Infertility and Control of Fertility

Learning Objectives

1. Describe principles of patient selection regarding contraceptives
2. Discuss the contraindications for various contraceptive methods
3. Review the indications regarding methods of emergency contraception
4. Review the basic steps for the initial evaluation of the infertile couple
5. Review the indications for the laboratory and various procedural tests for evaluating the infertile couple

1. Which of the following is NOT associated with currently available combined hormonal contraceptives?
   A. Decreased incidence of endometrial cancer
   B. Increased incidence of uterine fibroids
   C. Decrease in the amount of flow with cycles
   D. Decrease in prostaglandin release and dysmenorrhea with cycles

7% A. Decreased incidence of endometrial cancer
11% B. Increased incidence of uterine fibroids
81% C. Decrease in the amount of flow with cycles
1% D. Decrease in prostaglandin release and dysmenorrhea with cycles

Combined Hormonal Options

- Pill
- Ring
- Patch
  - Highly efficacious in women < 90kg
  - Safety Warning (FDA)
    - ~ 60% more estrogen per cycle than 35 mcg pill (11/2005)
    - > 3x risk of VTE compared to combined OCP

Combined Contraceptives

- Inhibits ovulation at pituitary and hypothalamus
- 25-year mortality from all causes same for OCP users vs. non-users
- Estrogen
  - Ethinyl estradiol
- Progestins
  - Drospirenone – no risk of hyperkalemia
  » Contraception 2008;78:377
Progestins

<table>
<thead>
<tr>
<th>First “Original pills”</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Levonorgestrel</td>
<td>- Norgestrel</td>
<td>- Norgestimate</td>
<td>- Drospirenone</td>
</tr>
<tr>
<td>- Alesse</td>
<td>- Ortho-Novum 1/35</td>
<td>- Ortho-Cyclen</td>
<td>- Yasmin</td>
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<td>- Levirida</td>
<td>- Ortho-Tri-cyclen</td>
<td>- Desogestrel</td>
<td>- Yazmin</td>
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<td>- Levlen</td>
<td>- Minocycline</td>
<td>- Micesta</td>
<td>- Anti-androgenic</td>
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<tr>
<td>- Norgestrel</td>
<td>- Desogen</td>
<td>- Desogen</td>
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<td>- Lo/Ovral</td>
<td>- Orthocept</td>
<td>- Cydgella</td>
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<tr>
<td>- Norethindrone acetate</td>
<td>- Ovcon 35</td>
<td>-</td>
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<tr>
<td>- Norethindrone</td>
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<tr>
<td>- Ethynodiol diacetate</td>
<td>- Demulen 1/35</td>
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</tbody>
</table>

What Generation of Progestin to Use?
- 2nd generation – higher androgenic component
- 3rd generation – Less androgenic, less metabolic effects on CHO and lipids
- Do the new oral contraceptives (3rd generation) increase the risk of thrombosis as compared with older products?

Meta-analysis Assessing Risk of VTE (Case-Control and Cohort Studies)
- Odds of developing VTE – with a third-generation OCP was 70% higher than with second-generation product
  - Odds ratio 1.7 (95% CI 1.4-2.0)
- Risk seems to be higher with first-time users
  - Odds Ratio 3.1 (95% CI 2.0-4.6)
- EXCESS RISK IS SMALL
  - 1.5 per 10,000 women per year
  - Additional risk of death is exceedingly small, 1 additional death in 25,000 women taking these products over 10 years
- Question – with the availability of many equally-useful choices, often less expensive, is the risk worth it?

Combined Contraceptives
- Benefits
  - Less risk of ectopic pregnancy
  - Increases bone mass
    - Reduces risk of postmenopausal hip fractures
  - Relieves dysmenorrhea
  - Improves symptoms of PCOS
  - High estrogen/progestin ratio
  - Low-dose pills useful for management of perimenopause

Combined Contraceptives
- Decrease
  - Iron deficiency anemia
  - Fibrocystic breast disease
  - Functional ovarian cysts (use high estrogen content) /fibroids
  - Pelvic inflammatory disease
    - Cervical mucus/reduced menstrual blood flow
    - Less retrograde menstruation
  - Ovarian and endometrial cancers
    - Protective effects persist up to 20 years after discontinuation
  - Endometriosis (use strong progestin component)

Estrogen and Progestins in OCPS
- Cochrane 2005
  - Low-dose estrogen (20 mcg) causes more irregular bleeding than > 20 mcg
  - Monophasic pills recommended as the first choice for women starting OCPs
2. Excess estrogen is associated with which of the following side effects not uncommonly seen in women using a combined OCP?

A. Decreased libido
B. Acne
C. Increased appetite
D. Hirsutism

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A. Decreased libido
B. Acne
C. Increased appetite
D. Hirsutism

Combined Contraceptives
Side Effects (Excess)

- Estrogen
  - N/V
  - Bloating/edema
  - Hypertension
  - Migraine HA
  - Breast tenderness
  - Decreased libido
  - Weight gain
  - Heavy bleeding
  - Leukorrhea

- Progestin
  - Acne
    - (Ortho-Tri-Cyclen approved for treatment)
  - Increased appetite
  - Hypertension
  - Fatigue
  - Depression
  - Hirsutism
  - Vaginal yeast infection

Combined Contraceptives
Side Effects (Deficiency)

- Estrogen
  - Spotting/breakthrough
  - Amenorrhea
  - Vaginal dryness

- Progesterone
  - Amenorrhea
  - Late breakthrough or heavy bleeding

3. Which of the following statements is true regarding combined hormonal contraception?

A. Combined OCPs should not be prescribed to women under the age of 30 that smoke
B. Women with SLE who are antiphospholipid negative may take combined OCPs
C. Concomitant use of the majority of antibiotics leads to contraceptive failure with combined OCPs
D. The risk of breast cancer is increased in women taking combined OCPs

3. Which of the following statements is true regarding combined hormonal contraception?

A. Combined OCPs should not be prescribed to women under the age of 30 that smoke
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C. Concomitant use of the majority of antibiotics leads to contraceptive failure with combined OCPs
D. The risk of breast cancer is increased in women taking combined OCPs
Progestin-only Methods More Appropriate Than Combined

ACOG 2006

- Smoking or obesity AND age over 35 [SOR B, A; respectively]
- Hypertension with vascular disease or > age 35 [SOR B]
- Lupus with vascular disease, nephritis [SOR A]
- Migraine with focal aura [SOR B]
- Current or personal history of VTE associated with pregnancy or estrogen unless on anticoagulation [SOR A]
- Coronary artery/Cerebrovascular disease [SOR C]

Progestin-only OCPs (POPS)

“Minipill”

- Affects cervical mucus viscosity, fallopian tube mobility, endometrial thickness
- 40% of women ovulate on POPs
- Must be taken q day at SAME time (2 h window)
- Back-up if > 3 h late
- Better if breastfeeding
- May not have the same degree of impact on lactation as is seen with estrogenic methods
- Fewer side effects
- Less protection against ectopic pregnancy
- Less favorable choice with DUB

DMPA

- Good choice for chronic medical problems
  - Decreases crisis in sickle cell disease
- No effect on BP; risk of VTE, CVA, MI [SOR: B]
- Side effects:
  - Weight gain, amenorrhea, hair loss, bone loss
- Loss of bone density
  - Should be used for > 2 y only if other methods are inadequate [SOR: B]
  - No current recs for BMD measurements

What Does the Evidence Say?

- Reduction of bone mineral density (in 7 cross-sectional studies and 5 prospective cohort studies) was 2-6%
  - Did not result in osteopenia
- Bone loss is regained even in young users (Scholes et al. 2005)
- No trial had fracture as an outcome

Bone Loss Prevention…

- WHO recommends using DMPA with caution in women
  - < 18
  - > 45
  - On chronic steroid therapy
  - > 2 years IF at high risk for osteoporosis
- ↑ dietary calcium + vitamin D may be partially protective

Candidates for DMPA Use

- Postpartum Contraception
- Smokers > 35
- Lactating
- Women who can tolerate a period of infertility after DMPA is discontinued
  - 70% conceive by 12 months
  - By 24 months, rates similar to other methods

Infertility and Control of Fertility
Drug Interactions with Combined Hormonal Contraception

- Drugs likely to lead to contraceptive failure
  - Rifampin – otherwise little effect from antibiotics [SOR:A]
  - Anticonvulsants (significant effect) - except valproic acid
  - Antifungals (griseofulvin)
  - HIV medications

Extended vs. 28-day Cycle OCPS

Cochrane 2005

- Similar pregnancy rates, safety profiles, compliance
- Some discontinuation rates for bleeding problems
  - Only 16% of women will be amenorrheic in the first three months
- Fewer headaches, less genital irritation, fatigue, bloating, dysmenorrhea

4. Which of the following is a contraindication to IUD use?
   A. Nulliparous woman
   B. History of diabetes mellitus
   C. Breastfeeding
   D. Current cervicitis

- A. Nulliparous woman
- B. History of diabetes mellitus
- C. Breastfeeding
- D. Current cervicitis

Contraindications to IUD

- Current STD/PID
  - Purulent cervicitis
- Undiagnosed abnormal vaginal bleeding
- Malignancy of the genital tract
- Uterine anomaly/fibroids distorting the cavity in a way incompatible with IUD insertion
- Allergy to any component of the IUD or Wilson’s disease (for copper-containing IUDs)
New Considerations for IUDs

- IUD insertion, not IUD use, is associated with PID
  - Cochrane
  - Systematic Review (Grimes, Mohllajee)
  - ACOG Practice Bulletin 2005
- DO NOT cause future infertility
- Nulliparas can use an IUD
  - Uterus sounds to depth of a minimum – 6cm

New Guidelines for IUDs

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG 2007</td>
<td>Asymptomatic women may use an IUD within 3 months of treated pelvic infection or septic abortion</td>
</tr>
<tr>
<td>ACOG 2007</td>
<td>All adolescents should be screened for GC and Chlamydia prior to insertion</td>
</tr>
<tr>
<td>Cochrane 2007</td>
<td>No benefit from doxycycline or azithromycin prior to insertion</td>
</tr>
</tbody>
</table>

Strategies to reduce barriers and increase use of implants and IUDS

- Encourage implants and IUDs for all appropriate candidates – including nulliparous women and adolescents
- Adopt same-day insertion protocols
  - Screening for Chlamydia, gonorrhea, and cervical dysplasia SHOULD NOT be required before implant or IUD insertion but may be obtained on the day of insertion, if indicated

Implantable Hormonal Devices
(July 18, 2006)

- Single rod, subdermal implantation
- 40mg/d of etonogestrel – period of up to three years
  - Heavier women may need a new implant every two years
- Inhibits LH surge
- Side Effects: Irregular bleeding
  - HA, acne, dysmenorrhea, emotional lability
  - NO significant side effect on BMD or lipid metabolism

5. Which of the following statements is true when considering barrier methods of contraception?

A. Latex condoms rapidly degenerate in the presence of water-based lubricants
B. According to the manufacturer, the “Today” sponge protects against STIs
C. Diaphragm use has been associated with an increased incidence of urinary tract infection
D. Consistent use of latex condoms results in a 50% reduction of HIV transmission

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Barrier Methods – *Key Points*

- **Sponge**
  - Does not protect against STIs (according to manufacturer)
  - Nonmenstrual Toxic Shock Syndrome (Sponge, Diaphragm, Cap)
  - 2 cases/100,000 users per year
- **Diaphragm**
  - Increased incidence of UTI
- **latex condom**
  - Consistent use results in 80% reduction of HIV
  - Use only water-based lubricants

Natural Family Planning

<table>
<thead>
<tr>
<th>Plusses</th>
<th>Minuses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adverse drug effects</td>
<td>No non-contraceptive benefits of some other methods</td>
</tr>
<tr>
<td>No medication or device cost; cannot “run out” of method</td>
<td>Requires periodic abstinence</td>
</tr>
<tr>
<td>Immediately reversible</td>
<td>Requires intensive education</td>
</tr>
<tr>
<td>Acceptable to all major religions</td>
<td></td>
</tr>
<tr>
<td>Expands couples’ communication and forms of sexual expression</td>
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</table>

Abstinence

- Convey to adolescents that this is expected, be realistic
- Abstinence teaching programs have some success
- Encouragement to practice abstinence can be a powerful tool to enhance empowerment for self care
- Advantages: no STDs, no cost, no pregnancy
- Disadvantages: difficult to maintain

Sexual Abstinence

- Educational programs that teach BOTH abstinence and contraception
  - Delay onset of sexual activity and reduce number of sexual partners
  - “Pledge” to remain abstinent: 50% honor pledge 12 months later
  - STIs same whether pledgers or non-pledgers

Contraceptive Use During Lactation

- All family planning choices are available to the postpartum lactating woman
- Choice and clinical ramifications merit additional counseling
6. A 39 yo female presents for EC advice after having unprotected intercourse last night. She is a G2P2 and 6 months ago had a lower leg DVT. Which of the following would be appropriate advice for this patient?

A. If hormonal contraceptives are prescribed, there is an increased risk of adverse fetal development
B. A copper IUD inserted within 5 days of intercourse would be comparable to hormonal methods in terms of pregnancy prevention
C. Previous venous thrombosis is an absolute contraindication to the use of emergency hormonal contraception
D. Contraception is unlikely to be effective at this point

Postcoital Treatments for Preventing Pregnancy

Recommended within 120 hours

- Option
  - Combination OCPs
    - Taken in 2 doses 12 hours apart
- Option – Progestin only
  - Plan B One-Step (June 2009)
    - Nausea and Vomiting – more common with combination OCPs
      - If vomiting occurs after 60 minutes, additional dosing may not be required
    - Prophylactic antiemetic
- Option – Copper IUD
  - Failure rate - <1%
  - Cost and concerns regarding infection

Single-Dose Levonorgestrel?

- World Health Organization - RCT
  - Levonorgestrel dose does not need to be split, but a single dose of 1.5 mg can be used.
  - The use of a single dose simplifies the use of levonorgestrel for EC without an increase in side effects.

ELLÀ™ (ulipristal acetate)
FDA Approved 13 August 2010

- Progestosterone agonist/antagonist whose likely main effect is to inhibit or delay ovulation.
  - Since May 2009, the prescription product has been available in Europe under the brand name ellaOne.
- Prescription-only product, single dose taken orally within 120 hours (five days)
- Side effects most frequently observed with ella in the clinical trials include: headache, nausea, abdominal pain, pain/discomfort during menstruation (dysmenorrhea), fatigue, and dizziness. Profile of side effects similar to that of FDA-approved levonorgestrel emergency contraceptives

Emergency Contraception (EC)

- Prevent fertilization by inhibition of ovulation
- Use after implantation does not interrupt an established pregnancy
EC Indications
ACOG - 2005
• Inadequately protected or unprotected intercourse in women who do not desire pregnancy (SOR A)
• No evidence that EC is unsafe for women with contraindications to OCPs or for those with medical conditions
• Should be offered up to 120 hours after unprotected intercourse (SOR B)

7. Of the following historical elements, which is the LEAST important when exploring fertility concerns?

A. History of pelvic infections
B. Partner’s (male’s) age
C. Frequency and timing of sexual intercourse
D. Menstrual history

Infertility
Am Soc Reprod Med Practice Comm 2000
• Defined: 1 year of attempted conception without successful pregnancy
  – 85% of fertile couples would have been successful by this time
  – Earlier evaluation
    • Oligomenorrhea/amenorrhea
    • Age > 35 years
    • Known or suspected pelvic pathology

Key Points on Infertility
Hunault et al. Fertil Steril 2002;78
• Likelihood of live birth is < 50%
• Duration of infertility is powerful prognostic factor
  – Couples with < 3 years duration have a 1.3X higher probability of conceiving than if longer duration
  – 1.5X higher success if female partner is < 30 years or conceived previously

Etiology
• Female factors
  – Ovarian dysfunction 40%
  – Tubal factors 30%
  – Endometriosis 15%
  – Other 10%
  – Uterine/cervical 3%
• Male factors
  – Unknown 40-50%
  – Primary hypogonadism 30-40%
  – Altered sperm transport 10-20%
  – Secondary hypogonadism 1-2%
Evaluation

- **History**
  - Coitus practice
  - Menstrual cycle details
  - Medical history
  - Medications
  - STDs
  - Previous infertility
  - Substance use
  - Caffeine use
  - Surgical history
  - Toxin exposure

- **Physical**
  - General exam
  - Evaluation for STDs

- **Female**
  - Breast formation
  - Galactorrhea
  - Hirsutism, acne, clitoromegaly

- **Male**
  - Hernia
  - Presence of vas deferens
  - Testicular mass
  - Varicocele
  - Signs of androgen deficiency

Essential History

- **Sexual**
  - Frequency of intercourse
  - Use of lubricants, etc.
  - Erectile dysfunction
  - Dyspareunia

- **Drug or alcohol use**
  - Particularly has a "toxic" effect on sperm

- **Caffeine**
  - Interferes with muscle contraction of fallopian tube

- **Medications including nonprescription**

8. Which of the following is considered one of the prudent first steps in the management of most infertile couples where the female is known to be ovulating?

A. Recommend a hysterosalpingogram
B. Perform an *in vivo* evaluation of sperm-mucus interaction
C. Perform an endometrial biopsy
D. Recommend measuring the basal body temperature

Primary Objectives at Work-Up

<table>
<thead>
<tr>
<th>“Rule Out”</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>Azoospermia</td>
<td>Semen analysis</td>
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<tr>
<td>Anovulation</td>
<td>Urinary LH and mid-luteal phase progesterone levels</td>
</tr>
<tr>
<td>Tubal Obstruction</td>
<td>Hysterosalpingogram (HSG) or Laparoscopy</td>
</tr>
<tr>
<td>Uterine cavity anomalies</td>
<td>HSG or sonohysterogram</td>
</tr>
</tbody>
</table>

Minimalist Evaluation

- **Semen analysis**
  - WHO
WHO Seminal Fluid Analysis

Reference Values

- Volume: > 2mL
- Sperm concentration: > 20 million/mL
- Total sperm number: > 40 million
- Sperm motility: > 50% motile
  (> 25% progressively motile)
- Sperm morphology: > 14% normal

Collect after 48 hours of no ejaculation

Minimalist Evaluation

- Semen analysis
  - WHO
- Hysterosalpingogram
  - Performed days 7-12
  - Denotes tubal architecture/integrity

Hysterosalpingogram

From: Google Images

9. Which of the following “tests” is helpful in assessing whether a patient is ovulating?

A. Urine FSH monitoring
B. Urine LH
C. Serum estrogen level
D. Prolactin level

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FSH Diagnosis

- FSH on cycle day 3
  - Women > 35
  - If prior extensive ovarian surgery
  - All women with unexplained infertility
- ↑ FSH (＞15-29 IU/L) are associated with
  - Poor ovarian response to exogenous gonadotropins
  - Reduced likelihood of successful conception

“Old Tests”

No longer recommended as routine investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Postcoital testing</td>
<td>Subjective, lack of predictive value for conception</td>
</tr>
<tr>
<td>Endometrial biopsy</td>
<td>Replaced by mid-luteal progesterone level</td>
</tr>
<tr>
<td>Basal Body Temperature recordings</td>
<td>Replaced by urinary LH surge kits</td>
</tr>
</tbody>
</table>

Mid-luteal Progesterone Level

- Measure 7 days after estimated ovulation by BBT chart
  - Should be at least 6.5 ng/mL, preferably ≥ 10 ng/mL to confirm ovulation

Luteal Phase Defect

- Poorly understood subtle hormonal alterations linked with infertility and habitual abortion
- May be related to chronic stress
  - Catecholamines block progesterone receptors
- Treatment: Clomiphene or progesterone in luteal phase

Urine LH Monitoring

- Commonly used to assist diagnostic and therapeutic timing
- BBT is retrospective, LH is prospective

Ovulation Factors

- 25% of infertile women are anovulatory
  - Majority with PCOS
- Clomiphene-resistant women (usually PCOS)
  - Add metformin alone or in combination
If Not Ovulating…

- Check FSH – to ensure that patient is not menopausal
  - Premature ovarian failure – consider donor oocytes
- Look for
  - Systemic disease
  - Anorexia nervosa, low body fat
  - PCOS/Chronic hyperandrogenic anovulation
  - Hypothalamic dysfunction
  - Stress

Exclude Other Etiologies

- Prolactinoma
  - MRI to r/o pituitary adenoma
- Virilizing tumors of adrenal or ovarian tumors
- Congenital adrenal hyperplasia
- Cushing’s syndrome

Insulinizing-Sensitizing Drugs for PCOS

- Metformin is recommended as first-line agent for anovulatory women with PCOS; also decreases hirsutism and menstrual irregularities
  - Full dose - 850 mg BID
  - First week of taking metformin, upset stomach/diarrhea common; side effect can be reduced by taking it after food and by starting with a very low dose (250 mg) and to increase slowly by 250 mg per week
- Metformin + clomiphene more effective in achieving ovulation than clomiphene alone; Metformin and clomiphene alone can be used as well
- No long-term safety data in young women

Other Female Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal</td>
<td>Tubal disease diagnosed by HSG, confirm with laparoscopy; Treatment – typically IVF</td>
</tr>
<tr>
<td>Cervical</td>
<td>Previous cryotherapy, LEEP, Conization; In-utero DES exposure</td>
</tr>
<tr>
<td>Endometrial</td>
<td>HSG: fibroids, polyps, anomalies; may need sonohysterogram/hysteroscopy</td>
</tr>
<tr>
<td>Peritoneal (endometriosis)</td>
<td>Accounts for majority of infertility in young women. Surgical ablation preferred over medical treatment if pregnancy desired</td>
</tr>
</tbody>
</table>

Male Factor

History: Paternity, surgery, alcohol use, smoking, marijuana, medications

| Physical: testicular volume, hernia, prostate, penile discharge | Tests: Sperm analysis, sperm penetration assay | Treatment: Intrauterine insemination, IVF, Donor |

Varicocele

Surgery or embolization

- Meshwork of distended blood vessels in the scrotum
- Result of dilatation of spermatic vein
- No evidence that treatment improves couples’ chance of conception when compared to expectant management

IVF

- Indications
  - Tubal disease
  - Persistent infertility after initial unsuccessful treatment
- Risks
  - Multiple births
  - Ovarian hyperstimulation
- Pregnancy rates
  - 29% with one cycle versus 4% with no treatment

Answers

1. B
2. A
3. B
4. D
5. C
6. B
7. B
8. A
9. B

Extra Slides

- The following slides were not covered in the lecture, but are included for your studies.

Female Factors Related to Infertility

Summary

<table>
<thead>
<tr>
<th>Site of Involvement</th>
<th>Examples of Disease</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>PCOS, Thyroid Disease, Cushing’s</td>
<td>Serum hormone levels, pelvic ultrasound, clomiphene trial</td>
</tr>
<tr>
<td>Uterus</td>
<td>Polyps, fibroids, congenital anomalies</td>
<td>Hysteroscopy, hysterosalpingogram</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervicitis, abnormal mucus-sperm interaction</td>
<td>Postcoital testing, cervical cultures</td>
</tr>
<tr>
<td>Fallopian tubes</td>
<td>Endometriosis, tubal anomalies, scarring, adhesions</td>
<td>Hysteroscopy, laparoscopy, hysterosalpingogram</td>
</tr>
<tr>
<td>Other</td>
<td>Endometriosis, idiopathic</td>
<td>Multiple tests, including all those listed above</td>
</tr>
</tbody>
</table>

WHO Medical Eligibility Criteria

<table>
<thead>
<tr>
<th>Duration of BF method</th>
<th>Progestin-only pills</th>
<th>Progestin-only implants/ IUD</th>
<th>Combined injectable contraceptives</th>
<th>Combined patch or ring</th>
<th>Low dose combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 weeks PP</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>≥ 6 w to &lt; 6 m PP (primarily breastfed)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>≥ 6 m PP</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

1 – No restriction
2 – Generally use
3 – Not usually recommended
4 – Not to be used

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