

INFERTILITY

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Overview

Infertility is defined as the failure to conceive after one year of regular, unprotected intercourse in women < 35 y, and after 6 months of regular, unprotected intercourse in women > 35 years.^{2,6} Primary infertility refers to a couple that has never been able to conceive while secondary infertility refers to difficulty conceiving after a couple has conceived at least once before. Causes include unexplained (28%), male factors (24%), ovarian dysfunction (21%), tubal factors (14%), and other (13%).²

Diagnostic Considerations

Fertility focused history: (adapted from Evaluation of Female Infertility)⁵

*Consider evaluating partners together and separately, as individuals may wish to reveal information about which their partner is unaware²

| Male | Female |
|--|---|
| Duration of infertility | Duration of infertility |
| Fertility in other relationships | Number & outcome of any prior pregnancies (including ectopic and miscarriages) with the same or a different partner |
| Medical and surgical history, including testicular surgery and history of mumps | Gynecologic history, including history of pelvic inflammatory disease, fibroids, endometriosis, cervical dysplasia; surgery of the cervix, ovary, uterus, fallopian tube, pelvis, or abdomen; intrauterine device use, other prior contraceptive use, diethylstilbestrol exposure in utero, uterine anomalies |
| | Menstrual history (age at menarche, cycle length, and regularity), presence of molimina or vasomotor symptoms (hot flashes), dysmenorrhea |
| | Changes in hair growth, body weight, or breast discharge |
| | Other medical and surgical history |
| General medication assessment | General medication assessment |
| History of chemotherapy or radiation | History of chemotherapy or radiation |
| Cigarette smoking*, alcohol, marijuana, other drug use; environmental and occupational exposures | Cigarette smoking*, alcohol, marijuana, other drug use; environmental and occupational exposures |
| Sexual or erectile dysfunction | Exercise and dietary history |
| Frequency of intercourse, use of lubricants (which may be toxic to sperm) | Frequency of intercourse, use of lubricants (which may be toxic to sperm). Presence of deep dyspareunia suggestive of endometriosis |
| Previous infertility testing and therapies | Previous infertility testing and therapies |
| Family history of birth defects, mental retardation, or reproductive failure | Family history of birth defects, mental retardation, or reproductive failure |
| | Pelvic or abdominal pain, symptoms of thyroid disease |

* Active and passive smoke exposure is associated with reduced fecundability,¹⁵ accelerates loss of reproductive function, and may advance menopause by 1-4 years. It may have adverse effects on sperm function and increases the risk of spontaneous abortion & miscarriage¹⁰

Investigations^{2,4,5,6,7,8,13}

Female partner

- Documentation of ovulation:
 - LH surge in urine using home prediction kit reliably predicts ovulation: LH detected in urine 14-48 h prior to ovulation
 - Single mid-luteal progesterone level (measured 1 week after ovulation or 1 week prior to menses - e.g. day 25 in 32 day cycle; day 21 in 28 day cycle) provides information about adequacy of luteal phase; progesterone level >3 ng/mL indicative of ovulation⁵
- Ovulatory dysfunction suspected:
 - FSH – elevated in ovarian failure
 - Prolactin (in absence of medications that affect serum prolactin levels such as typical and atypical antipsychotics; gastrointestinal medications cimetidine and metoclopramide; antihypertensive agents methyl dopa, reserpine, and verapamil; antidepressants clomipramine and desipramine; and opiates codeine and morphine¹²) – rule out hyperprolactinemia
 - TSH – rule out thyroid dysfunction
 - Assessment of polycystic ovarian syndrome (PCOS)¹⁴
 - Exclude medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome
 - 2/3 of following criteria (Rotterdam consensus):
 - oligo- or anovulation /irregular periods
 - clinical or biochemical evidence of hyperandrogenism
 - polycystic ovaries on transvaginal ultrasound (> 12 small antral follicles in ovary)
 - 17alpha-hydroxyprogesterone and testosterone (if suspect hyperandrogenism) – rule out late onset congenital adrenal hyperplasia and androgen-secreting tumours

3. Assessment of ovarian reserve (in women > 35 y)
 - a. Day 3 FSH (where day 1 is first day of menstrual flow)
 - i. < 10 mIU/mL suggests adequate ovarian reserve (sufficient production of ovarian hormones from small follicles in early cycle to suppress FSH)
 - ii. > 20 mIU / mL suggests poor ovarian reserve
 - b. Day 3 estradiol
 - i. Value <80 pg/mL suggests adequate ovarian reserve (conflicting data)
 - ii. ↑ basal estradiol levels are due to advanced premature follicle recruitment that occurs with poor ovarian reserve; helps eliminate false-negative day 3 FSH level
 - c. Transvaginal ultrasound for antral follicle count (AFC)
4. Other endocrinopathies (female) - fasting blood sugar / diabetes mellitus assessment
5. Assessment of tubal patency and uterine cavity
 - a. Hysterosalpingogram (HSG): may be diagnostic and therapeutic; high sensitivity and specificity for diagnosing distal tubal patency but lower sensitivity in identification of proximal tubal occlusion; may identify abnormalities of uterine cavity; can cause discomfort and cramping
 - b. Sonohysterogram with echovist: Better tolerated than HSG; may be less useful in assessing tube patency; more useful in assessment of intrauterine abnormalities

Male partner

1. Semen analysis (on 2 occasions)
 - a. Collected after 2-7 days of abstinence (collected in condoms without chemical additives and delivered to laboratory at body temperature within one hour of collection)
 - b. WHO lower reference limits (5th centiles and 95% confidence intervals) for semen characteristics:¹⁶

| Parameter | Lower reference limit |
|---|-----------------------|
| Semen volume (mL) | 1.5 (1.4-1.7) |
| Total sperm no (10 ⁶ per mL ejaculate) | 39 (33-46) |
| [Sperm] (10 ⁶ per mL ejaculate) | 15 (12-16) |
| Total motility (PR + NP, %) | 40 (38-42) |
| Progressive motility (PR, %) | 32 (31-34) |
| Vitality (live spermatozoa, %) | 58 (55-63) |
| Sperm morphology (normal forms, %) | 4 (3-4) |

2. If hypogonadism suspected based on semen analysis (severe oligospermia or azoospermia) - morning FSH and total serum testosterone (to differentiate primary from secondary hypogonadism)
3. Low volume of ejaculate
 - a. Transrectal ultrasound – rule out ejaculatory duct obstruction and evaluate for suspected hydroceles and/or tumours
 - b. Post-ejaculatory urinalysis – rule out retrograde ejaculation

Management Considerations^{8,9,11,14}

If tests are normal:

- Counsel regarding timing of intercourse (q1-2 days during 3 day interval ending on day of ovulation)
- Teach appropriate use of urine LH surge kits (to determine timing of ovulation)
- Use morning urine as it is most concentrated; if positive, pt should have intercourse (IC) that night so sperm waiting for egg next a.m.⁸
- Ovulation monitoring: progesterone level 1 week prior to menses (detects presence of ovulation)
- +/- mid-cycle TV US to determine timing of ovulation - follicle 23 mm at maturity just prior to rupture

Anovulation

- Treat underlying causes if present
- After 2-3 months, monitor ovulation → mid-cycle TV US, progesterone level 1 week prior to menses, IC on day of LH surge

PCOS

- First line: 5-10% weight reduction may restore ovulatory status in obese, anovulatory women with PCOS¹⁴
- Second line: See persistent anovulation below

Persistent anovulation (in women who are normogonadotropic)

- Clomiphene citrate: selective estrogen receptor modulator (SERM); interrupts estrogen feedback to hypothalamus and pituitary stimulating FSH production and secretion
 - Contraindications: liver disease, pregnancy, abnormal uterine bleeding
 - Cautions / adverse effects: Risk of multiple gestations, ovarian hyperstimulation syndrome (OHSS) (rare but serious), visual disturbances
 - Starting dose: 50 mg / day x 5 days starting on day 5
 - If ovulation not achieved, increase dose in increments of 50 mg to max of 100 mg / day in subsequent cycles
 - Monitor ovulation status during first cycle and with any increase in dose
 - REFER if no ovulation after 3 cycles
- Patient with oligo/amenorrhea:
 - Consider oral contraceptives x 2-3 months to establish a cycle (with use of barrier method to prevent pregnancy during this time), then start clomiphene on day 5
- Metformin: In infertile women with PCOS, metformin alone inferior to clomiphene in achieving live birth⁷
 - Consider adding to clomiphene in older women with clomiphene resistance and visceral obesity¹³
 - Adverse effects: gastrointestinal discomfort (common but decreases with time); lactic acidosis (very rare, caution in renal & hepatic impairment)

When to Refer to Infertility Specialists^{1,8}

| | |
|-----------------------------------|--|
| Female partner | <ul style="list-style-type: none"> • < 35 years with >18 m infertility; > 35 years with > 12 m infertility; > 40 y at first visit despite < 6 m of unprotected, frequent intercourse • History of endometriosis, pelvic inflammatory disease, or pelvic or abdominal surgery; history of chemotherapy and/or radiation; known or suspected uterine or tubal abnormalities/disease; pelvic pain; premature ovarian failure; abnormal results from pelvic exam |
| Male partner | <ul style="list-style-type: none"> • Poor sperm studies; history of sexually transmitted infection, urogenital surgery, or urogenital pathology • History of adult mumps, impotence or other sexual dysfunction; history of chemotherapy and/or radiation; history of subfertility with another partner |
| Couple | <ul style="list-style-type: none"> • If normal tests, refer if not pregnant after trial period of ovulation monitoring with timed intercourse x 3 exposures |
| Patient request or anxiety | |

Bottom Line

Family physicians are in a unique position to counsel women/couples about family planning as well as healthy pregnancies and to initiate basic investigations when infertility becomes a concern. Family physicians should provide realistic information about the chance of conceiving as well as costs and risks associated with various infertility treatments, and provide support through an often-long process that can cause significant emotional, social, and financial stress.

References can be found online at http://www.dfcu.utoronto.ca/programs/postgraduateprograme/One_Pager_Project_References.htm