or condoms, and must be kept warm (held against the body) until delivery.

Results are expressed in volume (ml), concentration of sperm per ml, percent motile, and percent normal forms. To obtain the total number of motile sperm, multiply volume (ml) x concentration (sperm/ml) x percent motile sperm x percent normal forms. Greater than 10 million total motile sperm is considered adequate.

**Female Partner**

- **Document ovulation:** May be done with over the counter ovulation kits. In a 28 day cycle, ovulation usually occurs at day 14. May be later in women with longer cycles (usually 14 days from the end of the cycle). Alternatively, serum progesterone level can be measured in the second half of the cycle (day 20-22 in a 28 day cycle). If a progesterone level is greater than 3 ng/mL, ovulation has occurred.

- **Day three FSH level:** Levels greater than 10 mIU/mL are associated with an extremely low pregnancy rate. The majority of fertile women have day three FSH levels that are greater than 10mIU/mL.

- **TSH level to test for occult thyroid disorder.**
Additional testing that may be ordered by the fertility specialist

- Clomiphene citrate challenge test (CCCT): This is a more sensitive test for ovarian reserve than day three FSH alone. Clomiphene citrate (100 mg po days five to nine of the cycle) is given. Day three and day 10 FSH levels are measured. An abnormal test is an elevated level of FSH (>15) on either day three or day 10. This test should be done on all couples with unexplained infertility, and all women over age 35. The likelihood of having an abnormal CCCT increases with advancing maternal age.

- Hysterosalpingogram (HSG, or tubogram): This test is done in the first half of the cycle, immediately after menses have ended, but before ovulation. Antibiotic prophylaxis with doxycycline 100 mg po bid for three days is routinely given starting the day before the test. The test involves injection of dye into the cervix followed by radiography to assess tubal patency (“fill and spill”) as well as shape of the intrauterine cavity. The test may be uncomfortable for the patient, and premedication with ibuprofen or Tylenol® is advisable. Occasionally, the flushing of the tubes is enough to remove debris and allow a pregnancy to occur in that cycle. Sonohysterogram, an alternative that is sometimes used, gives an adequate picture of the uterine cavity, but no information about tubal anatomy; fluid collecting intraperitoneally is presumptive evidence that at least one Fallopian tube is open.

- Laparoscopy: May be indicated if endometriosis or adhesions are suspected.

- Hysteroscopy: May be done if intra-uterine lesions (adhesions, polyps) are suspected, or if intrauterine abnormalities are noted on the HSG.

- Pelvic ultrasound: May be ordered if enlarged uterine size or ovarian masses are noted on exam.

### Treatment Options

#### Intrauterine Insemination (IUI)

**Indications:**
- mild male factor
- minimal endometriosis
- unexplained infertility

Success rates range 2-20 percent per cycle. Male partner’s sperm is collected, concentrated, and injected into the female partner’s cervix usually on two consecutive days at the time of ovulation. Ovulation is timed using an over-the-counter ovulation kit, blood LH levels, or ultrasound. Clomiphene citrate is often taken on days five to nine increasing the success rate of this treatment. Risks of complications are minimal and rare, and include infection, mild bleeding due to cervical or endometrial trauma, and cramping.

#### Therapeutic Donor Insemination (TDI)

**Indications:**
- severe male factor (oligospermia or azoospermia)
- women without partners
- lesbian couples

TDI involves timed insemination from an anonymous or a known donor. Use of frozen semen to prevent sexually transmitted disease is recommended by the FDA and the CDC. At sperm banks, donors are tested for sexually transmitted diseases, including HIV, chlamydia, gonorrhea, syphilis, CMV, HTLV I and II, and hepatitis. Commercial sperm banks are the source of donor sperm in the majority of cases. Sperm banks provide information about physical characteristics, medical history, education, and ethnic or racial background of donors. More recently, some donors have given permission to sperm banks to disclose their identities if requested by the child at some point in the future. Since success rates for cycles with frozen sperm are slightly less than with fresh sperm, this treatment should be continued for three to six cycles before consideration of adding or changing therapy.
Ovulation Induction

Indications:
- ovulatory dysfunction, unknown cause
- polycystic ovary disease (PCOD)
- hyperprolactinemia
- hypothalamic amenorrhea
- premature ovarian failure

Ovulation induction is associated with a favorable prognosis. When ovulation induction is successful, pregnancy rate per cycle approaches that of normally ovulating women for age group. To determine whether estrogen secretion is adequate a progestin challenge test can be done. This involves giving a progestin (such as medroxyprogesterone acetate) 10 mg daily for five days (after making sure the pregnancy test is negative). If there is a withdrawal bleed within 14 days of stopping the progestin, there is adequate estrogen secretion. Absence of a withdrawal bleed indicates low estrogen secretion due to pituitary or hypothalamic dysfunction, or premature ovarian failure. An FSH test distinguishes between these two diagnostic categories (low or normal in hypothalamic-pituitary dysfunction; high in premature ovarian failure).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Clomiphene citrate (Clomid™ )</td>
<td>50 to 150 mg po qd days 5-9 of cycle</td>
<td>$5/pill, or $15-45 per cycle</td>
<td>Appropriate initial treatment for patients with unexplained infertility or PCOD. Cervical mucus can become thick on this medication, and therefore IUI is often recommended if the patient does not conceive within three cycles. Approximately a 20-25 percent pregnancy rate per cycle. If no pregnancy after three to six cycles, other causes of infertility should be investigated. Risks include ovarian hyperstimulation syndrome (1 percent) and multiple births (5-10 percent).</td>
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<tr>
<td>Gonadotropin therapy, Human menopausal gonadotropins (HMG; e.g., Pergonal™) or purified FSH (Metrodin™, Follistim™, or Gonal-F™)</td>
<td>1-2 ampules IM (administered at home by patient or partner) starting day 3 of cycle. Dose is altered depending on number of follicles and estradiol level by day 7</td>
<td>Pergonal™: $66.50/ 75 IU Follistim™: $85/75 IU Gonal-F™: $50/37.5 IU $88/75 IU $169/150 IU</td>
<td>Requires the patient to come in approximately qod starting day seven of cycle for ultrasound measurement of follicle size and estradiol levels. When the lead follicle is 18-20 mm in size and estradiol levels are 400-1500, hCG is administered IM and 12-36 hours later; timed intercourse or insemination should occur. Success rates extremely high for patients with hypothalamic amenorrhea (over 90 percent cumulative pregnancy rates over six cycles), but slightly lower rates for patients with PCOD or unexplained infertility. Not recommended for women with premature ovarian failure due to low success rates. Complications include ovarian hyperstimulation syndrome (10-20 percent) and multiple births (25 percent, with 20 percent twins, 5 percent higher order multiple births).</td>
</tr>
<tr>
<td>Dopamine agonists (Bromocriptine™ or Dostinex™)</td>
<td>Bromocriptine: 2.5-7.5 mg po qd Dostinex 0.25-1 mg po 2x/week</td>
<td>Bromocriptine™: $51-154/mo. Dostinex™: $141-$562/mo.</td>
<td>Restores menstrual cycles in 90 percent of women with hyperprolactinemia. For women with elevated prolactin but normal menstrual cycles, bromocriptine alone is less likely to be beneficial.</td>
</tr>
<tr>
<td>Metformin (Glucophage™)</td>
<td>500 mg po qd</td>
<td>$14/mo.</td>
<td>Decreases insulin resistance, and in one study, when given in conjunction with clomiphene citrate, restored ovulation in 90 percent of patients.</td>
</tr>
</tbody>
</table>
### Assisted Reproductive Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Procedure</th>
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| In Vitro Fertilization (IVF) | • tubal factor  
  • severe endometriosis  
  • unexplained infertility  
  • male factor  
  Involves controlled ovarian hyperstimulation, which is aimed at producing multiple oocytes. Once the oocytes are mature, hCG is administered and 34 to 36 hours later, they are retrieved under ultrasound guidance with the patient under light general anesthesia. The oocytes are then combined with sperm in a Petri dish to allow for fertilization. The embryos are incubated in growth medium and then transferred back into the female partner’s uterus three to five days later; |
| Cryoembryo Transfer | Indicated for patients who have undergone a cycle of IVF in which excess eggs were cryopreserved.  
In this procedure, the excess cryopreserved fertilized embryos from the previous IVF may be transferred at a later time. The advantages of this procedure are that a repeat ovarian stimulation can be avoided. In addition, this procedure allows a woman with advanced maternal age to use embryos that were fertilized with oocytes from when she was younger; |
| IVF with Donor Oocytes | • premature ovarian failure  
  • perimenopause, or menopause  
  • failed IVF due to oocyte factors (comprises 50% of cases)  
  The donor may either be anonymous or selected by the couple. A legal contract is needed between the donor and the recipient couple prior to initiation of the procedure. Insurers do not cover the payment to the donor and screening of the donor; |
| Intracyto-plasmic Sperm Injection (ICSI) | • congenital absence of the vas deferens  
  • obstructive and non-obstructive azoospermia or men with less than one million total motile sperm  
  • previous vasectomy  
  ICSI involves direct injection of a single sperm into the cytoplasm of an oocyte. Success has been reported even with immotile and immature sperm. Success rates are the same as those reported for IVF, approximately 35% per embryo transfer; |
| Gestational Carrier | • women without a uterus  
  • women with a medical condition that preclude carrying a pregnancy to term  
  • male homosexual couples  
  Involves IVF (see above) with transfer of the embryos to a gestational carrier, which is a woman with a uterus who will carry the pregnancy to term. To avoid custody lawsuits, when oocytes are needed, use of a separate oocyte donor; (i.e., an individual who is different from the gestational carrier) is recommended. This is particularly important for male homosexuals or for women who lack functional ovaries or uterus, or who have a medical contraindication to pregnancy. At Brigham and Women’s Hospital, surrogate carriers (women who are inseminated with the male partner’s sperm and who carry the pregnancy) are not used. |

### Success Rates: Brigham and Women’s Hospital 2001 Data

<table>
<thead>
<tr>
<th>Type of Cycle</th>
<th>Percentage of cycles resulting in live births</th>
<th>Age of Woman (years)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 35</td>
</tr>
<tr>
<td>IVF (40 percent of which are ICSI)</td>
<td>41.8</td>
<td>34.8</td>
</tr>
<tr>
<td>Cryoembryo transfer from non-donor eggs</td>
<td>28.0</td>
<td>31.4</td>
</tr>
<tr>
<td>Donor eggs</td>
<td>All ages combined</td>
<td>Fresh embryos</td>
</tr>
</tbody>
</table>
Risks of Complications with Assisted Reproduction

Mild ovarian hyperstimulation syndrome (OHSS), including ovarian enlargement, lower abdominal bloating, and mild weight gain, occurs at a rate of 5-20 percent. Severe OHSS requiring hospitalization occurs in one percent of patients. Bleeding, infection, damage to internal organs at egg retrieval are all rare complications (<1%). Multiple gestation rates vary between programs, and with the age of the woman. National statistics from IVF cycles performed in 2000 with nondonor eggs show that 30.7 percent of liveborns were twins, and 4.3 percent were high order multiple births.

Observational cohort studies have shown an increased prevalence of ovarian cancer in infertile populations compared to controls. However, in these cohorts, patients who received injected medications for assisted reproduction showed no increase above that of the infertile cohort.

Male Factor

Men with persistently abnormal semen analyses may be evaluated by a urologist. The most common conditions associated with male factor infertility include varicocele, testicular failure, obstruction, and undescended testes. About 90 percent of male factor infertility is felt to be idiopathic, with or without varicoceles. Varicoceles are present in about 15 percent of normal men and in about 40 percent of men with male factor infertility. Some studies have shown increases in sperm counts and motility following surgical repair of varicocele, which is a simple outpatient procedure, with risk comparable to that of a herniorrhaphy. On the other hand, in many infertility centers, for patients with moderate male factor, IUI is attempted first, followed by IVF or ICSI, with good success rates. For patients with severe male factor infertility (severe oligospermia or azoospermia), either ICSI or therapeutic donor insemination should be the initial treatment.

Emotional Aspects of Infertility Treatments

Infertility treatment is a physically and emotionally bewildering experience for most patients, who often encounter feelings of depression, grief, anxiety, and chronic stress throughout the process. Frequent visits, administrative obstacles (including, and especially, approval by their insurance company), the need to orchestrate work life with doctors’ appointments, and the strain on the couple’s relationship all contribute to making infertility treatment among the most stressful experiences that patients can face.

The primary care clinician or the obstetrician-gynecologist can play an important role by acknowledging the stress, sadness, and even shame, that many couples and individuals experience as a result of their infertility. The primary care clinician also serves in educating patients about the process, as well as dispelling myths and fears. The physician can help reduce tensions by preparing patients for the emotional roller-coaster aspects to the treatments, by setting expectations about success rates, and by encouraging the couple to talk openly about the process.

The members of the couple may have different responses to infertility diagnosis and treatment. This may pose challenges to the relationship, which frequently interferes with the evaluation and treatment. Patients should be counseled that they are not alone. Acknowledging that people may have different attitudes toward informing family and friends and participating in support groups can also be helpful. Depression is a common finding in couples with infertility. Early recognition and referral for appropriate treatment is paramount.
There are mental health providers (e.g., psychiatrists, social workers, and psychologists) who specialize in infertility, and they should be used as a resource for primary care providers or obstetrician-gynecologists who care for infertile patients. There is usually a mental health professional associated with centers for reproductive medicine, as recommended by the American Society for Reproductive Medicine guidelines. These therapists see individuals alone or as a couple, and they can help not only with the emotional aspects of treatment, but also offer strategies for dealing with work or home conflicts that come up because of the need for frequent testing and treatments.

Support groups, offered at most reproductive medicine centers, are attractive options for individuals and couples with infertility, as they may help alleviate feelings of isolation. Finally, mind-body programs are available to help patients learn relaxation response and other stress-reduction techniques. These programs help patients gain awareness of how behaviors and attitudes can trigger stress. By practicing these techniques, patients report improvements in their sense of well being as they go through infertility treatments.

The primary care clinician or obstetrician-gynecologist should also understand that most couples are very anxious to get started on their evaluations and treatment. By performing as many preliminary tests as possible before the referral, and by expediting the referral to the infertility specialist, the clinician can help to alleviate some of the anxiety that many couples feel in the early stages of the process.

An important aspect of the care for couples with infertility is respecting their privacy. Many patients seek care in the institutions where they work or in their communities, and because of the necessity of frequent visits for testing and treatment, are anxious that coworkers may inadvertently discover their medical histories. Even for patients who are not health care workers, privacy is a paramount concern. Primary care clinicians should ask couples during the evaluation and treatment if they have any concerns about privacy issues and what can be done to make them feel more comfortable.

Resources

There are a number of resources available to patients to help them through this stressful process.

RESOLVE: Founded in Massachusetts, this is a self-help organization that provides support and information to couples undergoing infertility evaluation and treatment. www.resolve.org

RESOLVE
PO Box 541553
Waltham, MA
02454-1553

Telephone 781-647-1614 or 781-899-7207
Website: www.resolveofthebaystate.org
Email: admin@resolveofthebaystate.org

Internet sites: There is a wealth of information, and misinformation, on the web. It is important for doctors to review with patients the information that they have gathered, as often it can be incorrect or misleading.

Mind-Body Medical Institute: www.mbmi.org
Adoption Issues and Resources

Adoption is a reasonable option for single individuals or couples who have been unsuccessful with or do not wish to undergo fertility treatments. There are many issues for the prospective parents to consider: the age, ethnicity, or race of the child they wish to adopt, domestic vs. foreign adoption, and whether the couple would be willing to adopt a child with special needs. It is important to remember that the decision to adopt, while ultimately a very positive one, represents another loss to the infertile couple. Many couples are discordant in their views about adoption, and it can take some time and effort to arrive at a plan that is mutually satisfying. The costs of adoption are high, approximately $30,000, for either domestic or foreign adoption and are not covered by insurance. Costs are less for adoption of children with special needs.

There are many resources available to individuals considering adoption. Many couples find consultation with an adoption counselor to be very helpful in sorting through all the options.

Two resources available to couples considering adoption include:

- The Open Door Society http://www.odsma.org
- RESOLVE http://www.resolve.org

Domestic Adoption

Domestic adoption can be either public (through the Department of Social Services) or private (through an agency or lawyer). Most private domestic adoptions in this state are semi-open, meaning that couples will have some contact with the birth family before the birth and sometimes afterwards. The advantage of domestic adoption is that babies are very young, often right out of the hospital. Disadvantages include the expense and another level of uncertainty around waiting and being "matched" with a birthmother.

Foreign Adoption

Many organizations both in Massachusetts and nationwide help families adopt children from other countries. The children are slightly older in most cases, but are legally (in most countries) considered orphaned or abandoned, so some adoptive parents find this more "certain"). The international adoption process varies markedly by country, so it is essential to work with a good agency that can help negotiate the systems both in this country and in the country of adoption. Children of all ages and races are available from many different countries, most commonly in Asia, Latin America, and the former Soviet Union.