Infertility is an important public health problem with important psychological, economic, demographic, and medical implications. Infertility is a unique medical condition because it involves a couple, rather than a single individual. It is defined as failure of a couple to conceive after 12 months of regular intercourse without use of contraception in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older. Some clinicians use the term sub fertility to describe this failure to conceive unless the couple has been proven to be sterile. Fecundity, the probability of achieving a pregnancy in one menstrual cycle, is a more accurate descriptor because it recognizes varying degrees of infertility.

The World Health Organization (WHO) estimates that 60 to 80 million couples worldwide currently suffer from infertility. Infertility varies across regions of the world and is estimated to affect 8 to 12 % of couples worldwide. An estimated 3 to 5 % couples are infertile due to unknown or unpreventable conditions. A prevalence of infertility above this level suggests preventable or treatable causes. Infertility tends to be highest in countries with high fertility rates, an occurrence termed “barrenness amid plenty”.

The WHO estimates of primary infertility in India are 3.9 % (age-standardized to 25-49 year) and 16.8 % (age-standardized to 15-49 year), using the “age but no birth” definition. Estimates of infertility vary widely among India - from 3.7 % in Uttar Pradesh, Himachal Pradesh and Maharashtra, to 5 % in Andhra Pradesh, and 15 % in Kashmir. Moreover, the prevalence of primary infertility has also
been shown to vary across tribes and castes within the same region in India. (8, 10, 11)

Many of these estimates use different definitions of infertility and consider different time periods, which make direct comparisons difficult between any studies.

According to the World Health Organization (WHO taskforce study; 8500 infertile couples in high-income countries), female factor infertility accounted for 37% infertility, male factor infertility for 8%, and both male and female factor infertility for 35% (28). A fifth of couples had idiopathic infertility or they became pregnant during the study. Six factors accounted for close to 80% of female infertility: Ovulatory disorders (25%); Endometriosis (15%); Pelvic adhesions (12%); Tubal blockage (11%); other tubal abnormalities (11%) and Hyperprolactinemia (7%).

The uncertain causal relationship between an abnormality on infertility testing and the actual cause of infertility makes it difficult to estimate the relative frequency of the causes of infertility. The frequency of factors can only be a proxy for their relative importance and at best they can generate a pre-test probability of prevalence of a cause while evaluating an infertile couple. According to a population-based study (29) following factors accounted for infertility: Male factor (hypogonadism, post-testicular defects, seminiferous tubule dysfunction) — 26%; Ovulatory dysfunction — 21%; Tubal damage — 14%; Endometriosis — 6%; Coital problems — 6%; Cervical factor — 3%; Unexplained — 28%.

A study from Kashmir (10) reported that semen abnormalities (22.4%), anovulation (17.2%), ovarian failure (8.8%), hyperprolactinemia (8.4%) and tubal disease (7.2%) are common causes of infertility. The authors argued that the pattern of infertility in India is the same as in other parts of the world, except that infertile couples report late for evaluation.
In a 2011 study from Iran (30), researchers identified 2515 couples, 1991 (79%) of who had a definitive diagnosis following complete workup, including Hysterosalpingography. The mean age was 29.6 ± 6.0 years; the mean duration of infertility was 1.7± 1.8 years. Primary infertility accounted for close to two-thirds of the cases. Causes of infertility were male factor 45%, oligo-ovulation disorders 37% and tubal damage 18%. Infertility factors were identified in the woman alone in 30.6% of cases and the man alone in 29.2%. Two combined infertility factors were found in 18 % of patients, and three combined factors in 0.5%. The rate of unexplained infertility (which probably includes non-tubal endometriosis) was 20.7%.

There are sparse data on the prevalence of primary infertility in India. The prevalence of primary infertility among 897 sexually active women (mean age, 26 years) in a recent study from Mysore was 12.6 % (n = 113; 95% CI: 10.5-15.0%) and the main risk factor for primary infertility was HSV-2 seropositivity (adjusted odds ratio: 3.41; CI: 1.86, 6.26). (31)

**Normal fertility**

Several studies have helped understand the concept of fecundity and to establish normal parameters in studies of fertility potential:

- A study examined the number of months to conception in 5574 normal women who had unprotected intercourse and who became pregnant between 1946 and 1956. (32) Eighty-five percent of the women conceived within 12 months. Fecundity was 0.25 in the first three months of observation, and then decreased to 0.15 during the next nine months of observation.

- Another study of 200 healthy couples who desired pregnancy also noted that fecundity declined from 0.25 in the first three months to 0.11 in the next nine
months of observation. (33)Eighty-two percent of the couples conceived within 12 months.

- A study conducted in China reported that 518 newly married textile workers aged 20 to 34 years who intended to conceive did so at a rate of about 50% within two cycles and 88% within six months. (34)Monthly fecundity ranged from 0.30 to 0.35.

- A prospective European study investigated 346 users of natural family planning methods who were trying to achieve conception. (35)The estimated cumulative probabilities of conception for the total group at 1, 3, 6, and 12 months were 38, 68, 81, and 92%, respectively. The authors postulated that after six months, 50% of the remaining couples were sub fertile or infertile.

- A study of a random sample of 867 women from the general population having unprotected intercourse with a male partner reported pregnancy rates within 6, 12, and 24 months of 54, 76, and 89%, respectively. (36)

While these studies demonstrate that the large majority (80 to 90%) of apparently normal couples will conceive within the first year of attempted conception, they also show that the fecundity decreases over time and with increasing age of the female partner. Thus, the possibility of infertility may be suspected after only six months of unprotected intercourse without conception. Patients who have not achieved pregnancy after 12 months have even lower fecundity. Five to 15% of apparently normal couples will conceive in the second 12 months of attempted conception so that after 24 months of trying to become pregnant, 95% of couples will have conceived.
Several specialists have proposed a system of prognostic grading in conjunction with statements describing the couple's fertility history and diagnosis in order to reduce confusing terminology and to facilitate an appropriate treatment plan. (37) This system has not yet been widely accepted. In general, women who are under age 30, who have a less than two-year history of infertility, who have had a previous pregnancy, and who do not have tubal disease, anovulation, partners with male factor infertility, or endometriosis, have the best prognosis for treatment-independent conception. (38)

Prevalence of infertility

The National Survey of Family Growth interviewed 15,303 married women aged 15 to 44 to estimate the prevalence of infertility in the United States. (39) Married women were considered infertile if they reported they had not conceived over the past 12 months and were sexually active and not using contraception or surgically sterilized. From 1982 to 2002, the percentage of married women meeting these criteria for infertility fell from 8.5 to 7.4 %. In contrast, the estimated percent of married women with impaired fecundity increased from 11 % in 1982 to 15 % in 2002. Impaired fecundity was defined as a 36-month interval of unprotected sexual activity without conception or the woman's perception that it was physically impossible or difficult for her to conceive or her husband to father a child (does not include surgically sterile individuals).

Worldwide, the prevalence of infertility is highest in Eastern Europe, North Africa /Middle East, Oceania, and Sub-Saharan Africa. (6) Worldwide, in 2010, 1.9 % of women aged 20 to 44 years who wanted to have children were unable to have their first live birth and 10.5 % of women with a previous live birth were unable
to have an additional live birth. In this study, infertility was defined as “the absence of a live birth for women who desire a child and have been in a union for at least five years, during which they have not used any contraceptives”.

In 2007, Boivin and colleagues (40) searched literature to identify the prevalence of infertility. According to their review, 14 studies provided estimates of infertility prevalence in more developed countries, on the basis of surveys involving 52,253 women. In total, four estimates were for current infertility of 12-month duration, one was for current subfecundity of 12-month duration and one was for current infertility of 24-month duration. Nine estimates were for lifetime occurrence of infertility lasting 12 months and one was for lifetime infertility lasting 24 months. The prevalence of lifetime infertility ranged from 6.6% to 26.4%. Lifetime prevalence of infertility was remarkably similar in more (6.6 – 26.4%) and less (5.0 – 25.7%) developed countries. The prevalence of current infertility ranged from 3.5% to 16.7%. The representative estimate of current infertility for this range is a median 9% (95% CI, 5% to 15%) for 12 months delay among women aged 20–44 in married and consensual unions.

In the Boivin and colleagues study (40), an estimated 1.139 billion women aged 15–49 were in married or consensual unions in 2006 and they represented 17.5% of the 6.5 billion world population. The 804 million women aged 20–44 in married or consensual unions were 12.4% of the 6.5 billion total, and this category includes 122 million women in more developed countries and 682 million women in less developed countries. There are 72.4 million women aged 20–44 and living in married or consensual relationships who have infertility defined as currently experiencing 12-month delay in conception while not using contraception. On the basis of 2007 world
population, 72.4 million people were infertile and of these 40.5 million were seeking infertility medical care.

**Causes of infertility**

The WHO task force on Diagnosis and Treatment of Infertility performed a study of 8500 infertile couples and utilized standard diagnostic criteria to determine the medical conditions contributing to infertility.\(^{(28)}\) In developed countries, female factor infertility was reported in 37\% of infertile couples, male factor infertility in 8\%, and both male and female factor infertility in 35\%. Five\% of couples had unexplained infertility and 15\% became pregnant during the study. This study illustrates that infertility should not be assumed to result primarily from disorders in the female partner.

Some causes of infertility are easily identifiable, such as azoospermia (no sperm cells in the ejaculate), longstanding amenorrhea, or bilateral tubal obstruction. However, the situation is less clear in most couples: the sperm may be reduced in number, but are not absent; there may be oligomenorrhea with some ovulatory cycles; the woman may have partial tubal obstruction; or a menstrual history may suggest intermittent ovulation. It is often difficult to weigh or prioritize these findings when counseling infertile couples or planning treatment programs.

Adding to the complexity of the situation, there are few data regarding the predictive validity of these tests despite their widespread use. Thus, short of the absolute infertility factors mentioned (e.g., azoospermia or bilateral tubal obstruction), an abnormal test result cannot be said to be the cause of infertility in a particular couple.
The uncertain causal relationship between an abnormality on infertility testing and the actual cause of infertility makes it difficult to estimate the relative frequency of the causes of infertility. Nevertheless, it is informative to estimate the frequency with which various factors are found in association with infertility as a rough proxy for their relative importance. One population-based study reported the following results:

- Male factor (hypogonadism, post-testicular defects, seminiferous tubule dysfunction) — 26%
- Ovulatory dysfunction — 21%
- Tubal damage — 14%
- Endometriosis — 6%
- Coital problems — 6%
- Cervical factor — 3%
- Unexplained — 28%

The frequency of these factors in infertility is similar whether infertility is primary or secondary, and has not changed significantly over the past 25 years in developed countries. (42)
A comparison of studies on distribution of cause of infertility conducted in primary infertility clinics in different countries is tabulated below.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Anovulation</th>
<th>Male</th>
<th>Tubal</th>
<th>Unexplained</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elussein et al.</td>
<td>Sudan</td>
<td>2008</td>
<td>29.7%</td>
<td>36.2</td>
<td>19.5</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Chiamchanya &amp; Su-angkawatin</td>
<td>Thailand</td>
<td>2008</td>
<td>20.8%</td>
<td>74</td>
<td>21.5</td>
<td>4.7</td>
<td>55.6</td>
</tr>
<tr>
<td>Bayasgalan et al.</td>
<td>Mongolia</td>
<td>2004</td>
<td>-</td>
<td>25.6</td>
<td>32.8</td>
<td>9.8</td>
<td>18.8</td>
</tr>
<tr>
<td>Stewart-Smythe &amp; van Iddekinge</td>
<td>South Africa</td>
<td>2003</td>
<td>27%</td>
<td>82</td>
<td>81.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Philippov et al.</td>
<td>Siberia</td>
<td>1998</td>
<td>17.3%</td>
<td>45.1</td>
<td>31.6</td>
<td>2.2</td>
<td>38.7</td>
</tr>
<tr>
<td>Zargar et al.</td>
<td>India</td>
<td>1997</td>
<td>21.6</td>
<td>27.6</td>
<td>11.6</td>
<td>14.8</td>
<td>14.8</td>
</tr>
<tr>
<td>Thonneau &amp; Spira</td>
<td>France</td>
<td>1992</td>
<td>32</td>
<td>57</td>
<td>26</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>Haxton &amp; Black</td>
<td>Scotland</td>
<td>1987</td>
<td>31</td>
<td>17</td>
<td>18</td>
<td>32</td>
<td>-</td>
</tr>
<tr>
<td>Hull et al</td>
<td>UK</td>
<td>1985</td>
<td>21</td>
<td>24</td>
<td>14</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Dor et al.</td>
<td>Israel</td>
<td>1977</td>
<td>31.5</td>
<td>28</td>
<td>16.3</td>
<td>17.6</td>
<td>-</td>
</tr>
</tbody>
</table>
Timing of infertility evaluation

The general consensus among infertility experts is that infertility evaluation should be undertaken for couples who have not been able to conceive after 12 months of unprotected and frequent intercourse, but earlier evaluation should be undertaken based on medical history and physical findings, and in women over 35 years of age. Some authorities have proposed initiating an infertility work-up after six months of fertility-oriented intercourse without conception since prospective cohort studies have shown that a significant decline in fecundity occurs by this time. (34, 35)

The timing of initial evaluation of infertility depends upon the age of the female partner, as well as the couple's historical risk factors. Women experience a decline in fecundity as the ovary ages, especially after age 30. (43) Significantly delaying the evaluation and treatment of an infertile woman in her mid-thirties may diminish the success rate once therapy is initiated. For these reasons, in women between 35 and 40 years of age, the infertility evaluation should begin after six months of frequent unprotected intercourse without conception and the evaluation should be initiated within six months in women over 40 years of age.

Evaluation is also initiated promptly if the female partner has a history of risk factors for premature ovarian failure (previous extensive ovarian surgery, exposure to cytotoxic drugs or pelvic radiation therapy, autoimmune disease, smoking, strong family history of early menopause/premature ovarian failure), advanced stage endometriosis, or known or suspected uterine/tubal disease. Male factors can also be indications for initiating early evaluation of the male partner. These factors include a history of testicular trauma requiring treatment, adult mumps, impotence or other
sexual dysfunction, chemotherapy and/or radiation, or a history of sub fertility with another partner.

For younger couples who present with fewer than 12 months of attempted conception, the initial intervention should be teaching timed intercourse and advising that they wait at least 12 months before initiating the infertility evaluation.

In addition, changes in lifestyle factors that may improve fertility, including achieving an ideal body mass index, cessation of smoking, and limiting exposure to caffeine and alcohol are also a part of interventions. Evaluation is initiated sooner if the female partner has a history of oligomenorrhea /amenorrhea, chemotherapy and/or radiation, or endometriosis, known or suspected tubal disease, or if male risk factors are present.

**Infertility evaluation**

The recognition, evaluation, and treatment of infertility are stressful for most couples. The clinician should not ignore the couple's emotional state, which is often a mix of depression, anger, anxiety, and marital discord.

Couple may have multiple factors contributing to their infertility; therefore, a complete initial diagnostic evaluation, including a complete history and physical examination, should be performed. This will detect the most common causes of infertility, if present. Evaluation of both partners is performed concurrently.

The following tests are useful in most couples with infertility:

- Semen analysis to assess male factors
- Menstrual history, Hysterosalpingography to assess tubal patency and the uterine cavity.
Day 3 serum FSH and estradiol levels.

In select couples, the following additional tests may be warranted:

- Pelvic ultrasound to assess for uterine myoma and ovarian cysts
- Laparoscopy to identify endometriosis or other pelvic pathology
- Assessment of ovarian reserve in women >35 years of age; this may involve a Clomiphene challenge test, ultrasound for early follicular antral follicle count, day 3 serum inhibin B level, or Antimüllerian hormone measurement.
- Assessment of thyroid function.

**Diagnostic evaluation of the infertile female**

An infertility evaluation is usually initiated after one year of regular unprotected intercourse in women under age 35 and after six months of unprotected intercourse in women age 35 and older. However, the evaluation may be initiated sooner in women with irregular menstrual cycles or known risk factors for infertility, such as endometriosis, a history of pelvic inflammatory disease, or reproductive tract malformations.

The evaluation usually- but not always- moves through three tiers: an interested and experienced general practitioner, an obstetrician-gynecologist and a reproductive endocrinologist. The referral decisions depend upon the complexity of problem, results of infertility tests and skills, expertise and facilities available at a center.

Multiple tests have been proposed for evaluation of female infertility. Some of these tests are supported by good evidence, while others are not.
History and physical examination

Findings on history and physical examination may suggest the cause of infertility and thus help focus the diagnostic evaluation. The most important points in the history are:

- Duration of infertility and results of previous evaluation and therapy.
- Menstrual history (age at menarche, cycle length and characteristics, presence of molimina and dysmenorrhea), which helps in determining ovulatory status. For example, regular monthly cycles with molimina (breast tenderness, ovulatory pain, bloating) suggest the patient is ovulatory and characteristics such as severe dysmenorrhea suggest endometriosis.
- Medical, surgical, and gynecological history (including sexually transmitted infections, pelvic inflammatory disease, and treatment of abnormal Pap smears) to look for conditions, procedures, or medications potentially associated with infertility.
- Thyroid disease, galactorrhoea or hirsutism
- Obstetrical history to assess for events potentially associated with subsequent infertility or adverse outcome in a future pregnancy.
- Coital frequency and sexual dysfunction
- Family history of birth defects, mental retardation, genetic mutations including family members with infertility
- Personal and lifestyle history including age, occupation, exercise, rest, dieting/changes in weight, smoking, and alcohol use, all of which can affect fertility.
Physical examination

The physical examination should assess for signs of potential causes of infertility: body mass index (BMI), incomplete development of secondary sexual characteristics (hypogonadotropic hypogonadism), a body habitus that is short and stocky, with a squarely shaped chest (Turner syndrome), abnormalities of the thyroid gland, galactorrhea, or hirsutism, acne, male pattern baldness, virilization (hyper- or hypothyroidism, hyperprolactinemia, polycystic ovary syndrome, adrenal disorder), tenderness or masses in the adnexae or posterior cul-de-sac (pouch of Douglas) (chronic pelvic inflammatory disease or endometriosis) palpable tender nodules in the posterior cul-de-sac, uterosacral ligaments, or rectovaginal septum (endometriosis), vaginal/cervical structural abnormalities or discharge (müllerian anomaly, infection, or cervical factor), uterine enlargement, irregularity, or lack of mobility (uterine anomaly, leiomyoma, endometriosis, or pelvic adhesive disease).

Diagnostic evaluation should be conducted in a systematic, expeditious and cost-effective manner so as to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility. The pace and extent of evaluation should take into account the couple’s preferences, patient age, the duration of infertility and unique features of the medical history and physical examination.

ovulatory disorders

The WHO classifies ovulatory disorders into three groups:

- WHO class 1 — Hypogonadotropic hypogonadal anovulation is the least common, occurring in 5 to 10 percent of women. Examples of women in this
category are women with hypothalamic amenorrhea from functional etiologies such as excessive exercise or low body weight.

- WHO class 2 — Normogonadotropic normoestrogenic anovulation is the most common, accounting for 70 to 85 percent of cases. Women with polycystic ovary syndrome usually fall into this category.

- WHO class 3 — Hypergonadotropic hypoestrogenic anovulation occurs in 10 to 30 percent. Women with primary gonadal failure (previously called premature ovarian failure) or gonadal dysgenesis comprise the majority of these cases.

Hyperprolactinemic anovulation is a separate category; gonadotropin concentrations in this condition are usually normal or decreased.

**Ovulatory function**

Ovulatory dysfunction is identified in approximately 25% of all infertile women and accounts for up to 40% of infertility in women.(44) The spectrum of ovulatory disorders ranges from amenorrhoea through oligomenorrhoea to irregular cycles. It commonly results in obvious menstrual disturbances (oligo/amenorrhea), but can be more subtle. The underlying cause should be sought because specific treatment may be indicated and some conditions may have other health implications and consequences. The most common causes of ovulatory dysfunction include polycystic ovary syndrome, obesity, weight gain or loss, strenuous exercise, thyroid dysfunction, and hyperprolactinemia. However, the specific cause of ovulatory dysfunction often remains obscure. Methods for evaluating ovulatory function may include any of the following:
Menstrual history gives a rich insight into the ovulatory function. In most ovulatory women, menstrual cycles are regular and predictable, occurring at intervals of 25–35 days, exhibiting consistent flow characteristics, and accompanied by a set of minimal symptoms. Some degree of variation is entirely normal; in a study of more than 1,000 cycles, variations in inter-menstrual interval exceeding 5 days were observed in 56% of patients within six months and in 75% of those followed for one year. (45) Although a history of regular and consistent menses strongly suggests normal ovulatory function, an objective measure is warranted in infertile women. Patients with abnormal uterine bleeding, oligomenorrhea, or amenorrhea generally do not require specific diagnostic tests to establish a diagnosis of anovulation.

**Basal body temperature records**

Basal body temperature (BBT) charts are the least expensive method for detecting ovulation, but interpretation of the charts can be difficult and subject to wide inter-observer variation. (66) Temperature changes are sufficient to retrospectively identify ovulation, but they occur too late to be useful for timing intercourse.

In cycles monitored with BBT, the period of highest fertility spans the seven days prior to the mid-cycle rise in BBT. Whereas ovulatory cycles generally are associated with clearly biphasic BBT recordings and anovulatory cycles typically result in monophasic patterns. Some ovulatory women cannot document clearly biphasic BBT patterns. (46) Grossly short luteal phases (< 10 days of temperature elevation) may identify women with more subtle ovulatory dysfunction. The test cannot reliably define the time of ovulation and can become tedious. Consequently, BBT is no longer considered the best or preferred method for evaluating ovulatory function for most infertile women.
Serum progesterone determinations provide a reliable and objective measure of ovulatory function as long as they are obtained at the appropriate time in the cycle. Given the range of normal variation in ovulatory cycles, a serum progesterone measurement generally should be obtained approximately one week before the expected onset of the next menses, rather than on any one specific cycle day (e.g., cycle day 21). A progesterone concentration > 3ng/mL provides presumptive but reliable evidence of recent ovulation(46). Although higher threshold values have been used commonly as a measure of the quality of luteal function(e.g.,10 ng/mL)(47) the criterion is not reliable because corpus luteum progesterone secretion is pulsatile and serum concentrations may vary up to 7-fold within an interval of a few hours.(48)

Urinary luteinizing hormone (LH) determinations using various commercial “ovulation predictor kits” can identify the mid cycle LH surge that precedes ovulation by one to two days. Urinary LH detection provides indirect evidence of ovulation and helps to define the interval of greatest fertility: the day of the LH surge and the following two days. Results generally correlate well with the peak in serum LH, particularly when the test is performed on midday or evening urine specimens. (49)

**Endometrial biopsy**

Endometrial biopsy (EB) and histology can demonstrate (1) a secretory endometrium, which is indirect evidence that ovulation has occurred, and (2) whether the maturity of the secretory endometrium is in phase (i.e., consistent with menstrual cycle date) or out of phase (i.e., luteal phase defect) which results from the action of progesterone and thus implies ovulation. “Dating” the endometrium using traditional histological criteria was long considered the “gold standard” among methods for evaluating the quality of luteal function and for diagnosis of luteal phase deficiency (LPD).
However, careful studies have since demonstrated clearly that histological endometrial dating is not a valid diagnostic method because it lacks both accuracy and precision (50) and because the test cannot distinguish fertile from infertile women. (51) Therefore, endometrial biopsy is no longer recommended for the evaluation of ovulatory or luteal function in infertile women and should be limited to those in whom specific endometrial pathology (e.g., neoplasia, chronic endometritis) is strongly suspected.

Although endometrial receptivity during the implantation window is crucial for achieving pregnancy, histological assessment of endometrial response has a poor correlation with fertility. For example, when repeated endometrial biopsies are performed in normal fertile women, half will have a single out-of-phase biopsy (using two-day or greater lag criteria) and over one-quarter will have sequential out-of-phase biopsies. Thus, it appears that histological dating does not discriminate fertile from infertile couples. (50) 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 worthwhile.

The American Society of Reproductive Medicine (ASRM) affirmed the lack of benefit of the endometrial biopsy in the evaluation of the infertile female and does not recommend use of this test (65).

Other evaluations aimed at defining the best choice of treatment may be indicated for anovulatory infertile women. Serum thyroid-stimulating hormone (TSH) and prolactin determinations can identify thyroid disorders and/or hyperprolactinemia, which may require specific treatment. In women with amenorrhea, serum follicle-stimulating hormone (FSH) and estradiol measurements can distinguish women with ovarian failure (high FSH, low estradiol), who may be candidates for oocyte donation,
from those with hypothalamic amenorrhea (low or normal FSH, low estradiol), who will require exogenous gonadotropin stimulation for ovulation induction.

In anovulatory infertile women, failure to achieve pregnancy after three to six cycles of successful ovulation induction should be viewed as an indication to perform additional diagnostic evaluation or, if evaluation is complete, to consider alternative treatments.

Ovulatory disorders frequently respond to ovulation induction with clomiphene citrate, an estrogen antagonist that increases gonadotropin release. Of 201 anovulatory women with mean age of 28 years and mean duration of infertility of 1.9 years, approximately half ovulated after the initial clomiphene citrate dose (50 mg for five days), 22% at the next dosage of 100 mg, and overall 36% had live births. (52)

**Ovarian reserve**

The concept of ‘‘ovarian reserve’’ views reproductive potential as a function of the number and quality of remaining oocytes. Decreased or diminished ovarian reserve (DOR) describes women of reproductive age having regular menses whose response to ovarian stimulation or fecundity is reduced compared to those women of comparable age. Tests utilized to assess ‘‘ovarian reserve’’ include cycle day 3 FSH and estradiol measurements, a clomiphene citrate challenge test, an early follicular phase antral follicle count (via transvaginal ultrasonography), or a serum Antimüllerian hormone (AMH) level. These tests may provide prognostic information in women at increased risk of diminished ovarian reserve, such as women who: i) are over age 35 years; ii) have a family history of early menopause; iii) have a single ovary or history of previous ovarian surgery, chemotherapy, or pelvic radiation therapy; iv) have unexplained infertility; v) have demonstrated poor response to
gonadotropin stimulation; or vi) are planning treatment with ART. (53) Measures of ovarian reserve do not establish a diagnosis of diminished ovarian reserve, but instead help to predict response to ovarian stimulation with exogenous gonadotropins and, to a lesser extent, the likelihood for achieving a successful pregnancy with ART (19). However, poor results with any of the tests do not necessarily imply inability to conceive.

**Cycle Day 3 FSH and Estradiol**

FSH obtained on cycleday 2–5 is commonly used as a measure of ovarian reserve. High values (10-20 IU/L) have been associated with both poor ovarian stimulation and the failure to conceive. (54) Assays standardized against the WHO 2nd International Standard demonstrate high specificity (83%–100% range) for predicting poor response to stimulation (usually defined as <2–3 follicles or 4% retrieved oocytes). (54) However, sensitivity for identifying women who will respond poorly varies widely (10%–80%). Basal estradiol alone should not be used to screen for DOR. The test has value only as an aid to correct interpretation of a “normal” basal serum FSH value.

**Antral follicle count (AFC)**

Ultrasound examination can be used to determine the number of antral follicles (defined as follicles measuring 2 to 10 mm in diameter). On transvaginal ultrasound, a low AFC ranging from 4 to 10 antral follicles between days two and four of a regular menstrual cycle suggests poor ovarian reserve. AFC thresholds will vary by center and should be prospectively tested within a center to be most useful as a predictive tool. (55) Most clinicians perform an AFC during the early follicular phase, although a retrospective cohort study showed no difference in the predictive
value of AFC for poor ovarian response when measured at different phases of the menstrual cycle. (56) Although AFC is a good predictor of ovarian reserve and response, it is less predictive of oocyte quality, the ability to conceive with IVF, and pregnancy outcome. (56)

**Anti-müllerian hormone (AMH)**

Anti-müllerian hormone (AMH) is a member of the TGF-beta family and is expressed by the small (<8 mm) preantral and early antral follicles. The AMH level reflects the size of the primordial follicle pool. In adult women, AMH levels gradually decline as the primordial follicle pool declines with age. (57)

The AMH level appears to be an early, reliable, direct indicator of declining ovarian function; however, there is no consensus on the appropriate threshold value. (58) A serum AMH level above 0.5 ng/mL is consistent with good ovarian reserve, while lower levels suggest the presence of a depleted ovarian follicle pool. Levels less than 0.15 ng/mL suggest the patient will have a poor response to IVF.

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.

**Tubal patency**

Tubal disease is an important cause of infertility and should be specifically excluded. Approximately 20% of infertile women have tubal disease. The methods for evaluating tubal patency are complementary and not mutually exclusive. (41) Accurate diagnosis and effective treatment of tubal obstruction often requires more than one of the following techniques:
Hysterosalpingography (HSG), using either a water- or lipid-soluble contrast media, is the traditional and standard method for evaluating tubal patency and may offer some therapeutic benefit. HSG can document proximal and distal tubal occlusion, demonstrate salpingitis isthmica nodosa, reveal tubal architectural detail of potential prognostic value, and may suggest the presence of fimbrial phimosis or peritubular adhesions when escape of contrast is delayed or becomes loculated, respectively. The positive predictive value (PPV) and negative predictive value (NPV) of HSG are 38% and 94%, respectively. (42) Findings suggesting proximal tubal obstruction require further evaluation to exclude artifacts resulting from transient tubal/ myometrial contractions or relating to catheter position.

Sonohysterosalpingography (SHSG) or Saline infusion sonography (SIS) is a test to determine tubal patency using fluid and ultrasound. In this procedure, under ultrasound scanning, a slow and deliberate injection of about 200 ml physiologic saline is introduced into the uterine cavity via Foley catheter number 12. An inflated bulb of the catheter prevents leakage of fluid outside uterine cavity. By visualizing the flow of saline along the tube and observing it as a shower at fimbrial end, tubal patency can be tested. Presence of free fluid in pouch of Douglas also confirms tubal patency. Although tubal patency can be observed by the appearance of fluid in the cul de sac with the saline infusion, the test does not differentiate between unilateral or bilateral patency. (36)

When tubal disease is suspected either on the basis of history of pelvic infection or because of abnormal HSG result, confirmation and assessment by laparoscopy are indicated. Laparoscopy and chromotubation with a dilute solution of methylene blue or indigo carmine (preferred) introduced via the cervix can demonstrate tubal patency or document proximal or distal tubal obstruction. The
procedure also can identify and correct tubal factors such as Fimbrial phimosis or peritubal adhesions, which may not be identified with less invasive methods such as HSG. Fluoroscopic/ hysteroscopic selective tubal cannulation will confirm or exclude any proximal tubal occlusion suggested by HSG or laparoscopy with chromotubation and provides the means for possible correction via recanalization using specialized catheter systems. (43)

HSG is obtained in all patients to look for tubal occlusion, unless laparoscopy is planned, especially in patients with secondary infertility. HSG also provides information about the uterine cavity. HSG is not useful for detecting peritubal adhesions or endometriosis. Diagnostic laparoscopy and chromotubation are required in women suspected of having endometriosis or pelvic adhesions related to a previous pelvic infection or surgery. Ablation of implants and lysis of adhesions, when indicated, can be performed during the same procedure.

A meta-analysis of 20 studies involving 4179 patients compared HSG and laparoscopy with chromotubation (the gold standard); the calculated sensitivity and specificity for diagnosis of tubal patency were only 65 and 83 percent, respectively. (59) However, when subgroups of women undergoing HSG were analyzed, HSG appeared to have very high specificity and sensitivity for diagnosing distal tubal occlusion or major distal tubal adhesions, but much lower specificity for diagnosing proximal tubal occlusion.

Diagnostic HSG also appears to have therapeutic effects. A systematic review of 12 randomized trials found that pregnancy rates were significantly higher in subfertile women who underwent tubal flushing with oil soluble media than in those who did not undergo HSG (OR 3.30, 95% CI 2.00-5.43), and that pregnancy rates
were similar whether oil or water soluble media were used (OR 1.21, 95%CI 0.95-1.54). (60)

**Chlamydia antibodies**

Chlamydia trachomatis IgG antibody testing is a simple, noninvasive test with some evidence supporting its use as a method for predicting the presence of tubal disease. Studies suggest that antibodies to Chlamydia are more predictive of infertility than an abnormal HSG. (61) A negative test is associated with <15 percent likelihood of tubal pathology and thus does not require further assessment. (62) False positives are due to cross reactivity with C. pneumoniae, do not distinguish between remote and persistent infection, and do not indicate whether infection resulted in tubal damage (62); therefore, an HSG is performed if the test results are positive. Women at high risk of tubal disease would be screened by HSG primarily.

**Hysterosalpingo-contrast sonography**

Hysterosalpingo-contrast sonography (HyCoSy) uses ultrasound to view the uterus, tubes, and adnexae before and after transcervical injection of echogenic contrast media. It is a safe, well tolerated, quick and easy method for obtaining information on tubal status, the uterine cavity, the ovaries, and the myometrium using conventional ultrasound. In comparative studies, performance has compared favorably with HSG. A meta-analysis involving over 1000 women who underwent diagnostic imaging because of tubal-related infertility found HyCoSy and HSG were 83 percent concordant for detecting tubal pathology. (63) Using laparoscopy with chromotubation as the reference standard, HyCoSy showed false occlusion in 85 tubes (10.3 percent) and false patency in 55 tubes (6.7 percent); HSG showed false occlusion in 19 tubes (12.5 percent) and false patency in 17 tubes (11.2 percent).
Tubal spasm and tubal fistula, as well as operator error, accounted for the misdiagnoses.

**Cervical factors**

Abnormalities of cervical mucus production or sperm/mucus interaction rarely are the sole or principal cause of infertility. Examination of cervical mucus may reveal gross evidence of chronic cervicitis that warrants treatment. The postcoital test (PCT), in which a specimen of cervical mucus obtained shortly before expected ovulation is examined microscopically for the presence of motile sperm within hours after intercourse, was the traditional method for diagnosis of cervical factor infertility. However, because the test is subjective, has poor reproducibility, is inconvenient to the patient, rarely changes clinical management, and does not predict inability to conceive, the PCT is no longer recommended for the evaluation of the infertile female(34, 35)

**Postcoital test**

The postcoital test has poor diagnostic potential and predictive value] that is due, in part, to the lack of consensus on a normal versus abnormal test result and to low inter- and intraobserver reproducibility. (64) In addition, interventions designed to improve cervical factor infertility have not been effective, while widely used infertility therapies, such as intrauterine insemination and IVF bypass the cervix. Thus so improving cervical factors becomes irrelevant. Importantly, a randomized trial that compared the outcome of infertility investigations with and without the postcoital test showed no difference in pregnancy rates at 24 months. Thus, incorporation of the postcoital test in standard infertility evaluations increases the number of tests and treatments, but has no effect on the pregnancy rate.
UTERINE ABNORMALITIES

Abnormalities of uterine anatomy or function are relatively uncommon causes of infertility in women, but should be excluded. Methods for evaluation of the uterus include the following: Hysterosalpingography (HSG) defines the size and shape of the uterine cavity and can reveal developmental anomalies (unicornuate, septate, bicornuate uteri) or other acquired abnormalities (endometrial polyps, submucous myoma, synechiae) having potential reproductive consequences. However, HSG has relatively low sensitivity (50%) and positive predictive value (PPV; 30%) for diagnosis of endometrial polyps and submucous myoma in asymptomatic infertile women (36). Ultrasonography (US) can be used to diagnose uterine pathology, including myoma. (37) Sonohysterography, involving transvaginal ultrasonography after introduction of saline into the uterine cavity, better defines the size and shape of the uterine cavity and has high PPV (>90%) and negative predictive value (NPV) for detection of intrauterine pathology such as endometrial polyps, submucous myoma, synechiae. (36, 38, 39) Hysteroscopy is the definitive method for the diagnosis and treatment of intrauterine pathology. As it is also the most costly and invasive method for evaluating the uterus, it generally can be reserved for further evaluation and treatment of abnormalities defined by less invasive methods such as HSG and sonohysterography. (40)

PERITONEAL FACTORS

Peritoneal factors such as endometriosis and pelvic or adnexal adhesions may cause or contribute to infertility. History and/or physical examination findings may raise suspicion but rarely are sufficient for diagnosis. Peritoneal factors also should be considered in women with otherwise unexplained infertility. Transvaginal
ultrasonography can reveal otherwise unrecognized pelvic pathology that may have reproductive implications, such as an endometrioma. (46) Laparoscopy with direct visual examination of the pelvic reproductive anatomy is the only method available for specific diagnosis of peritoneal factors that may impair fertility. However, the impact of minimal and mild endometriosis on fertility is relatively small (47, 48), and most women with significant adnexal adhesions have historical risk factors (pelvic pain, moderate or severe endometriosis, previous pelvic infection or surgery) or an abnormal HSG. Consequently, laparoscopy is most clearly indicated for those with symptoms or risk factors or an abnormal HSG or ultrasonography that have no other clear indications for ART (e.g., severe male factor infertility); its yield in asymptomatic women with normal imaging is low. Given individual circumstances, there may be a place for diagnostic laparoscopy for young women with a long period (>3 years) of infertility but no recognized abnormalities.

ROLE OF LAPAROSCOPY

The role of laparoscopy in the evaluation of infertility is controversial. Laparoscopy is invasive and expensive. Findings at laparoscopy usually do not alter the initial treatment of the infertile couple when the initial infertility evaluation is normal or when it shows severe male factor infertility. Couples with a normal infertility evaluation (i.e., unexplained infertility) typically undergo a trial of ovarian stimulation with or without intrauterine insemination and many will conceive without further intervention. Couples with tubal or male factor infertility are typically offered IVF as one of their treatment options.
No randomized trials have assessed the cost effectiveness and timing of diagnostic laparoscopy prior to ovulation induction in couples with unexplained infertility. Laparoscopy is indicated in women in whom endometriosis or pelvic adhesions/tubal disease is suspected based on physical examination, HSG, or history (e.g., current dysmenorrhea, pelvic pain, or deep dyspareunia; previous complicated appendicitis, pelvic infection, pelvic surgery, or ectopic pregnancy). When laparoscopy is planned, chromotubation to assess tubal patency and hysteroscopy to evaluate the uterine cavity are also performed.

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 for ovulation induction. Endometriosis, if identified, can be excised/ablated at the time of the diagnostic procedure and pelvic adhesions can be lysed.

A meta-analysis of 20 studies involving 4179 patients compared HSG and laparoscopy with chromotubation (the gold standard). The estimated sensitivity and specificity for diagnosis of tubal patency were only 65 and 83 percent, respectively. However, when subgroups of women undergoing HSG were analyzed, HSG appeared to have very high specificity and sensitivity for diagnosing distal tubal occlusion or major distal tubal adhesions, but much lower specificity for diagnosing proximal tubal occlusion.

Proximal tubal occlusion on HSG often represents testing artifact due to tubal spasm or poor catheter positioning leading to unilateral tubal perfusion. Given these deficiencies, findings of proximal tubal occlusion on HSG could be confirmed by a secondary test such as a repeat HSG, fluoroscopic or hysteroscopic selective tubal
perfusion, or laparoscopic chromotubation if definitive diagnosis will influence
further management.

Diagnostic HSG also appears to have therapeutic effects. A systematic review
of 12 randomized trials found that pregnancy rates were significantly higher in
subfertile women who underwent tubal flushing with oil soluble media than in those
who did not undergo HSG (OR 3.30, 95% CI 2.00-5.43), and that pregnancy rates
were similar whether oil or water soluble media were used (OR 1.21, 95%CI 0.95-
1.54)

MALE INFERTILITY

Approximately 8% to 15% of couples are unable to conceive after one year of
unprotected intercourse. A male factor is solely responsible in approximately 20% of
infertile couples and contributes in another 30% to 40% of couples. A male infertility
factor is often defined by abnormal semen parameters but may be present even when
the semen analysis is normal.

The causes of male infertility can be divided into four main areas:

- Hypothalamic pituitary disease (secondary hypogonadism) – 1 to 2 percent
- Testicular disease (primary testicular defects including Y chromosome
  microdeletions) – 30 to 40 percent
- Post-testicular defects (disorders of sperm transport) – 10 to 20 percent
- Idiopathic – 40 to 50 percent
Concurrent male and female infertility

Treatment of male infertility involves the couple. The distribution of male and female causes among infertile couples has not been well defined. In a 1982 to 1985 World Health Organization multicenter study, 20 percent of cases were attributed to male factors, 38 percent to female factors, 27 percent had causal factors identified in both partners, and 15 percent could not be satisfactorily attributed to either partner. (67)

It is therefore essential that the female partner be thoroughly investigated and treated while the male partner is being evaluated. Problems in the female partner, such as anovulation or irregular ovulation, hyperprolactinemia, endometriosis, and tubal obstruction, should be treated with medications or laparoscopic surgery simultaneously with or before treatment of the male partner. Treatment of the female partner can often compensate for male factor subfertility due to mild to moderate decreases in semen parameters, resulting in pregnancy without treatment of the male.

Causes of Male Infertility

Male infertility can be due to a variety of conditions, many, but not all, of which can be identified and treated. The condition is termed idiopathic when the cause of abnormal semen parameters cannot be identified. It is also possible for infertile men to have normal sperm counts but the sperms are qualitatively abnormal—either incapable of oocyte fertilization or possessing genetic abnormalities that adversely impact fetal development.
Indications for evaluation

Couples who fail to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse merit evaluation for infertility. The threshold for testing is reduced to six months if medical history and physical findings suggest a gross risk factor or the female partner is older than 35 years. (1) The minimum tests of the male partner of an infertile couple should include a reproductive history and analysis of at least one semen sample. Men need to be tested further if their initial evaluation is abnormal.

Reproductive History

The reproductive history should include: 1) coital frequency and timing; 2) duration of infertility and prior fertility; 3) childhood illnesses and developmental history; 4) systemic medical illnesses like diabetes mellitus; 5) previous operations; 6) medications and allergies; 7) Sexual history including sexually transmitted infections; and 8) exposures to gonadal toxins including environmental and chemical toxins and heat. A history of previous fertility does not exclude the possibility of a newly acquired, risk factor for male infertility. Evaluation for men with primary infertility (never having fathered a pregnancy) doesn’t differ from that done for secondary infertility (having previously fathered a pregnancy).

Physical Examination

All infertile men need to have their physical examination done. Particular attention should be directed to the genitalia including: (i) examination of the penis,
noting the location of the urethral meatus; (ii) palpation and measurement of the
testes; (iii) the presence and consistency of both the vasa and epididymides; (iv) the
presence or absence of a varicocele; (v) secondary sex characteristics, including body
habitus, hair distribution, and breast development.

**Semen Analysis**

Semen analysis is routinely used to evaluate the male partner in infertile
couples and to assess the reproductive toxicity of environmental or therapeutic agents.
Although widely used thresholds for normal semen measurements have been
published by the World Health Organization (WHO), (68) the available norms for
sperm concentration, motility, and morphology fail to meet rigorous clinical,
technical, and statistical standards. In recognition of these limitations, the
nomenclature in the most recent WHO manual for semen evaluation was changed
from “normal” to “reference” values. Two prospective studies (33, 69) of semen
quality and fertility concluded that the current WHO reference values should be
reconsidered.

A comparison of semen measurements between fertile and infertile men was
used in the 1950s by MacLeod and Gold. (70) In these earlier studies, however,
modern methods of semen evaluation were not used, and data were obtained from
male partners in infertile couples regardless of the fertility status of the female
partners.

Instead of a single value for each semen measurement that presumably
distinguishes between “normal” and “abnormal,” Guzick and colleagues (71)
estimated the best two values that allow for the delineation of three groups — fertile,
determinate, and subfertile. The authors argued that the classification system they
proposed is clinically meaningful and is appropriate to what they felt, biologically, was a continuous function.

In the above Guzik study, sperm parameters that predicted male fertility were a sperm concentration greater than 48 million/mL, sperm motility greater than 63%, and sperm morphology greater than 12% normal (strict criteria). Parameters that predicted male subfertility were a sperm concentration less than 13.5 million sperm/mL, sperm motility less than 32%, and sperm morphology less than 9% normal. Values between the fertile and subfertile thresholds were considered “indeterminate”. There was extensive overlap between the fertile and the infertile men within both the subfertile and the fertile ranges for all three measurements. Although each sperm parameter could predict fertility and subfertility, none was a powerful discriminator. The percentage of sperm with normal morphologic features had the greatest discriminatory power.

The authors argued that normal reference values for semen parameters do not reflect normal sperm concentration in the general population, nor do they equate with the minimum values required for conception; men with semen variables outside the reference ranges may be fertile and, conversely, men having values within the reference range still may be infertile.(71)

The semen analysis provides information on semen volume as well as sperm concentration, motility, and morphology (72)Methods for semen analysis are discussed in many textbooks, and detailed laboratory protocols have been published by the WHO. (73)The current WHO criteria for evaluating sperm morphology (73)are similar to the “strict criteria ” described by Kruger (74), in that relatively few sperm are classified as having normal morphology, even in semen obtained from fertile men.
WHO lower reference limits

The WHO has published revised lower reference limits for semen analyses. (75) The following parameters represent the generally accepted 5th percentile (lower reference limits and 95% confidence intervals in parentheses), derived from a study of over 1900 men whose partners had a time-to-pregnancy of ≤12 months. (75)

- Volume — 1.5 mL (95% CI 1.4-1.7)
- Sperm concentration — 15 million spermatozoa/mL (95% CI 12-16)
- Total sperm number — 39 million
- Spermatozoa per ejaculate (95% CI 33-46)
- Morphology — 4 % normal forms (95% CI 3-4), using "strict" Tygerberg method
- Vitality — 58 % live (95% CI 55-63)
- Progressive motility — 32 % (95% CI 31-34)
- Total (progressive + nonprogressive motility) — 40 % (95% CI 38-42)

Semen volume

The mean semen volume in the WHO study was 3.7 mL; the lower reference limit was 1.5 mL. (75) A low volume in the presence of azoospermia (no sperm) or severe oligozoospermia (severely subnormal sperm concentration) suggests genital tract obstruction, (e.g.; congenital absence of the vas deferens and seminal vesicles or ejaculatory duct obstruction). Congenital absence of vas deferens is diagnosed by physical examination and low semen pH, whereas ejaculatory duct obstruction is diagnosed by the finding of dilated seminal vesicles on transrectal ultrasonography.
Sperm concentration

The lower reference limit for sperm concentration is 15 million/mL (95% CI 12-16). (75) However, some men with sperm counts considered to be low can be fertile, while others above the lower limit of normal can be subfertile (69, 71) and, for the purposes of fertilization in vitro, 10 million/mL or even less can be satisfactory. (76)

If no spermatozoa are seen, the semen should be centrifuged and the pellet examined for the presence of spermatozoa before the diagnosis of azoospermia is given. The presence of any sperm in the pellet will allow intracytoplasmic sperm injection (ICSI) to be performed with ejaculated spermatozoa instead of sperm collected by testicular aspiration.

Sperm motility

Sperm motility is assessed microscopically and is classified as progressive motility, non-progressive motility, and immotile spermatozoa. At least 40% of spermatozoa should be motile and at least 32% should have progressive motility.

Sperm morphology

The criteria for normal morphology were previously based mainly on shape, as observed microscopically. They now also include length, width, width ratio, area occupied by the acrosome, and neck and tail defects (74, 75) These criteria are called "strict" criteria and have good predictive value in terms of fertilization in vitro and pregnancy rates after in vitro fertilization (IVF). (74) Based upon these correlations between "strict criteria" sperm morphology and IVF pregnancy rate, the lower limit of normal sperm morphology was estimated to be about 4% of spermatozoa. (75)
**Prediction of fertility**

The standard semen analysis provides descriptive data, which do not always distinguish fertile from infertile men. In one prospective data of 430 couples, among those with a sperm concentration $\geq 40 \times 10^6$/mL, 65% achieved pregnancy, compared with 51% of those with lower sperm concentrations (69). In a study of male partners in 765 infertile couples in which the female partners had normal infertility workup and in 696 control fertile couples recruited from prenatal classes. (71)

- There was extensive overlap between fertile and infertile men in sperm concentration, motility, and morphology.

- The subfertile ranges were a concentration less than 13.5 million/mL, less than 32% motility, and less than 9% normal morphology using "strict criteria."

- The fertile ranges included sperm concentration greater than 48 million/mL, greater than 63% motility, and greater than 12% normal morphology.

- Values in between these ranges were not useful in discriminating fertile from infertile couples (termed intermediate by the authors). The likelihood of infertility generally increased with decrease in any of the three parameters.

- The percentage of sperm with normal morphology had the greatest discriminatory power. It should be noted that none of the semen parameters was a powerful discriminator although each of these helped to distinguish between fertile and infertile men.

Lack of sperm in the ejaculate does not indicate the absence of testicular sperm production; these patients should be evaluated for retrograde ejaculation, congenital absence of the vas deferens, and other causes of obstructive azoospermia.
Other procedures and tests for assessing male infertility

Endocrine Evaluation

Hormonal abnormalities of the hypothalamic-pituitary-testicular axis are well-recognized, but uncommon, causes of male infertility. Endocrine disorders are extremely uncommon in men with normal semen parameters. Men need endocrine evaluation if their semen parameters are abnormal, especially (i) if the sperm concentration is < 10 million/mL; (ii) they have impaired sexual function; or (iii) the physical signs suggest a specific endocrinopathy. Opinions are divided on the merits of ordering endocrine evaluation for all infertile men. The minimum initial hormonal evaluation should include measurement of serum follicle-stimulating-hormone (FSH) and total testosterone concentrations. When the total testosterone level is low (< 300 ng/mL), a more extensive evaluation is indicated and should include a second measurement of total testosterone and measurements of serum free testosterone, luteinizing hormone (LH), and prolactin. Serum gonadotropin concentrations vary because they are secreted in pulses. Yet a single measurement usually is enough to detect the clinical endocrine status. The relationships among serum testosterone, LH, FSH, and prolactin concentrations help to provide an understanding of the source of abnormal total testosterone levels. A markedly raised serum FSH concentration indicates an abnormality in spermatogenesis. Hypothyroidism should also be ruled out in infertile men by measurement of the thyroid-stimulating hormone (TSH) concentration. Evidence is emerging that serum inhibin B concentration might impact infertility evaluation of infertile men with low sperm counts much better than FSH. (77)
Ultrasonography

Because nearly the entire male genital tract can be imaged easily and accurately, ultrasonography is a useful tool for detecting abnormalities of the male genital tract that may adversely affect fertility. However, ultrasonography is only indicated for a minority of infertile male patients.

Basal hormone levels in various clinical states.

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>FSH</th>
<th>LH</th>
<th>Sterone</th>
<th>prolactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal spermatogenesis</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal spermatogenesis</td>
<td>High/normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>hypergonadotropic hypogonadism</td>
<td>High</td>
<td>High</td>
<td>Normal/low</td>
<td>Normal</td>
</tr>
<tr>
<td>Prolactin-secreting pituitary tumor</td>
<td>Normal/low</td>
<td>Normal/low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Many men with abnormal spermatogenesis have a normal serum FSH, but a marked elevation of serum FSH is clearly indicative of an abnormality in spermatogenesis.

**Scrotal ultrasonography**

Scrotal pathology, such as varicoceles, spermatoceles, absent vasa, epididymal induration, and testicular masses can be identified by ultrasonography. Scrotal ultrasonography can identify clinically elusive varicoceles, but detection of such lesions has not resulted in better outcomes. (78) Scrotal ultrasonography can be helpful for better defining non-specific physical signs or abnormalities (including masses) and can be performed in men having testes located in the upper scrotum, a small scrotal sac, or other anatomy that hinders physical examination.

**Specialized Clinical Tests on Semen and Sperm**

In some cases, semen analyses have failed to predict fertility accurately, spurring a search for other methods that might improve the diagnostic evaluation of the infertile male. Generally, such specialized clinical tests should be reserved for circumstances where results clearly will help to direct treatment.

**Tests for Anti-sperm Antibodies**

Anti-sperm antibodies (ASA) are a rare cause of male subfertility that do not require routine testing and are typically treated with ICSI. Testing for ASA has traditionally been done when the semen analysis indicates isolated asthenospemia (with normal sperm concentration) or sperm agglutination. Risk factors for ASA formation include trauma, torsion, biopsy, orchitis, testicular cancer, and vasectomy. One recent study has suggested that detection of serum ASA correlates with the presence of spermatogenesis in men with azoospermia and can obviate the need for diagnostic testicular biopsy to help determine whether obstruction is present. Men with azoospermia and ASA are likely to have reproductive tract obstruction.(79)
Sperm DNA Fragmentation Tests

For an embryo to develop normally, it is important that the DNA is normal. The term “DNA fragmentation” refers to denatured or damaged sperm DNA that cannot be repaired. Sperm DNA can get damaged because of intrinsic factors, such as protamine deficiency and mutations affecting DNA compaction, or from extrinsic factors such as heat, radiation, and gonadotoxins.

Genetic Screening

Genetic abnormalities can cause infertility by affecting sperm production or sperm transport. Men with non-obstructive azoospermia and severe oligospermia (< 5 million/mL) are at increased risk for having a genetic abnormality compared to fertile men. (80)The most common genetic abnormalities found in such men are numerical and structural chromosomal aberrations that impair testicular function, and Y-chromosome microdeletions that are associated with isolated defects in spermatogenesis.

Karyotypic chromosomal abnormalities

Infertile men are more likely to have chromosomal abnormalities – more so if their sperm count is low. About 10% – 15% azoospermic men, about 5% men with severe oligospermia (< 5 million/mL), and < 1% men with normal sperm concentrations (81) are likely to have chromosomal abnormalities. Klinefelter syndrome- characterized by 47, XXY chromosomes–occurs in about two-thirds of all chromosomal abnormalities observed in infertile men. Inversions and balanced translocations – other structural autosomal abnormalities, have also a higher prevalence in infertile men than in the general population. Men with gross karyotypic abnormality are also likely to breed babies that often die in utero or are born with
chromosomal and congenital defects. Therefore, men with non-obstructive azoospermia or severe oligospermia need to be screened with a high-resolution karyotype before using their sperm to perform ICSI.

**Y-chromosome microdeletions**

Men with severely impaired spermatogenesis are more likely to have microdeletions of clinically relevant regions of the Y chromosome (7% of infertile men vs. 2% of normal men). The proportion of men with Y-chromosome microdeletions increases to 16% in men with azoospermia or severe oligospermia (82). Such microdeletions are too small to be detected by standard karyotyping, but can be detected by polymerase chain reaction techniques.

**UNEXPLAINED INFERTILITY**

It is relatively simple to identify the cause of infertility in women with ovulatory disorders or tubal disease, and in men with semen abnormalities. These categories account for the source of infertility in approximately 75% of couples. Infertility in the remaining 25% of couples is due to endometriosis (8%), miscellaneous factors like cervical factor, immunological factor, uterine synechiae (2%), or is unexplained (15%).

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 and older. (83)Both members of the couple as well as the managing physician are frustrated and plagued by feelings of inadequacy when no positive findings can be identified during the course of an
infertility evaluation. This situation obviously requires of the physician a combination of delicacy, patience, and considerable attention to each detail of the evaluation which has just been completed.

Researchers estimate that after proper and comprehensive investigation, no cause will be identified for infertility in 10% to 20% of infertile couples. (41) Lunenfeld and Insler (84) reported that among 6549 infertile couple the prevalence of unexplained infertility ranged from 3.5% to 22%. The large variation in the prevalence of unexplained infertility could be explained on the basis of lack of standardized protocols used in the different studies for investigation of mechanical factor (tubal and uterine disorders), and specifically in the decision to perform or not to perform laparoscopy. Also, the spectrum of couples seeking healthcare for infertility related issues also shapes the prevalence of unexplained infertility. For example, a fifth of couples investigated for infertility in a 2011 study from Israel (30) had unexplained infertility - laparoscopy was sparingly used in this study.

**Possible etiologies**

Several possibilities have been proposed to explain why some couples fail to conceive in the absence of an identifiable cause. Subtle changes in follicle development, ovulation, and the luteal phase have been reported in some of these women. (83, 85-88) In other couples, the male partner's semen analysis shows sperm concentration and motility at the lower end of the normal range. Implantation failure, subtle cervical factors, or problems with sperm and egg transport or interaction are other possibilities. Many cases of unexplained infertility are probably caused by the presence of multiple factors (e.g. female partner over 35 years of age and male partner...
with low normal semen parameters), each of which on their own do not significantly reduce fertility, but can reduce the pregnancy rate when combined.

Couples with unexplained infertility who are treated with IVF demonstrate reduced oocyte fertilization and embryo cleavage rates compared to couples in whom tubal factor is the cause of the infertility, although the rates of live birth per transfer are equivalent for both groups. This was illustrated in a study that showed that the oocyte fertilization and the embryo cleavage rate for unexplained and tubal factor infertility were 52 and 60%, respectively. (89) Couples with unexplained infertility also had a higher rate of complete fertilization failure when treated with IVF than couples with tubal factor infertility (6 versus 3%). These results suggest that couples with unexplained infertility probably have subtle functional abnormalities in oocyte and/or sperm function. In this sense, IVF is also a diagnostic procedure.

Oligoovulation unrelated to ovarian failure can usually be treated successfully with ovulation induction; these women achieve fecundity equivalent to that of normal couples (i.e., 15 to 25% probability of achieving a pregnancy in one menstrual cycle). (90) However, normal fecundity is achieved at the expense of an increased risk of multiple pregnancies.

**THE POLYCYSTIC OVARY SYNDROME (PCOS) AND INFERTILITY**

In 1935, Stein and Leventhal (91) described several women presenting with oligo/amenorrhoea combined with the presence of bilateral polycystic ovaries (PCOS) established during surgery. Three of these seven women also presented with obesity, while five showed signs of hirsutism. Only one woman was both obese and
had hirsutism. These findings imply that in case PCOS is diagnosed by morphology in women with oligo/anovulation, not all the features which are believed to be associated with PCOS need to be present. Likewise, with the use of transvaginal ultrasonography it has become evident that all women with oligo/amenorrhoea, obesity and hirsutism do not have the typical PCO morphology.

PCOS is a common disorder of chronically abnormal ovarian function and hyperandrogenism, which affects 5–10% of women of reproductive age. It has significant and diverse clinical implications including reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, adverse cardiovascular risk profiles) and psychological features (increased anxiety, depression and worsened quality of life). The key features of the disorder include abnormal gonadotropin dynamics, excessive androgen production, insulin resistance (IR) and alteration in beta cell function. (92)

Diagnostic criteria for PCOS have been subject of lengthy debates among clinicians. (93) At present there are two main definitions for polycystic ovary syndrome, which are the topics of intense debate. The 1990 National Institutes of Health (NIH) criteria require the presence of chronic anovulation plus clinical or biochemical signs of hyperandrogenism, whereas the 2003 Rotterdam criteria require the presence of two or more of: chronic anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries. The definition has raised controversial and unresolved issues that have implications for clinical diagnosis. Specialty groups still tend to differ in their use of diagnostic criteria and diagnostic work up, as well in their choice of first- and second-line treatment. (94) At the US National Institutes of Health Conference in 1990, three key features of PCOS were generally agreed upon; oligomenorrhoea, hyperandrogenism (clinical or laboratory evidence), and the
absence of other endocrine disorders (congenital adrenal hyperplasia, hyperprolactinaemia, thyroid dysfunction, and androgen-secreting tumors). The presence of polycystic ovaries, as shown by ultrasonography, was not included in the definition. In contrast, it was consented during the 2003 Rotterdam consensus workshop that PCOS should be considered a syndrome of ovarian dysfunction, with features of hyperandrogenism and PCO morphology. (95) Taking the heterogeneity of the syndrome into consideration, none of the criteria was considered absolutely required for the diagnosis. The new criteria broaden rather than replace the previous NIH criteria for PCOS diagnosis. Under the new criteria, the prevalence of PCOS among the general female population could well rise up to 10%. According to the Rotterdam consensus criteria, additional PCOS phenotypes include PCO and hyperandrogenism in women with normal menstrual cycles and especially women presenting with PCO and anovulation without androgen excess. Increased body weight has been one of the features for the diagnosis of PCOS in the classical description by Stein and Leventhal. Among diagnosed PCOS cases today, indeed, obesity with body mass index (BMI) > 27 kg/m² is very common. It is stated that some 50% of women with PCOS are obese. Increased body weight in PCOS is often due to increased visceral fat, i.e. central obesity, characterized by increased waist-to-hip ratio or waist circumference.

Rotterdam criteria — Although there are several proposed diagnostic criteria for polycystic ovary syndrome (PCOS), 2012 National Institutes of Health Workshop recommendations suggest that the Rotterdam 2003 criteria be used for now. Using these criteria, two out of three of the following are required to make the diagnosis of PCOS:

- Oligo- and/or anovulation
Clinical and/or biochemical signs of hyperandrogenism

Polycystic ovaries (by ultrasound)

In addition, other conditions that mimic PCOS must be excluded (e.g. disorders that cause oligo/anovulation and/or hyperandrogenism, such as thyroid disease, nonclassic congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting tumors).

The ultrasound criteria for polycystic ovaries (PCO) have evolved since the first ultrasound description of PCO in 1986. The current Rotterdam criteria, considered to have sufficient specificity and sensitivity to define PCO, include the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL; calculated using the formula 0.5 x length x width x thickness). One ovary fitting this definition is sufficient to define PCOS.

It was suggested that the earlier criteria of follicle distribution, increase in stromal echogenicity, and ovarian volume be eliminated as diagnostic criteria. (3) The transvaginal rather than trans- abdominal approach should be used when performing the ultrasound. The current Rotterdam ultrasound criteria for the diagnosis of polycystic ovaries are precise, but often loosely applied.

Other proposed criteria

The NIH criteria allow for a clinical diagnosis without the use of an imaging study. In addition, the NIH criteria require the presence of irregular menses, while the other criteria do not. In contrast to the Rotterdam criteria, the Androgen Excess PCOS task force agreed that there were insufficient data to define women with ovulatory
dysfunction and polycystic ovaries, but no evidence of hyperandrogenism, as having PCOS.

The use of multiple classification systems creates confusion for clinicians and patients. A summary report from the National Institutes of Health Evidence-based Methodology Workshop on PCOS in December 2012 concluded that the Rotterdam criteria should be adopted for now because it is the most inclusive. (96) They also suggested that the name “PCOS” be changed because it focuses on polycystic ovarian morphology which is neither sufficient nor necessary for the diagnosis.

The diagnosis of polycystic ovary syndrome is confirmed once other disorders have been ruled out biochemically. If the patient has both oligoovulation and hyperandrogenism, a transvaginal ultrasound to document polycystic ovaries is not necessary.

PCOS is an important cause of both menstrual irregularity and androgen excess in women. When fully expressed (hirsutism, irregular menstrual cycles, obesity, and a classic ovarian morphology on transvaginal ultrasound), PCOS can be readily diagnosed. However, there has been considerable controversy about specific diagnostic criteria when not all of these classic features are evident.

The prevalence of polycystic ovary syndrome, as defined by the 1990 NIH criteria in unselected population of women of reproductive age is between 6.5 and 8%. Adoption of the Rotterdam criteria for the diagnosis of this disorder will increase the prevalence of polycystic ovary syndrome because the scope for inclusion is broader than it is with the 1990 NIH criteria. In a study of women with normogonadotrophic anovulatory infertility (WHO Class 2), the prevalence of PCOS
was 1.5 fold higher when defined by the Rotterdam criteria than when defined by the 1990 NIH criteria. (97)

About 6.2% of 129 white and 3.4% of 145 black women have PCOS. In a 2013 community based study from China (15,924 women), the prevalence of PCOS was 5.6% (894/15,924). PCOS tended to occur in younger women (P < 0.05) who had menstrual problems, hyperandrogenism, and higher probability of infertility, metabolic syndrome and insulin resistance. (98) Its prevalence depends in part upon the diagnostic criteria used to define the disorder. (99) As an example, in a report of 827 women with World Health Organization class II oligoovulation (euestrogenic normogonadotropic ovulatory dysfunction), 456 (55 %) were classified as having PCOS by the NIH 1990 criteria (irregular menses, biochemical and/or clinical hyperandrogenism, and other causes of hyperandrogenism excluded). In contrast, 754 (91 %) women were considered to have PCOS using the Rotterdam 2003 criteria (which requires two out of three of the following: oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (by ultrasound). (97)

PCOS can be defined in a number of ways. Histopathologically (i.e. by the presence of polycystic ovaries upon oophorectomy or wedge resection) between 1.4–3.5% of unselected women and 0.6–4.3% of infertile women demonstrate evidence of PCOS. (100) Defined by the ultrasonographic appearance of polycystic ovaries, 21–23% of unselected women appear to be affected. (101-103). However, this is probably an over-estimation, because ultrasonographic diagnosis of PCOS lacks specificity. Up to 25% of patients assigned a diagnosis of PCOS by ultrasonography may be entirely asymptomatic(104), and not all patients with hyperandrogenemia demonstrate
polycystic ovaries (101, 104-106) even when using the more sophisticated computerized measurements of ovarian stroma. (107)

Hirsutism is defined as excess terminal (thick, pigmented) body hair in a male distribution pattern, and is commonly noted on the upper lip, chin, around the nipples (periareolar), and along the linea alba of the lower abdomen. Adolescent hyperandrogenemia is considered to be an early manifestation of adult PCOS, and clinical manifestations of PCOS often have a peripubertal onset. Two studies of peripubertal girls suggest that obesity contributes to the hyperandrogenemia, as increasing body mass index (BMI) was associated with increases in serum total testosterone, free testosterone, and DHEA-S concentrations.

Screening women for hirsutism in a clinical setting has traditionally involved a full body examination, which many patients and practitioners consider invasive. Knochenhauer et al. (97) chose to look only at the chin and lower abdomen as predictors for total body hirsutism, which was based on the investigators’ clinical experiences. Examination of only the chin and abdomen is a simple and reliable screening method for detecting hirsutism. Furthermore, reducing the number of body areas assessed may increase the willingness of study participants or patients to be evaluated. By simplifying the method of evaluation and by reducing the number of body areas evaluated, the potential for error and for inter-observer variability may be lowered.

The prevalence of hirsutism (detected by modified F.G. score) in women with PCOS varies considerably: 27% (89), 73% (98); 65-75% of white, black and south-east Asian women (79, 99); 91% (100); 91% (101). The prevalence of hirsutism in PCOS varies by ethnicity: Japanese women with PCOS are less likely to be hirsute compared to Hispanic and Italian women living in the United States and South Asian
women living in the United Kingdom are more likely to be hirsute compared with PCOS women of European descent. (22)

Depending upon the androgen measured and the technique employed, between 50 and 90 % of PCOS women have elevated serum androgen levels. Although serum free testosterone may be the more sensitive test for the presence of hyperandrogenic disorders (79), currently available direct assays lack enough accuracy to justify its routine use for evaluation of PCOS. In one report of 1000 consecutive women with androgen excess, most of whom had PCOS, 78 % had high serum androgens. (102) Total testosterone, free testosterone, and DHEAS concentrations were elevated in 38, 55.5, and 40 %, respectively. Among women with PCOS, DHEAS is increased in about 16 % of women who have normal total and free testosterone levels. A mildly elevated level in the setting of normal free testosterone is unlikely to affect management. Some hyperandrogenic women have mildly elevated serum prolactin levels, but the significance is uncertain. Levels of prolactin in excess of 40 mg/dL should prompt for evaluation of other causes.

Some groups recommend measuring free testosterone instead of or in addition to total testosterone, because it is the most sensitive test to establish the presence of hyperandrogenemia. However, commercially available free testosterone assays are often unreliable. If measured, it should be done in a reliable endocrine lab. Another option is to order free testosterone from a commercial laboratory that calculates it from total testosterone and sex hormone binding globulin (SHBG) measurements using a formula demonstrated to give results that agree closely with those of equilibrium dialysis.
ENDOMETRIOSIS AND INFERTILITY

Endometriosis, a major contributor to pelvic pain and subfertility, (1) is characterized by endometrial-like tissue outside the uterus, primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the diaphragm, pleura, and pericardium. Endometriosis affects 6 to 10% of women of reproductive age, 50 to 60% of women and teenage girls with pelvic pain, and up to 50% of women with infertility. (108,109) Peritoneal disease, is dependent on estrogen for growth, derived from retrograde menstruation of steroid hormone–sensitive endometrial cells and tissues which implant on peritoneal surfaces and elicit an inflammatory response. This response is accompanied by angiogenesis, adhesions, fibrosis, scarring, neuronal infiltration, and anatomical distortion, resulting in pain and infertility. (110)

Endometriosis, defined as the presence of endometrial-like tissue outside the uterus, induces a chronic, inflammatory reaction. Endometriosis commonly affects the pelvic organs and peritoneum and is found in 5% to 10% of infertile women. Younger women with mild endometriosis spontaneously conceive at a rate of 2% to 3% per month, far below the healthy monthly rate of 20%. (111)

Studies suggest that 25% to 50% of infertile women have endometriosis and that 30 to 50% of the women with endometriosis are infertile. Infertile women are 6 to 8 times more likely to have endometriosis than fertile women. (112) Apparent risk factors for endometriosis include a low body mass index, alcohol and smoking. Although endometriosis is known to be associated with infertility, the cause and effect relationship has not been established. Endometriosis can result in adhesions or distorted pelvic anatomy that precludes fertility. Women with endometriosis can have an increased volume of peritoneal fluid as well as increased peritoneal fluid.
concentrations of prostaglandins and cytokines produced by macrophages, which can result in systemic inflammation. These alterations may have adverse effects on oocyte, sperm, embryo or fallopian tube function. (112)

Implants of endometriosis cause inflammation and bleeding and lead to Fallopian tube blockage or development of severe pelvic adhesions. Pelvic surgeries, even when meticulously performed, can lead to pelvic adhesions. Women with endometriosis may also have endocrine and ovulatory disorders, including luteal phase dysfunction, abnormal follicular growth as well as premature LH surge. (113) In addition, endometriosis can also cause impaired implantation.

Up to 50% of women with endometriosis are infertile, and agreement about treatment options has been difficult to establish. The association between endometriosis and infertility is derived from comparisons of fertile and infertile women, animal models, donor sperm studies, and in vitro fertilization results. Although medical management of endometriosis-associated infertility has not been proven outside of in vitro fertilization, surgical ablation or resection, is cost-effective and offers the potential for improvement in cycle fecundity. (114)

African and Asian women are less likely than Caucasian women to have endometriosis (odds ratio, 0.6 (95% CI, 0.4-0.9). (115) These women were older (mean age, 31); heavier (mean BMI 23.1 kg/m²) and had higher LH concentration compared to those who did not have endometriosis (median [IQR]): (16.7[13.1-36.2] vs. 7.8 [3.8-11.4]). (116)

Pelvic pathology, by laparoscopic evaluation, accounted for 27% causes of infertility in a study Jayakrishnan et al. (117) Nayak et al in a 2013 study of 300 patients (118) reported 30% incidence of pelvic pathology. In addition, the most
common laparoscopic abnormality was endometriosis (14%) and adnexal adhesion (12%) in primary and secondary infertile patients, respectively. In contrast to the Study by Godinjak et al. (119) Nayak and colleagues reported equal prevalence of tubal block in women with primary and secondary infertility.

Follow-up of women with pelvic pain and laparoscopically identified disease has shown that 17 to 29% of lesions resolve spontaneously, 24 to 64% progress, and 9 to 59% are stable over a 12-month period. (13)

Currently, the definitive method to diagnose and stage endometriosis and evaluate the recurrence of disease after treatment is visualization at surgery. The revised scoring system of the American Society for Reproductive Medicine is used to determine the disease stage (ranging from I, indicating minimal disease, to IV, indicating severe disease) on the basis of the type, location, appearance, and depth of invasion of the lesions and the extent of disease and adhesions. Nonsurgical diagnostic approaches such as transvaginal ultrasonography and magnetic resonance imaging (MRI) perform poorly in the detection of peritoneal and ovarian implants and adhesions. However, both imaging methods perform well in detecting ovarian endometriomas, with ranges of 80 to 90% sensitivity and 60 to 98% specificity (120)

A large meta-analysis of randomized trials evaluating ovarian suppression with combined oral contraceptives, GnRH agonists, medroxyprogesterone acetate, or Danazol as compared with placebo or no treatment in women with various stages of endometriosis showed no significant differences in spontaneous pregnancy or live birth rates. Thus, these agents are not recommended for the treatment of infertility and should not delay the pursuit of effective fertility therapies.(121)
Gonadotropin therapy and intrauterine insemination, as well as IVF, are efficacious treatments in women with infertility and endometriosis. In a large randomized trial comparing four treatment strategies in 932 couples with stage I or II endometriosis or unexplained infertility, cumulative pregnancy rates during four treatment cycles were as follows: intracervical insemination (10%), intrauterine insemination (18%), gonadotropin therapy and intracervical insemination (19%), and gonadotropin therapy and intrauterine insemination (33%). A meta-analysis of 14 randomized, controlled trials showed that women with endometriosis were less likely than women with tubal-factor infertility to conceive by means of IVF (odds ratio, 0.81; 95% CI, 0.72 to 0.91).

In a systematic review of three randomized trials including 165 women with advanced endometriosis and infertility, GnRH agonist therapy for 3 to 6 months before IVF, as compared to no treatment before this procedure, significantly increased the live birth rate (odds ratio, 9.19; 95% CI, 1.08 to 78.22).

Ablation of endometriotic lesions with lysis of adhesions is recommended for the treatment of infertility related to stage I or II endometriosis.