INFERTILITY

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Created: September 2011, Last Updated: January 2014

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 unaware\(^2\)

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<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Duration of infertility</td>
<td>Duration of infertility</td>
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<tr>
<td>Fertility in other relationships</td>
<td>Number &amp; outcome of any prior pregnancies (including ectopic and miscarriages) with the same or a different partner</td>
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<tr>
<td>Medical and surgical history, including testicular surgery and history of mumps</td>
<td>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</td>
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<td>Changes in hair growth, body weight, or breast discharge</td>
<td>Menstrual history (age at menarche, cycle length, and regularity), presence of molimina or vasomotor symptoms (hot flashes), dysmenorrhea</td>
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<tr>
<td>Other medical and surgical history</td>
<td>Other medical and surgical history</td>
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*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 & miscarriage.\(^10\)*

Investigations\(^2,4,5,6,7,8,13\)

Female partner

1. Documentation of ovulation:
   a. LH surge in urine using home prediction kit reliably predicts ovulation: LH detected in urine 14-48 h prior to ovulation
   b. 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 ovulation\(^2\)
2. Ovulatory dysfunction suspected:
   a. FSH – elevated in ovarian failure
   b. Prolactin (in absence of medications that affect serum prolactin levels such as typical and atypical antipsychotics; gastrointestinal medications cimetidine and metoclopramide; antihypertensive agents methyldopa, reserpine, and verapamil; antidepressants clomipramine and desipramine; and opiates codeine and morphine\(^12\)) – rule out hyperprolactinemia
   c. TSH – rule out thyroid dysfunction
   d. Assessment of polycystic ovarian syndrome (PCOS)\(^14\)
      i. Exclude medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome
      ii. 2/3 of following criteria (Rotterdam consensus):
         1. oligo- or anovulation /irregular periods
         2. clinical or biochemical evidence of hyperandrogenism
         3. polycystic ovaries on transvaginal ultrasound (> 12 small antral follicles in ovary)
      e. 17alpha-hydroxyprogesterone and testosterone (if suspect hyperandrogenism) – rule out late onset congenital adrenal hyperplasia and androgen-secreting tumours

Dr. Michael Evans developed the One-Pager concept to provide clinicians with useful clinical information on primary care topics.
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower reference limit</th>
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<tbody>
<tr>
<td>Semen volume (mL)</td>
<td>1.5 (1.4-1.7)</td>
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<tr>
<td>Total sperm no (106 per mL ejaculate)</td>
<td>39 (33-46)</td>
</tr>
<tr>
<td>[Sperm] (106 per mL ejaculate)</td>
<td>15 (12-16)</td>
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<tr>
<td>Total motility (PR + NP, %)</td>
<td>40 (38-42)</td>
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<tr>
<td>Progressive motility (PR, %)</td>
<td>32 (31-34)</td>
</tr>
<tr>
<td>Vitality (live spermatozoa, %)</td>
<td>58 (55-63)</td>
</tr>
<tr>
<td>Sperm morphology (normal forms, %)</td>
<td>4 (3-4)</td>
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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 Considerations⁸,⁹,¹¹,¹⁴

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.⁶
- 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

<table>
<thead>
<tr>
<th>Female partner</th>
<th>Male partner</th>
<th>Couple</th>
<th>Patient request or anxiety</th>
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</table>
| • < 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  
| • 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  
| • If normal tests, refer if not pregnant after trial period of ovulation monitoring with timed intercourse x 3 exposures  

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.dfcm.utoronto.ca/programs/postgraduateprogram/One Pager_Project_References.htm