



Complete Summary

GUIDELINE TITLE

Infertility. A guide to evaluation, treatment and counseling.

BIBLIOGRAPHIC SOURCE(S)

Brigham and Women's Hospital. Infertility. A guide to evaluation, treatment, and counseling. Boston (MA): Brigham and Women's Hospital; 2003. 11 p. [7 references]

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SCOPE

DISEASE/CONDITION(S)

Infertility

GUIDELINE CATEGORY

Counseling
Evaluation
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Health Care Providers

Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide physicians with clear clinical pathways to identify and treat infertility

TARGET POPULATION

Infertile couples

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Detailed history of both partners
2. Initial testing, including semen analysis of male partner, and documentation of ovulation, day three follicle stimulating hormone (FSH) levels, and thyroid stimulating hormone (TSH) levels in female partner
3. Additional testing as needed, such as clomiphene citrate challenge test (CCCT), hysterosalpingogram (HSG, or tubogram), laparoscopy, hysteroscopy, pelvic ultrasound

Treatment/Counseling

1. Intrauterine insemination (IUI)
2. Therapeutic donor insemination (TDI)
3. Ovulation induction
4. Medications to stimulate ovulation
 - Clomiphene citrate [Clomid]
 - Gonadotropin therapy. Human menopausal gonadotropins (HMG; e.g., Pergonal) or purified FSH (Metrodin, Follistim, or Gonal-F)
 - Dopamine agonists (Bromocriptine or Dostinex)
 - Metformin [Glucophage]
5. Assisted reproductive therapy
 - In vitro fertilization (IVF)
 - Cryoembryo transfer
 - IVF with donor oocytes
 - Intracytoplasmic sperm injection (ICSI)
 - Gestational carrier
6. Counseling regarding options, risks associated with assisted reproduction, male factor infertility, and emotional aspects of infertility treatments

MAJOR OUTCOMES CONSIDERED

Pregnancy outcomes (i.e., rates of pregnancy and rates of live births)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches using Medline.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was reviewed by the Women's Health Guidelines Editorial Review Board.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

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

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

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 follicle stimulating hormone (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 10 mIU/mL.
- Thyroid stimulating hormone (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 orally [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 clomiphene citrate challenge test 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 twice a day (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 intrauterine lesions (adhesions, polyps) are suspected or if intrauterine abnormalities are noted on the hysterosalpingogram.
- 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

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 luteinizing hormone (LH) levels, or ultrasound. Clomiphene citrate is often taken on days five to nine, increasing the success rate of this treatment.

Therapeutic Donor Insemination (TDI)

Indications

- Severe male factor (oligospermia or azoospermia)
- Women without partners
- Lesbian couples

Therapeutic donor insemination (TDI) involves timed insemination from an anonymous or a known donor. Use of frozen semen to prevent sexually transmitted disease is recommended by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). At sperm banks, donors are tested for sexually transmitted diseases, including human immunodeficiency virus (HIV), chlamydia, gonorrhea, syphilis, cytomegalovirus (CMV), human T-cell lymphotropic virus (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

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 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).

Refer to the original guideline document for a chart referencing drugs used to stimulate ovulation, including dosages, cost, and additional comments.

Assisted Reproductive Therapy

	Indications	Procedure
In Vitro Fertilization (IVF)	<ul style="list-style-type: none"> • Tubal factor • Severe endometriosis • Unexplained infertility • Male factor 	Involves controlled ovarian hyperstimulation, which is aimed at producing multiple oocytes. Once the oocytes are mature, human chorionic gonadotropin (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 advantage of this procedure is 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	<ul style="list-style-type: none"> • Premature ovarian failure • Perimenopause, or menopause • Failed IVF due to oocyte factors (comprises 50% of 	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 to not cover the payment to the donor

	Indications	Procedure
	cases)	and screening of the donor.
Intracytoplasmic Sperm Injection (ICSI)	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.

Risks of Complications with Assisted Reproduction

Refer to the section "Potential Harms" of this document or to the original guideline document.

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, intrauterine insemination (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

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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Guidelines are based on a comprehensive review of recent medical literature and reflect the expertise of leading clinicians within Brigham and Women's Hospital.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate evaluation, treatment, and counseling related to infertility
- Improved pregnancy outcomes

POTENTIAL HARMS

- 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 to 20 percent. Severe OHSS requiring hospitalization occurs in one percent of patients. Bleeding, infection, and 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 in vitro fertilization (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.
- 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.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Brigham and Women's Hospital. Infertility. A guide to evaluation, treatment, and counseling. Boston (MA): Brigham and Women's Hospital; 2003. 11 p. [7 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003

GUIDELINE DEVELOPER(S)

Brigham and Women's Hospital (Boston) - Hospital/Medical Center

SOURCE(S) OF FUNDING

Brigham and Women's Hospital

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Brigham and Women's Hospital Web site](#).

Print copies: Available from the Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. Telephone: (800) BWH-9999.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Brigham and Women's Hospital. Infertility. A guide to help couples build healthy families. Boston (MA): Brigham and Women's Hospital; 2003. 14 p.

Print copies: Available from the Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. Telephone: (800) BWH-9999.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on May 4, 2004.

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