CHAPTER

20

Female Subfertility

DEFINITIONS

- **Fecundability:** probability of conception during a single menstrual cycle
  - Normal → 20%

Table 20-1 Ballpark Estimates of Overall Chances of a Live Birth Based on Duration of Attempting to Conceive

First Month	6 mo	1 y	2 y
1/5	1/10	1/20	1/40
20%	**10%**	**5%**	**<1%**

- **Fecundity:** probability of achieving a live birth within a given time frame, such as a month; declines with female age and time attempting conception

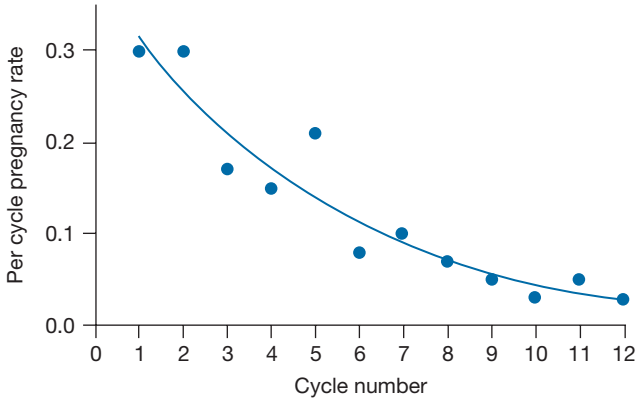

Figure 20-1 Fecundability among a cohort of healthy couples.
Source: Reprinted from Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. *Fertil Steril*. 1996;65(3):503-509, with permission from Elsevier.

- **Infertility**
  - **Less than 35-year-old female:** failure to conceive after 1 year of regular, unprotected intercourse OR due to an impairment of a person's capacity to reproduce either as an individual or with their partner[1]
  - **Greater than or equal to 35-year-old female:** failure to conceive after 6 months of regular, unprotected intercourse
  - **Greater than 40-year-old female:** Evaluation and treatment may be warranted immediately.
  - Incidence of infertility approximately 1/10 US women aged 15 to 49 years[2]

NORMAL REPRODUCTION

- Approximately 50% of healthy women become clinically pregnant during the first two cycles, and between 80% and 90% during the first 6 months.[3,4]
- "Fertile window": 6 days leading up to and including the day of ovulation,[5] with peak fertility starting approximately 2 days prior to ovulation (Figure 20-1)

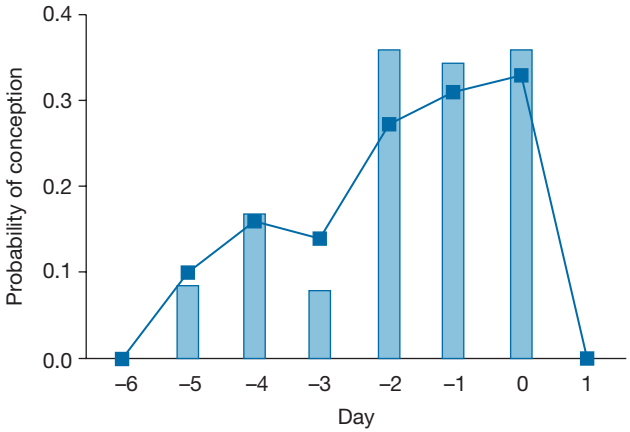

Figure 20-2 Probability of conception by day of intercourse relative to ovulation. "O" signifies the day of ovulation.

Source: Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med.* 1995;333:1517-1521.

- Best fertility rates when intercourse occurs every 1 to 2 days during fertile window.[5]
  - Shorter abstinence periods (even daily ejaculation) do not seem to affect sperm parameters.
  - Abstinence less than 1 day may decrease sperm DNA fragmentation.
  - Abstinence more than 5 days may ↓ counts.
  - Abstinence 10 days or more may ↓ all sperm parameters
- Many lubricants, olive oil, and saliva affect sperm function; hydroxyethylcellulose-based lubricants, mineral oil, and canola oil are okay.[5]

- Oviduct[6]:
  - Progressive ↓ in the proportion of ciliated cells from the fimbria (>50%) to the isthmus (<35%).
  - The strokes of cilia are synchronized and oriented toward the uterine cavity at the time of ovulation.
  - The tubal epithelium is the likely site for sperm storage.
  - Density of sperm: isthmus > ampulla
  - Postovulation, the oocyte takes approximately 8 hours to reach the ampullary-isthmic junction (site of fertilization); the embryo remains in the tube a further 72 hours.
- At coitus, millions of sperm are deposited into the anterior vagina with the first anatomical barrier being the cervix, where spermatozoa with poor morphology and motility are filtered out when they stick to the cervical mucus. The second anatomical barrier is at the uterotubal junction. Finally, only a few thousand sperm enter the oviduct, and less than 100 sperm reach the site of fertilization. As soon as they enter the oviduct, they form a sperm, maintaining fertilizing capacity for several days.[7]
- **Sperm populate the oviduct within 5 minutes of coitus**; there is a constant level of sperm in the oviduct from 15 to 45 minutes following deposition of sperm in the proximal vagina.[8]
  - Following intrauterine insemination (IUI), it takes approximately 30 seconds for sperm to reach the oviduct.[9]
- **Sperm** survive in vaginal secretions up to 1.5 days and **in cervical mucus up to 4 days after coitus.**[8]

MONITORING OVULATION (FIGURE 20-3)

- Basal body temperature (BBT) chart: normal → biphasic, 12- to 14-day luteal phase[10]
  - The BBT thermal shift occurs **after ovulation** in response to ↑ progesterone (P_4) production; therefore, it is not very effective for timing coitus.
  - **Luteinizing hormone (LH) urine detection/ovulation predictor kits (OPKs)**
    - **LH stimulates resumption of meiosis (germinal vesicle [GV] → meiosis II [MII]).**
    - The rise in **serum** LH begins approximately 36 hours before ovulation.
    - The LH surge appears in **urine** approximately 12 hours after it appears in serum.
    - Therefore, **a positive urine LH kit occurs approximately 24 hours (95% confidence interval [CI], 14-26 hours) before ovulation.**[11]
      → Note: **Ovulation occurs approximately 36 hours after human chorionic gonadotropin (hCG) exogenous administration.**
    - Despite an OPK-positive LH surge, 7% of women may actually be anovulatory.[12]
    - False-negative results can occur if peak LH less than 40 IU/I; may occur in up to 35% of ovulatory cycles.[13]
  - **Fertility monitors** assess LH, estrogen, and P_4 levels.
  - Serum P_4: midluteal (7-8 days post-LH surge or 7 days before expected menses)[10]
    - **Greater than 3 ng/mL =** ovulatory
    - No reliable measure of "adequate" P_4 levels given the pulsatile nature

- Endometrial biopsy (not used): not valid to detect ovulation[14]
- Postcoital test (not used): poor validity, lack of standard methodology, and unknown reproducibility[15]

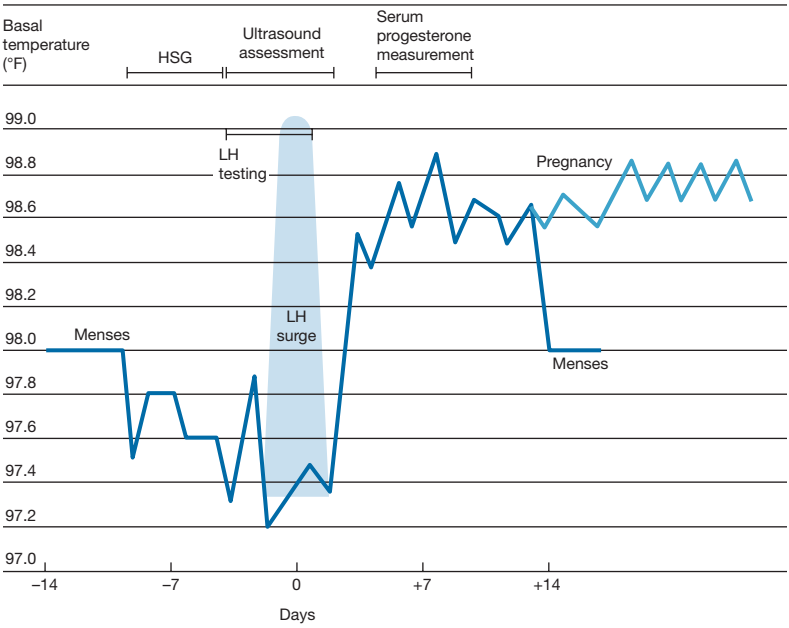

Figure 20-3 Ovulation monitoring.
HSG, hysterosalpingogram; LH, luteinizing hormone.
Source: Taylor HS, Fritz MA, Pal L, Seli E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th ed. Wolters Kluwer; 2020. Figure 25.4.

- **Lifestyle and fertility**[5]
  - No convincing data that a particular diet affects fertility beyond weight loss for overweight and obese
  - Smoking increases the risk of infertility, ectopic pregnancy, and miscarriage and decreases ovarian reserve and age at menopause.
  - Moderate alcohol and caffeine intake probably okay; role of cannabis unclear
  - Marijuana has a negative effect on fertility.
    - Women who use marijuana could have a more difficult time conceiving a child than women who do not use marijuana.[16]
    - Women smoking marijuana have fewer oocytes retrieved with in vitro fertilization (IVF).[17]
    - Marijuana smokers had more than double the adjusted probability of pregnancy loss than those who were past marijuana smokers or had never smoked marijuana.[18]
    - In men, consuming cannabis several times a week for 5 years caused a reduction in the volume and number of spermatozoa and changes in morphology and motility, with sperm hyperactivity and reduction in their fertilization capacity.[19]
  - Vaping may have a negative effect on fertility.

ETIOLOGY OF INFERTILITY

Table 20-2 Causes of Female Infertility

Cause of Infertility	%
Female factors (single)	
Tubal factor	40
Ovulatory dysfunction	40
Unexplained infertility	10
Unusual problems	10

Male factor in 35% of infertile couples.

Source: From Taylor HS, Fritz MA, Pal L, Seli E. *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th ed. Wolters Kluwer; 2020.

MATERNAL AGE

Fertility decreases with maternal age (Figure 20-4).

Table 20-3 Prevalence of Subfertile Women Based on Age

Age	Subfertile (%)
19-26 y old	8
27-34 y old	14
35-39 y old	18

Source: From Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Obstet Gynecol*. 2004;103(1):51-56.

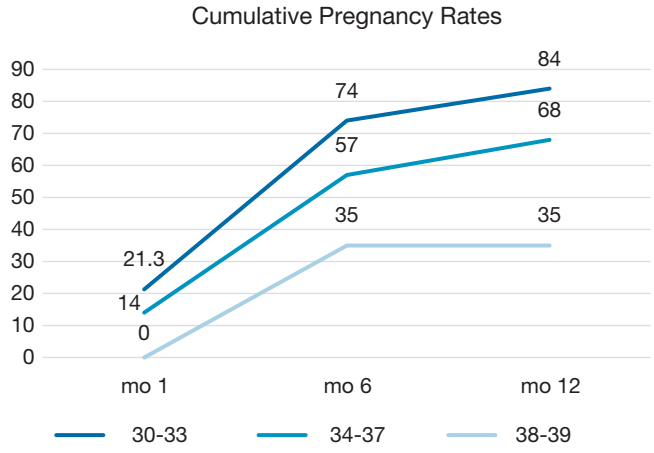

Figure 20-4 Effect of age on natural cumulative pregnancy rates.

Source: From Steiner AZ, Jukic AM. Impact of female age and nulligravidity on fecundity in an older reproductive age cohort. *Fertil Steril*. 2016;105(6):1584-1588.e1, with permission from Elsevier.

EVALUATION OF THE INFERTILE FEMALE[10]

- Evaluation is warranted in women meeting the abovementioned definition of infertility.
- Earlier evaluation and treatment should be considered in:
  - Women aged 35 years or above (should be evaluated after 6 months due to more rapid decline in fertility with age)
  - Irregular or absent menses
  - Concern for uterine, tubal, or peritoneal disease
  - Stage 3 to 4 endometriosis
  - Concern for male subfertility
  - Women planning sperm donation

Coital History

- Coital frequency
- Sexual dysfunction in either partner
- Dyspareunia may suggest salpingitis or endometriosis.
- Months of unprotected heterosexual intercourse, if applicable

Menstrual History

- Age at menarche
- Length/regularity of cycles: normal = 21 to 35 days
- Dysmenorrhea: Severe may be indicative of endometriosis or adenomyosis.
- Molimina: Breast tenderness, bloating, mood changes, fatigue, mild headaches, and/or sleep disturbances prior to menstruation suggestive of ovulatory cycles
- Day of +OPK or other markers of ovulation

Obstetric History

- Number of pregnancies with the outcome of each
- **Months to conception**
- Pregnancy loss, intrapartum or postpartum complications

Past Medical History

- Assess risk for tubal disease:
  - Abdominal infections, sexually transmitted infections (STIs), pelvic inflammatory disease (PID)
  - Postpartum or postabortion infections
  - Appendicitis (ruptured?)
- Autoimmune or endocrine conditions (including galactorrhea, acne, hirsutism)
- Use of gonadotoxic medications or radiotherapy

Surgical History

- Ovarian cysts
- Appendectomy
- Tubal surgery (ie, ectopic, hydrosalpinx, tubal ligation)
- Dilatation and curettage

Family History

- Endometriosis
- Recurrent pregnancy loss

- Premature ovarian insufficiency/early menopause
- Inherited thrombophilia
- Birth defects/developmental delay
- Reproductive issues
- Venous thromboembolism

Social History

- Smoking, alcohol, recreational drug use
- Occupational exposures
- Risk factors for STIs

Physical Examination

- Weight and body mass index (BMI), blood pressure
- Body hair distribution, thyromegaly, breast development, galactorrhea, clitoromegaly, male escutcheon, adnexal mass, uterosacral nodularity, uterine size/contour
- Vagina: Women who are amenorrheic with polycystic ovary syndrome (PCOS) are well estrogenized, whereas hypothalamic amenorrhea is associated with vaginal atrophy.

Imaging

See also Chapter 41.

- Transvaginal ultrasound (TVUS)
  - Uterine appearance
  - Ovarian morphology
  - Antral follicle count (AFC) for ovarian reserve
  - Endometrium reaches a plateau in growth at approximately cycle day 9.[20]

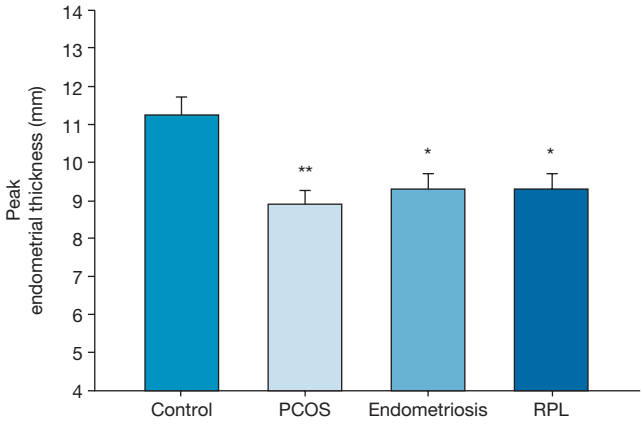

Figure 20-5 Peak endometrial thickness by diagnosis.
PCOS, polycystic ovary syndrome; RPL, recurrent pregnancy loss.
Source: Reprinted from Bromer JG, Aldad TS, Taylor HS. Defining the proliferative phase endometrial defect. *Fertil Steril*. 2009;91(1):698-704, with permission from Elsevier.
*P<0.05, **P<0.01

- Hysterosalpingogram (HSG), sonohysterogram/saline infusion sonography (SHG/SIS), or hysterosalpingo-foam sonography (HyFoSy)
  - Perform cycle day (CD) 5 to 10 (may need to vary based on cycle length).
  - SHG is less sensitive for tubal anatomy, but better for uterine anomalies.
  - Consider prophylactic antibiotics in high-risk patients:
    - Azithromycin 1 g orally (po) night before HSG.
    - Doxycycline 100 mg po twice daily (bid) × 5 days starting 2 days prior to HSG[21]
      ➔ Can also start after the procedure only if hydrosalpinx diagnosed

Laboratory Testing

- Choice of labs depends on history.
- Ovarian reserve testing (all patients): anti-Müllerian hormone (AMH)
  - AMH is adversely impacted after unilateral oophorectomy, but live birth rate (LBR) remains similar.[22,23]
  - Ovarian reserve and reproductive potential with unproven fertility:
    - May not predict reproductive potential in patients with unproven fertility[24,25]
    - May have a longer time to conception if AMH greater than 1 ng/mL[26]
  - TVUS AFC and AMH have comparable efficacies for assessing ovarian reserve.[27]
  - Can also differentiate between potential etiologies for amenorrhea or oligomenorrhea (ie, PCOS if AMH >5.4 ng/mL)[28]
- Universal thyroid screening no longer recommended; only test thyroid-stimulating hormone (TSH) if symptoms of hypothyroidism or risk factors, including menstrual irregularities[29] (see Chapter 33)
- Prolactin (PRL) only tested with menstrual abnormalities: normal less than 20 mg/mL (see Chapter 32)
- PCOS/hirsutism laboratory tests: **free testosterone** (AM follicular phase), **total testosterone**, **dehydroepiandrosterone sulfate (DHEAS)**, **17-hydroxyprogesterone**, $\mathbf{P_4}$ (if unsure of the time of cycle), **HbA1c** (or 2-hour GTT), **24-hour urinary cortisol** if patient is hypertensive
- Recommended routine prenatal labs at the time of initial evaluation: rubella/varicella titers, type and screen, genetic carrier screening
- *Chlamydia trachomatis* titers if subfertile less than 1 year (controversial):
  - 1:256 or more immunoglobulin G serum antibody titers → treat with doxycycline (both partners)
  - Associated with tubal occlusion, odds ratio (OR), 2.4 (95% CI, 1.7-3.2) (comparing fertile control subjects to infertile control subjects)[30]

SPECIFIC DISORDERS AND TREATMENT

Abnormal Semen Analysis

- See Chapter 21.

Tubal Disease

- Risk factors: history of PID, ruptured appendicitis, endometriosis, septic abortion, inflammatory bowel disease, or prior tubal surgery
- Hydrosalpinx
  - Remove or clip hydrosalpinx.
  - Meta-analysis: hydrosalpinx ↓ pregnancy rate (PR) by 50% and ↑ spontaneous abortion ×2.[31]

Table 20-4 Potential Mechanisms by Which Hydrosalpinx Decreases Conception Rate

Mechanism of Hydrosalpinx Adverse Effect
↓ Nutrients in hydrosalpinx fluid
Toxic effect of fluid on embryos[32] and/or sperm[33]
↓ Endometrial: αvβ3, LIF, HOXA10[34]
Embryo washout effect from fluid
↑ Endometrial peristalsis due to hydrosalpinx fluid
↓ Endometrial and subendometrial blood flow[35]
↑ Endometrial inflammatory cells[36]

Source: Strandell A, Lindhard A. Why does hydrosalpinx reduce fertility? The importance of hydrosalpinx fluid. *Hum Reprod.* 2002;17(5):1141-1145 by permission of Oxford University Press.

- Ligation of the hydrosalpinx or salpingectomy restores to normal PR.[37]
- Number needed to treat (NNT) calculation: 7 to 8 women would need to have a salpingectomy before IVF to gain one additional live birth.[38]
- A cost-effectiveness analysis of salpingectomy prior to IVF proved this to be a reasonable intervention.[39]
- Salpingectomy if hydrosalpinx seen on ultrasound:
  - Salpingectomy restores endometrial HOXA10 expression.[40]
  - May impair ovarian stimulation during IVF[41]

Table 20-5 Live Birth Rate in 192 Women With Hydrosalpinx Randomized to Remove or Not Remove Hydrosalpinx Prior to IVF

	Birth Rate (%)[a]
Salpingectomy	28.6
No intervention	16.3

IVF, in vitro fertilization.
[a]$P < .05$
IVF, in vitro fertilization.
Source: Strandell A, Lindhard A, Waldenström U, Thorburn J, Janson PO, Hamberger L. Hydrosalpinx and IVF outcome: a prospective, randomized multicentre trial in Scandinavia on salpingectomy prior to IVF. *Hum Reprod.* 1999;14:2762-2769 by permission of Oxford University Press.

- Two randomized controlled trials (RCTs) for ultrasound-guided hydrosalpinx aspiration during IVF resulted in greater clinical PRs than for controls (31.3% vs 17.6%). Small numbers however and fluid likely to reaccumulate postaspiration.[42,43]
  - Utilize Unasyn (ampicillin sodium and sulbactam sodium) 1.5 g intravenous (IV). intraoperatively and then azithromycin 500 mg × 3 days following procedure
- Salpingectomy is preferred but extended doxycycline therapy may be an effective option when surgery is not feasible.[44,45]

Tubal Reversal

- Tubal length (≥4 cm) after reanastomosis is most important determinant of success; duration of sterilization not important; 65% PR after tubal anastomosis of any surgical approach[46,47]
- Consider female age and the presence of male factor when counseling.

- Pregnancy success rates after microsurgical tubal reversal: clip > ring> coagulation = Pomeroy[48]
- Rate of ectopic pregnancy after tubal reversal is 6.8%.[47]

Uterine Abnormalities

- Hysteroscopic resection of adhesions, septum, submucosal leiomyoma, polyp
- Fibroids negatively impact LBRs and IVF outcomes (possibly regardless of cavity distortion) (see Chapter 16).
- Polyps
  - Prevalence in reproductive-aged women = 0.9% to 5.8%[49]; strongly correlated with increasing age
  - In eumenorrheic, infertile women with a normal ultrasound, the incidence of uterine polyps with hysteroscopy was 6% (n = 41/678).[50]
  - Polyps may regress spontaneously.[51]
  - Endometrial micropolyps are associated with endometrial inflammation/chronic endometritis.[52,53]
  - Mechanism for subfertility:
    - Overexpression of endometrial aromatase, glycodelin, and inflammatory markers; underexpression of HOX-10 and HOX-11[54-56]
    - Impaired implantation from distortion of endometrial architecture and dysregulated molecular expression
- RCT of polypectomy versus no polypectomy[57,58]
  - Spontaneous PR of 29% for the polypectomy group versus 3% in the control group
  - Clinical PR of 63% in the polypectomy group compared with 28% in the control group with subsequent follicle-stimulating hormone (FSH)/IUI); **NNT = 3**
  - No difference with respect to the size of polyps

Endometriosis

- Medical therapy: suppressive not curative
- See Chapter 15.

Unexplained Infertility

- Definition: more than one open fallopian tube, ovulatory female partner, AND "adequate" total motile sperm[59]
- 30% infertile couples[60]
- First-line treatment: controlled ovarian hyperstimulation (COH, with letrozole or Clomid) + IUI[59]
  - **IUI alone or COH alone does not increase PRs over expectant management.**
- Ultrasound monitoring to time IUI has no significant effect on success rate in patients with unexplained infertility, although reasons to perform ultrasound include[61]:
  - Ambiguous OPKs
  - Patient preference
  - Assess response in order to plan future cycles appropriately (ie, no response? under response? over response?)

- Older patients with unexplained infertility may consider bypassing COH/IUI and starting directly with IVF.[62]
  - **FORT-T** RCT trial: higher PRs (49%) and fewer cycles (↓ 36%) in patients (38-42 years) who underwent immediate IVF compared to clomiphene citrate (CC)/IUI (22%) or FSH/IUI (17%)
- No added benefit of FSH/IUI after three unsuccessful cycles of CC/IUI before proceeding to IVF[63]
  - **FASTT** trial: CC/IUI ×3 → FSH/IUI ×3 → IVF versus accelerated group (CC/IUI ×3 → IVF); decreased time to pregnancy (8 vs 11 months) and significant cost savings in accelerated group
- Treatment usually does not make the difference between conceiving and not conceiving; the difference lies in conceiving sooner rather than later. The risks of the "sooner" option in terms of multiple pregnancy, ovarian hyperstimulation syndrome, emotional stress, and financial costs may be unacceptably high.[64]

Ovulatory Dysfunction

- Approximately 15% of infertile couples, 40% of infertile women[10]
- Usually, but not always, presents with menstrual abnormalities[10]
- Most common causes (specific etiology not always identified): PCOS, thyroid dysfunction, weight change (up or down), thyroid dysfunction, obesity, hyperprolactinemia[10]
- Treat endocrine abnormalities (see Chapters 32 and 33).
- Induce ovulation with Clomid or letrozole.
  - In anovulatory infertile women, failure to achieve pregnancy after 3 to 6 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 (ie, IVF).

OVULATION INDUCTION/CONTROLLED OVARIAN HYPERSTIMULATION

- Agent selected depends on diagnosis and ovarian reserve.
- Follicular size and number should be monitored by ultrasound for at least one cycle; follicular goal based on diagnosis, that is, goal for anovulatory infertility may be one to two, goal for unexplained fertility may be two to three dominant follicles, based on age.
- Risk of multiples (age-based) must be weighed against increasing success rates.
- Impact of a baseline ovarian cyst larger than 10 mm:
  - Diminished rate of ovulation: 80.9% with baseline cyst versus 97.6% without a cyst[65]
  - May be associated with a 35% lower clinical PR in COH/IUI cycles: 15% without a cyst versus 9.3% with a cyst, relative risk (RR) 0.63 [0.36-1.1].[66]
  - Note: The Society of Radiologists in Ultrasound as well as the American College of Radiology's Ovarian-Adnexal Reporting and Data System (O-RADS) do not recommend any follow-up for a simple cyst 3 cm or larger in premenopausal women.[67,68]

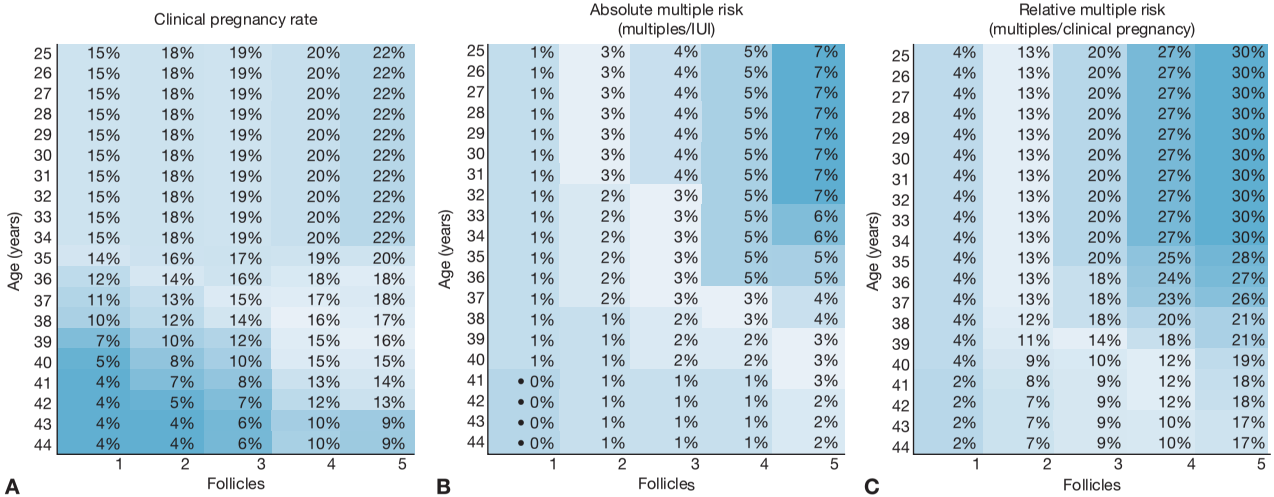

Figure 20-6 Multiple pregnancy and clinical pregnancy rate by follicle number after ovarian stimulation with intrauterine insemination (IUI).

Follicle number across the bottom of the graphs are ≥14 mm in size.

Source: From Evans MB, Stentz NC, Richter KS, et al. Mature follicle count and multiple gestation risk based on patient age in intrauterine insemination cycles with ovarian stimulation. *Obstet Gynecol*. 2020;135(5):1005-1014.

- **Clomiphene citrate (CC)**
  - Selective estrogen receptor modulator (SERM)
  - Requires intact hypothalamic-pituitary-ovarian axis: blocks hypothalamus and pituitary from "seeing" the negative feedback from FSH-induced estradiol (E_2) and thus ↑ FSH
  - Follow follicular size and number with ultrasound and increase CC by 50 mg until follicular recruitment obtained (max 150 mg) and then hold steady.
  - Side effects:
    - Hot flashes (most common)
    - Abdominal bloating/discomfort
    - Headache
    - Breast tenderness
    - OHSS (rare)
    - Rare visual changes (**palinopsia** = prolonged afterimages or shimmering of the peripheral field) that may be irreversible.[69] CC should be stopped with any visual changes.
  - Half-life approximately 5 days
  - Success rates (and risk of multiples) depend on age and diagnosis.
  - CC may inhibit E_2-induced endometrial epithelial cell proliferation by inhibiting the recruitment of steroid receptor coactivator-1 (SRC-1) and estrogen receptor α.[70]
    - If patient starts to have thin endometrial lining with CC cycles, need to switch agents.
  - ⅔ of patients who conceived reach this end point within the first three ovulatory CC treatment cycles → often recommended to move on to more aggressive measures if no pregnancy after three to four cycles (see Figure 20-8).[71]

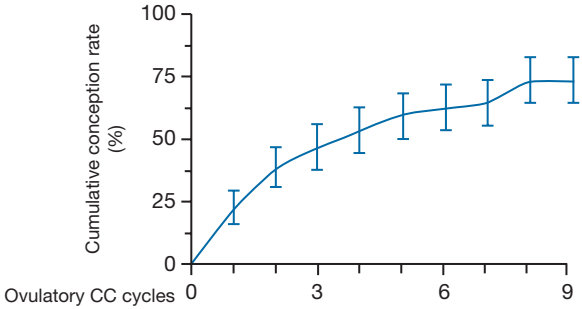

Figure 20-7 Cumulative conception rate based on the number of ovulatory clomiphene citrate (CC) cycles.

Source: Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab*. 1999;84(5):1617-1622.

- **Letrozole:**
  - Aromatase inhibitor[72,73]
  - Letrozole use for ovulation induction is off-label.
  - Despite earlier claims to the contrary, compared to CC, there is no difference in the rate of congenital malformations.[73,74]

- Side effects:
  - Headache
  - Hot flashes
  - Myalgias or joint pain
  - Abdominal discomfort/nausea
- Half-life approximately 2 days
- Starting dose is 2.5 mg/d for 5 days, typically starting on cycle day 3, 4, or 5; if ovulation does not occur, the dose should be increased to 5 mg/d and potentially up to 7.5 mg/d.
- PPCOS II trial: 750 patients with PCOS, up to five cycles of ovulation induction with letrozole versus CC; letrozole had improved ovulation (62% vs 48%) and higher LBRs (27.5% vs 19.1%) with comparable rates of pregnancy loss and adverse side effects.[73]

- **Gonadotropins (FSH or FSH/LH combinations)**
  - Mostly indicated for hypothalamic-pituitary dysfunction (eg, hypothalamic amenorrhea) or those unresponsive to oral medications
  - Informed consent essential
    - Risk of multiple gestation (~20%)
    - Risk of ovarian hyperstimulation depends on the stimulation protocol.
  - Exogenous FSH does not seem to increase the risk of fetal aneuploidy.[75]
  - There is a suppressive effect of FSH treatment on endogenous LH secretion—mechanism unknown.[76]
    - Luteal phase support: RCT in patients using FSH/IUI randomized to Crinone 8% gel (every day [qd]) versus no support: LBR/cycle 17.4% versus 9.3% ($P < .05$).[77]
- **"Hybrid" cycles**
  - Denote utilizing both letrozole and FSH in an effort to limit cost as well as maintain efficacy and perhaps diminish high-order multiples[78]
  - Reduced rate of multiple gestations compared to CC or gonadotropins for ovarian hyperstimulation[72]
  - When used in conjunction with FSH, letrozole reduces FSH dose; PR often equivalent to FSH only.[79]
  - Letrozole, 5 to 7.5 mg/d, days 3 to 7 + FSH injections (50-150 IU/day starting on day 7 until the day of trigger)

Table 20-6 Pregnancy Outcomes for Different Ovarian Stimulation Protocols With Unexplained Infertility

Method + IUI	Clinical Pregnancy Rate (%)[a]
FSH	21.4
FSH + CC	11.1
Letrozole + FSH	22.2

CC, clomiphene citrate; FSH, follicle-stimulating hormone; IUI, intrauterine insemination.
[a]$P < .05$.
Source: Mitwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Hum Reprod*. 2003;18(8):1588-1597 by permission of Oxford University Press.

- **Potential risks of ovarian stimulation**
  - Large systematic review of 52 studies exploring the risk of malignancy and the use of fertility drugs[80]
    - **No increased risk of breast, colon, or cervical cancer**
    - Uterine cancer risk is not affected, but infertility patients are at increased risk, independent of treatment.

  - Potential risk of ovarian cancer, but further studies needed; confounding variables in infertility population that also increase the risk of ovarian malignancies
- **Glucocorticoids**
  - Reserved for patients with PCOS with DHEAS high normal or above
  - Glucocorticoid treatment (dexamethasone 0.5 mg/d) can suppress androgen levels in some cases.[81]
  - Trials support ↑PRs (40%-75% vs 5%-35%) in CC and letrozole-resistant women.[82-84]

Intrauterine Insemination

- Catheter used to bypass cervix and release sperm at the top of the uterus; requires sperm washing
- No difference in LBRs between patients who received simple wash versus density gradient-prepared sperm[85]
- Indications include abnormal semen analysis, no male partner, sexual dysfunction, or combined with ovarian stimulation for unexplained infertility.
- Often paired with controlled ovarian stimulation or natural cycle
- No difference in PR based on whether IUI is timed by LH surge, hCG administration, or "hCG boost" after LH surge[86,87]
- Success rate depends on female age, diagnosis, and semen parameters.

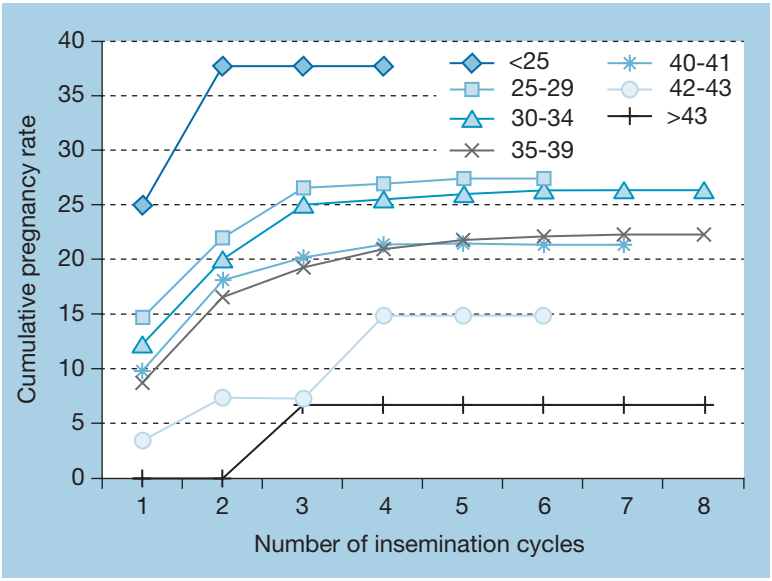

Figure 20-8 Age-based cumulative pregnancy rates after intrauterine insemination (IUI).

Source: Schorsch M, Gomez R, Hahn T, Hoelscher-Obermaier J, Seufert R, Skala C. Success rate of inseminations dependent on maternal age? An analysis of 4246 insemination cycles. *Geburtshilfe Frauenheilkd.* 2013;73(8):808-811.

- See Tables 20-7, 20-8 and 20-9 below summarizing data on total motile sperm counts and live birth rates.

Table 20-7 Live Birth Rate Based on Prewash Total Motile Count (TMC)

Total Motile Count (Million)	Live Birth Rate (%)
Van Voorhis et al[88]	
47% no female disorder, 28% oligo-ovulatory, 13% tubal, 12% endometriosis	
<10	1.4 (3/214)
≥10	6.8% (223/3,265)
Khalil et al[89]	
13.7% unexplained, 12.2% anovulation, 11% misc, 10.1% tubal factor, 8.2% male factor	
<5	5.3% (15/282)
5-10	11.9% (21/176)
10-20	13.9% (37/267)
≥20	12.7% (221/1,741)
Gordon et al[90]	
34.2% unexplained, 17.2% oligo-ovulatory, 15.1% other, 11.9% male factor, 11.3% combined, 10.5% diminished ovarian reserve	
<2	0% (0/18)
2-10	10.3% (12/116)
≥10	10.3% (105/1,020)

This includes natural-IUI, CC-IIUI, and gonadotropins-IUI.
Studies only included if there is a live birth rate outcome and at least 1,000 cycles analyzed.
CC, clomiphene citrate; IUI, intrauterine insemination.
Source: Van Voorhis BJ, Barnett M, Sparks AE, Syrop CH, Rosenthal G, Dawson J. Effect of the total motile sperm count on the efficacy and cost-effectiveness of intrauterine insemination and in vitro fertilization. *Fertil Steril.* 2001;75(4):661-668; Khalil MR, Rasmussen RE, Erb K, Laursen SB, Rex S, Westergaard LG. Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles. *Acta Obstet Gynecol Scand.* 2001;80:74-81; and Gordon CE, Hammer KC, James K, et al. Optimizing pregnancy outcomes in intrauterine insemination cycles by stratifying pre-wash total motile count and patient-specific factors: a patient counseling tool. *J Assist Reprod Genet.* 2022;39(12):2811-2818.

Table 20-8 Clinical Pregnancy Rate Based on Postwash Total Motile Count (TMC)

Total Motile Count (Million)	Clinical Pregnancy Rate (%)
Muthigi et al[91]	
Unspecified infertility diagnosis	
<1	3.9% (48/1,231)
1-1.99	7.4% (120/1,611)
2-8.99	12.8% (2,653/20,799)
≥9	16.7% (11,496/68,830)

Source: Reprinted from Muthigi A, Jahandideh S, Bishop LA, et al. Clarifying the relationship between total motile sperm counts and intrauterine insemination pregnancy rates. *Fertil Steril.* 2021;115(6):1454-1460, with permission from Elsevier.

Table 20-9 5-Year Natural Cycle Live Birth Rate Based on Prewash Total Progressive Motile Count (TPMC)

TPMC (Million)	Live Birth Rate (%)
Keihani et al[92]	
Excluded patients with major female factor infertility	
<20	48.3% (342/709)
≥20	68.1% (2,073/3,044)
<50	57.9% (1,049/1,812)
≥50	71.3% (3,030/4,249)

Source: Keihani S, Verrilli LE, Zhang C, et al. Semen parameter thresholds and time-to-conception in subfertile couples: how high is high enough? *Hum Reprod.* 2021;36(8):2121-2133 by permission of Oxford University Press.

- **Timing of IUI**
  - For natural and ovulation induction cycles:
    - When using LH kits: insemination the day following a surge
    - When using hCG trigger: insemination is best performed approximately 34 to 40 hours later (PR/cycle ~15% for 36 hours post-hCG vs ~9% for 24 hour).[93]

MULTIPLE PREGNANCY RISKS

- All fertility medications are associated with some risk of multiple pregnancy.
- Maternal complications: hypertensive disorders of pregnancy, gestational diabetes, cesarean delivery, postpartum hemorrhage, postpartum depression[94]
- Preterm birth → cerebral palsy, low birth weight, hypoxic-ischemic encephalopathy, lung immaturity[95]

Table 20-10 Prevalence of Cerebral Palsy With Multiples

0.15%	Singletons (General Prevalence)
1.5%	Twins
8%	Triplets
43%	Quadruplets

Source: Yokohama Y, Shimizu T, Hayakawa K. Prevalence of cerebral palsy in twins, triplets and quadruplets. *Int J Epidemiol.* 1995;24(5):943-948 by permission of Oxford University Press.

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INTERPREGNANCY INTERVAL

- A retrospective cohort study concludes that an interpregnancy interval of at least 12 months is recommended to reduce the risk of adverse perinatal outcomes, regardless of using fertility treatment.[96]
- The American College of Obstetricians and Gynecologists (ACOG) recommends against interpregnancy intervals less than 6 months and suggests patient counseling about potential risks for interpregnancy interval less than 18 months.[97]
  - Observational studies show a likely modest increase in risk 6 to 18 months, with some data quality concerns.
  - Risks may be increased in women who had a C-section with interval less than 18 months.
- An infant born between 18 and 59 months after the delivery of a previous child had the lowest risk of low birth weight, preterm, and/or small size for gestational age.[98]

APPENDIX 20-1

Table 20-11 Non–Assisted Reproductive Technology Treatment Outcomes

Diagnostic Group	Treatment (Unit)	Live Birth Rate (%)
Amenorrhea	None (3 y)	6
	Clomid (cycle)	19
	Gonadotropins (cycle)	21
Oligomenorrhea	None (3 y)	46
	Clomid (cycle)	9
	Gonadotropins (cycle)	21
	Metformin + Clomid (cycle)	11
	Ovarian cauterization (1 y)	38
Hyperprolactinemia	None (3 y)	30
	Bromocriptine (1 y)	31
Tubal obstruction	None (3 y)	5
	Tubal surgery (1 y)	18
Other tubal disease	None (3 y)	22
	Tubal surgery (1 y)	28
	Gonadotropins + IUI (cycle)	8
Endometriosis, I-II	None (3 y)	25
	Laparoscopic ablation (1 y)	18
	CC + IUI (cycle)	5
	Gonadotropins + IUI (cycle)	8
Endometriosis, III–IV	None (3 y)	10
	Surgery (1 y)	30
	Gonadotropins+ IUI (cycle)	8
Azoospermia	None (3 y)	5
	Therapeutic donor insemination (cycle)	13
Oligospermia	None (3 y)	32
	IUI (cycle)	5
	Gonadotropins + IUI (cycle)	5
Unexplained infertility	None (3 y)	36
	CC + IUI (cycle)	5
	Gonadotropins + IUI (cycle)	8

CC, clomiphene citrate; IUI, intrauterine insemination.

Source: Collins JA, Van Steirteghem A. Overall prognosis with current treatment of infertility. *Hum Reprod Update*. 2004;10(4):309-316 by permission of Oxford University Press.

APPENDIX 20-2

Table 20-12 Odds of Pregnancy Based on Baseline Chance and Over Three Attempts

Baseline Chance of Pregnancy (%)	Chances After Three Attempts (%)
5	14
8	22
10	27
12	32
15	39
20	49
25	58
30	66
35	73
40	78
45	83
50	88

APPENDIX 20-3

Table 20-13 Probability for Natural Conception by Age and Month of Trying

	Month				
	1	2	3	6	12
<25 yo	50%	40%	30%	20%	4%
25-34 yo	40%	30%	20%	10%	2%
35-40 yo	30%	20%	10%	5%	1%

yo, years old.

Source: Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod*. 2003;18(9):1959-1966 by permission of Oxford University Press.

APPENDIX 20-4

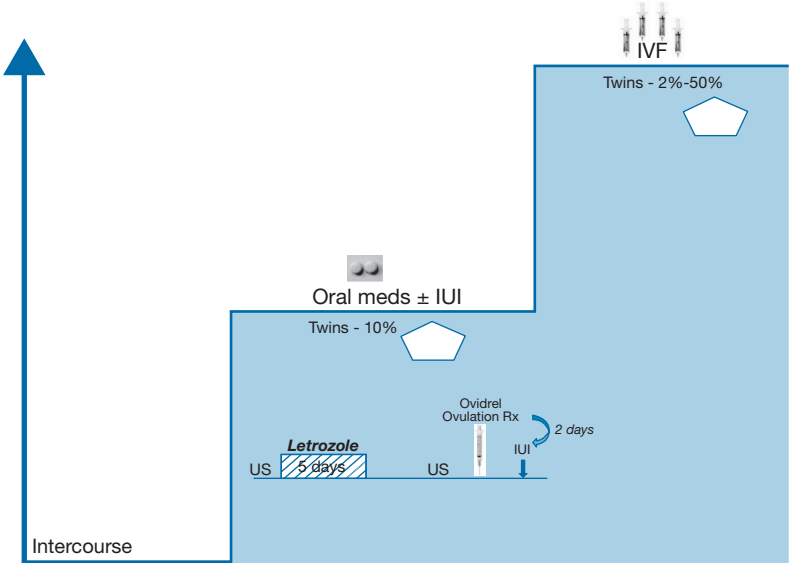

Figure 20-9 Summary of stair-wise treatment options.
IVF, in vitro fertilization; IUI, intrauterine insemination; Oral meds, clomiphene citrate; US, ultrasound.

APPENDIX 20-5

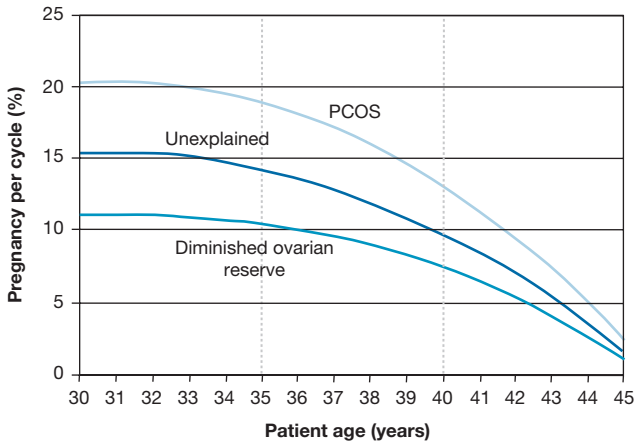

Figure 20-10 Success rates using controlled ovarian hyperstimulation based on age and diagnosis.
PCOS, polycystic ovary syndrome.
Source: Author generated figure.

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