Infertility: Applying New Developments to Office Practice

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Infertility: 3 Major Developments

- Development of Assisted Reproductive Technologies
- More women attempting pregnancy in later reproductive years
  - Older, nulliparous, married, affluent, insured
  - Greater sense of urgency to become pregnant
- Infertile couples more likely to seek medical care
  - Less social stigma for infertile couples
  - Fewer babies to adopt
  - High tech interventions attractive to older couples

Advances in Infertility Management

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<th>Traditional</th>
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<td>BBT, EMB dating</td>
<td>Ov Prediction Kit</td>
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<td>Ovulation induction</td>
<td>Clomiphene</td>
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<td>Luteal phase defect</td>
<td>Progesterone</td>
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<td>Ovulatory quality</td>
<td>none</td>
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<td>Cervical factor</td>
<td>PCT, E₂, antibodies</td>
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<td>Uterine factor</td>
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<td>Tubal factor</td>
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<td>Male factor</td>
<td>Vas surgery</td>
<td>ICSI</td>
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<tr>
<td>Unexplained infertility</td>
<td>none</td>
<td>CC + IU1</td>
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</table>
Should PCP’s Offer Infertility Svc?

- Can set referral point based on expertise
- Explain referral point in advance
- Must have relationship with ART provider(s)
  - May affect work-up content
  - Phone consults during work-up
  - Clear referral threshold points
  - Continuity of care

Infertility: Definitions

- Infertility
  - No pregnancy in 12 months of unprotected intercourse
- Pregnancy rates with “normal” fertility
  - 1 month: 25%
  - 6 months: 60%
  - 9 months: 75%
  - 12 months: 85%
  - 18 months: 90%

Infertility: Definitions

- Initiate the infertility evaluation
  - Woman < 35 years old: @ 12 months
  - Woman 35-39 years old: @ 6 months
  - Woman ≥ 40 years old: @ 3 months
  - After 6 or more cycles insemination
  - Hx or risk factors for infertility: @ 0-6 months
- 1/2 couples starting infertility services will become pregnant in the following year
- 60% couples with unexplained infertility < 3 years will become pregnant in next 3 years
Infertility: Causes

- Infertility in 15% of repro age couples
- Overall causes in couples
  - 35%: Male factor
  - 35%: Tubal/peritoneal factor
  - 15%: Ovulatory factor
  - 10%: Unexplained
  - 5%: Unusual causes (cervix, uterus)

Specific Causes of Infertility

- Tubal/Peritoneal Factor
  - Tubal lumenal occlusion (prior episode of PID)
  - Peritoneal adhesions (prior peritonitis or surgery)
  - Endometriosis
- Ovulatory Factor
  - Anovulation: PCOS, hyperprolactinemia
  - Luteal phase insufficiency
  - Poor “quality” ovulation (poor ovarian reserve)
- Cervical Factor
  - “Hostile” mucus: anti-sperm antibodies, infection
  - Scant mucus: “hypoestrogenic” effect

Primary Prevention of Infertility

- Prevention of tubal factor infertility
  - Chlamydia screening annually in women <26 yo
  - Targeted Ct + GC screening if risky behaviors
  - Prevent PID with barrier contraception
  - Avoid ectopic pregnancy and endometriosis with use of hormonal contraceptives
- Prevention of ovulatory factor infertility
  - Completion of childbearing by mid-late 30’s
- Prevention of male infertility
  - Prevent epididimitis
Age and Fertility

- Starting at age 30, then increasing, women have
  - More ovulation and peritoneal factor infertility
  - Higher miscarriage rates (34% if ≥ 40 yo)
  - More pregnancy related maternal conditions
  - Higher rates of congenital anomalies
- 1/3 of women who defer pregnancy to mid-late 30s will have fertility problems; 1/2 women ≥ 40 yo
- ART in older women
  - IVF success <5% per cycle, <10% multiple cycles
  - Good rates in 40-50 yo with “young” donor eggs

Visit 1: Male History

Past medical history
- Fathered previous pregnancies within 3 years
- Genital trauma or surgery
- Genital infections; GC, Chlamydia, mumps
- Environmental heat: spa, pants, sitting time

Coital factors
- Coital frequency
- Coital technique, esp ejaculation factors
Visit 1: Male History

Current exposures
- Drugs: b-blockers, Ca channel blockers, cimetidine, HMG-CoA reductase inhibitors
- Toxic chemicals, esp. metals and dyes
- Street drug and alcohol use
- Cigarette smoking

Visit 1: Male Examination

- Utility is controversial
  - “Preferable” to do exam, but little contribution if semen analysis is normal
- Male examination
  - Masculine traits
  - Varicocele
  - Hypospadias
  - Urethral discharge
  - Prostatitis

Visit 1: Female History

- Prior infertility; evaluation, treatments
- Hx of PID; postpartum, postTAB infection
- Pelvic pain, dysmenorrhea; endometriosis
- Medical: diabetes, thyroid; pelvic surgery
- Medictions, alcohol, street drugs
- Cigarette smoking
- Galactorrhea
- Menstrual patterns
  - Cycle length range (best 25-35 days apart)
  - Molimenal symptoms (if present, ovulating)
Visit 1: Female Examination

- Weight, BMI, waist circumference (PCOS)
- Skin: axial hirsuitism, acne, male-pattern balding (PCOS)
- Breasts: galactorrhea (\(^{\uparrow}\text{prolactin}\))
- Cervix: mucopus, friability (infection)
- Uterine corpus
  - Size, shape (fibroids, uterine anomalies)
  - Corpus tenderness (PID)
  - Fixed retroflexion (EM)
- Adnexa: tenderness (PID, EM), mass (EM, tumor)

EM: endometriosis  PCOS: polycystic ovary syndrome

Visit 1: Laboratory

- **Women**
  - CBC, ESR
  - TSH, prolactin
  - Ovarian reserve testing (if indicated)
  - Screen for gonorrhea, chlamydia (if indicated)
  - Microscopy of cervical mucus
- **Men**
  - Semen analysis if has not fathered children
    - Abstain for 3 days before sampling
    - Check with your lab for collection rules
  - If has fathered kids, can postpone till PCT

Visit 1: Pelvic Ultrasound

- Diagnostic pelvic ultrasound
  - \(>10\) to 12 follicles per ovary (PCOS)
  - Persistent hemorrhagic cysts with low-level echoes (endometriosis)
  - Anatomical conditions: fibroids, polyps, and Müllerian anomalies (uterine septum)
  - Decreased ovarian volume and reduced antral follicle count associated with reduced fertility
- Serial TV ultrasound used to document ovulation
Visit 1: Counseling

- Time intercourse just before ovulation
  - Use menstrual calendar to predict ovulation
    » Shortest cycle length minus 14 days
  - Ovulation prediction kit to confirm
- Coital frequency and technique
  - Every other day intercourse starting 4-5 days before expected ovulation
  - Lay supine with knees up x 20 minutes
  - No sperm-toxic lubricants (vegetable oil is ok)

Visit 1: Counseling

- Stop smoking (both partners)
- If BMI > 30, recommend/assist with weight loss
- Preconceptional care
  - Folic acid 400 mcg PO per day
  - Rubella serology; immunize if seronegative
  - Change medications to safer FDA pregnancy category
    » Antihypertensives
    » Anti-epileptic drugs
  - Blood glucose control in diabetics

Male Evaluation: Semen Analysis

- Semen Analysis (SA): Normal values
  | Volume: 2-5 ml | Motility: > 50% |
  | Count: > 20 million/cc | Normal forms: > 30% |
  | WBC: < 10 /HPF | pH > 7.2 |

- Management of SA Results
  - Normal: proceed with evaluation
  - Oligospermia: repeat in 10 weeks
  - If repeat semen analysis is low
    » 2-20 million: IUI
    » < 2 million: ICSI (ART program)
Documentation of Ovulation

- Regular menstrual cycles with molimena
- Mid-luteal phase progesterone ≥ 9 ng/ml
  - Time blood draw 7 days before expected menses
  - Evaluate result relative to onset of actual menses
- LH surge: positive ovulation prediction kit
- Pelvic ultrasound evidence of ovulation
- Outdated indicators
  - Secretory endometrium on endometrial biopsy
  - Basal body temperature elevation

Ovulation Prediction Kits (OPK)

- Has replaced basal body temperature (BBT) to confirm ovulation
- Positive with LH surge; ovulation in 24-36 hours
- Accuracy: 98% for LH surge; sl less for ovulation
- Result is “visual” positive or meter-read
- Positive test indicates
  - Presence of ovulation (natural or induced)
  - Ideal timing for intercourse or IVF

Ovulation Prediction Kits

- 5-9 urine dipsticks/ cycle; all have control stripe or box
- Perform with late afternoon urine sample
- Start testing 3-4 days before expected ovulation
- Best time for intercourse is day after positive
Ovarian Reserve Testing

- Starting in the early 30s, as women age
  - “Good eggs” are depleted owing to prior ovulation
  - Remaining oocytes are more likely to be aneuploid
- With reduction of inhibin from failing ovary, exaggerated FSH, E₂ levels early in cycle
- Indications for ovarian reserve testing
  - 30-40 years old
  - Unexplained infertility
  - Poor response to clomiphene
  - Family history of early menopause
  - Cigarette smoking
  - Previous ovarian surgery

- Single day 3 FSH test
  - FSH >10-15 mIU/ml is abnormal
  - Check with lab regarding specific threshold
- Clomiphene citrate Challenge Test (CCCT)
  - Give clomiphene 100 mg day 5-9
  - Day 3 FSH and E₂, then day 10 FSH
  - Values predictive of poor outcome
    - FSH day 3 >10 mIU/ml, day 10 >15mIU/ml
    - E₂ day 3 >70-80 pg/ml
- Less valuable in women > 40 yo, since low FSH doesn’t necessarily predict fertility

Infertility: Step 2

- Review lab results
  - If hyperprolactinemia, evaluate
  - If hypothyroidism, treat with T₄ replacement
  - If abnormal SA x 2, refer to urologist or ART
- Review menstrual calendar and OPK results
  - If ovulatory, proceed HSG (+ PCT)
  - If clearly anovulatory, induce ovulation
  - If polymenorrhea or cycle irregularity, evaluate for luteal phase defect
Anovulation: Presentations

- Amenorrhea, oligomenorrhea, or DUB
- Absence of molumenal symptoms
- Cycle length < 24 or > 34 days
- Prior need for ovulation induction
- Physical findings of PCOS
  - Obesity
  - Axial hirsuitism, acne
- Galactorrhea
- No ovulation with OPK or low luteal-P level

PCOS and Anovulatory Infertility

- NIH: PCOS is a clinical diagnosis characterized by
  - Chronic oligo-anovulation
  - Hyperandrogenism: obesity, hirsuitism, acne
  - Exclusion of other disorders
- Insulin resistance \(\rightarrow\) hyperinsulinemia
  - ↑ risk of type 2 diabetes, metabolic syndrome
- Laboratory evaluation for sequelae of PCOS
  - Screen for Type 2 DM with 2o PGL (75 gm)
  - Lipid panel (cholesterol, LDL, HDL, TG)
  - If virilized, order testosterone, DHEAS

Anovulation: Interventions

- Induce menses: MPA or micronized P x 10 days
- Start clomiphene on day 3, 4, or 5
  - 50 mg QD x5d (ovulation 5-7 days after last CC)
- OPK starting 4 days after last clomiphene
- Patient must chart when next menses starts
- If light or no menses, do pregnancy test before next clomiphene cycle
Anovulation: Further Management

- If no ovulation, increase CC by 50 mg to 150 mg
  - “Clomiphene Challenge Test” when dose is 100 mg
- If not ovulating, try
  - Metformin alone x 8-12 weeks, then
  - Metformin (every day) + CC (5 days/cycle)
- If ovulating, but not pregnant in 4 cycles
  - Perform HSG; if normal,
  - Initiate CC+ IUI
- If galactorrhea and normal PRL, Rx bromocriptine

Infertility Management: UpToDate 2006

<table>
<thead>
<tr>
<th>Step</th>
<th>Intervention</th>
<th>Cost</th>
<th>Mult gestation risk</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Weight loss (if BMI &gt;27)</td>
<td>Low</td>
<td>Baseline</td>
</tr>
<tr>
<td>2</td>
<td>Clomiphene citrate (CC)</td>
<td>Low</td>
<td>Modest increase</td>
</tr>
<tr>
<td>3</td>
<td>Metformin alone</td>
<td>Low</td>
<td>Baseline</td>
</tr>
<tr>
<td>4</td>
<td>CC + metformin</td>
<td>Low</td>
<td>Modest increase</td>
</tr>
<tr>
<td>5</td>
<td>CC + glucocorticoid</td>
<td>Low</td>
<td>Modest increase</td>
</tr>
<tr>
<td>6</td>
<td>FSH injections</td>
<td>High</td>
<td>Markedly increased</td>
</tr>
<tr>
<td>7</td>
<td>Ovarian surgery</td>
<td>High</td>
<td>Baseline</td>
</tr>
<tr>
<td>8</td>
<td>In vitro fertilization (IVF)</td>
<td>High</td>
<td>Markedly increased</td>
</tr>
</tbody>
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Management of Infertility Caused by Ovulatory Dysfunction

- If BMI >30, weight loss of ≥ 10% body weight
- Rx clomiphene to induce ovulation
- If DHEAS is >2 mg/ml, clomiphene + steroid
- If no pregnancy, Rx clomiphene + metformin
- Initiate low dose FSH injections
- Add metformin to low dose FSH injections
- Consider laparoscopic ovarian drilling or IVF
**Clomiphene, Metformin, or Both for Infertility in the PCOS**

RCT 626 women with PCOS treated for 6 months

<table>
<thead>
<tr>
<th></th>
<th>Clomiphene</th>
<th>Metformin</th>
<th>Both</th>
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<tbody>
<tr>
<td>Ovulation</td>
<td>49%</td>
<td>29%</td>
<td>60%</td>
</tr>
<tr>
<td>Conception</td>
<td>30%</td>
<td>12%</td>
<td>38%</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>6%</td>
<td>0</td>
<td>3%</td>
</tr>
<tr>
<td>Live birth</td>
<td>22.5%</td>
<td>7.2%</td>
<td>26.8%</td>
</tr>
</tbody>
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Legro RS et al., NEJM 2007; 356:551-566

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**Rate of Live Birth**

- Clomiphene
- Metformin
- Combined

Days from Randomization to Live Birth

Legro RS et al., NEJM 2007; 356:551-566

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**Rate of Live Birth**

- BMI < 30
- BMI 30–34
- BMI ≥ 35

Days from Randomization to Live Birth

Legro RS et al., NEJM 2007; 356:551-566
Infertility: Luteal Phase Defects

- Ovulation occurs, but corpus luteum fails early (LP <11d) or insufficient progesterone
- Polymenorrhea, irregular cycles, or regular cycles
- Post-ovulatory progesterone (if well timed):
  - ≤ 3 ng/mL: anovulatory; 4-8 ng/mL: LPD
  - ≥ 9 ng/mL: normal
  - Can pool 3 random samples day 5-9 days post-ov
- Treatment:
  - Clomiphene cycling; start at 100 mg x5 days
  - Luteal phase P supplementation

Luteal Phase Supplementation

- Use x14 days, then stop if negative pregnancy test
  - If pregnant, use till placental autonomy 10-12 wks
- Micronized P (Prometrium) 100 mg PO TID
- Progesterone vaginal suppository 25 mg BID
- Progesterone vaginal gel
  - Crinone 8% gel (90 mg) QD
- Adverse effects
  - Breast enlargement, pain
  - Constipation, GI upset, bloating
  - Somnolence, headache
  - Depression

Post-coital Test: Technique

- No longer routine, since subjective interpretation and poor correlation with pregnancy rates
- Evaluates sperm-cervical mucus interaction
  - Schedule 1-3 days before expected ovulation
  - Abstain x 48h, then intercourse 2-8 hrs before PCT
  - Retrieve mucus with cytobrush or cannula
- Normal findings
  - Quant (+4), clarity (clear), SBK (>8 cm), fern (+4)
  - Mucus WBC count (<5 wbc/ HPF)
  - Sperm quantity (> 20/ HPF correlates >20 million/ cc)
  - Sperm motility (> 1-3 progressively motile/ HPF)
Vaginal Moisturizers
- Non-toxic to sperm
- Sperm motility equal to natural vaginal fluid (vs. lubricants)
- Less vaginal irritation if hypoestrogenic from clomiphene
- Viscosity similar to other vaginal lubricants


Intrauterine Insemination (IUI)
- Used in:
  - Cervical factor infertility
  - Unexplained infertility
- Can be done with partner or donor semen
- Sample in lab; washed of antigens, antibodies
- Return to provider; place 1-4 days before expected ovulation
- Thaw; place catheter to internal os, inject
- DO NOT perform IUI with unwashed semen

Infertility: Step 3
Evaluate uterine and tubal factor
- Hysterosalpingogram (HSG) with oil-based dye
  - 2-5 days after end of menses, before ovulation
  - If PID history or high ESR, avoid HSG
- If both tubes blocked, refer for ART
- If not blocked, timed intercourse x 3-6 months before next step
- If endometrial abnormality, evaluate with SIS (saline-infusion sonography) or hysteroscopy
Infertility: Step 4

- Evaluate peritoneal factor with diagnostic laparoscopy with tubal dye irrigation
  - Indications: suspicion of EM, pelvic/ adnexal adhesions, significant tubal disease
  - If present, lyse adhesions, treat endometriosis
  - Not necessary if normal HSG+ no EM
- If negative evaluation (unexplained infertility)
  - Refer to ART program
  - Superovulate with clomiphene or HMG+IUI
  - Little value in women > 40 years old

Office Based Infertility Evaluation

High Risk Conditions
- Age > 35 (or 40) years old
- Infertile > 3 years
- Anatomical defect (tubal damage, adhesions, myoma)
- Major maternal medical condition
- Severe endometriosis
- Unexplained infertility, not responsive to treatment
- Need for ovum donor, because patient has...
  - Poor ovarian reserve
  - Ovarian failure (premature, natural)
  - Surgical oophorectomy

Office Based Infertility Evaluation

“High Risk” factors
- None
- Present
- Ovulation status (Hx, OPK, or P level) + day3 FSH
  - Ovulatory
  - Anovulatory
  - Poor ovarian reserve
- HSG
  - Induce 4 ovulatory cycles
  - Pregnant
  - Not pregnant
- Normal
  - Abnormal
  - Next
  - Refer for ART
Ovulatory, HSG normal
- Wait 3-6 months, then either
  - Diagnostic laparoscopy with tubal dye
    - Normal
    - Abnormal
      - “Unexplained infertility”
  - IUI + induce ovulation x4 cycles
    - Pregnant
    - Not pregnant
      - Refer for ART

ART Procedures
- Male Factor Infertility
  - Sperm retrieval from epididimis, then
  - Intra-cytoplasmic sperm injection (ICSI)
- Ovulatory Factor Infertility
  - Superovulation with HMG, rFSH, GnRH
    (performed with IUI)
  - Donor ovum + partner sperm; embryo then
    transferred to uterus or fallopian tube

ART Procedures
- Transfer techniques
  - In-vitro fertilization (IVF) with single embryo
    - Intrauterine embryo transfer
    - Zygote intrafallopian transfer (ZIFT)
  - Gamete intrafallopian transfer (GIFT)
    - Ovum and sperm placed in fallopian tube
- Other ART services
  - Pre-implantation genetic diagnosis (PGD) for single gene defects (e.g., Tay-Sach’s, Huntington’s)
  - Embryo cryopreservation