ESTROGENS, PROGESTINS AND SPERMICIDES

GOAL
To understand the role of estrogen, progestins and other agents used in contraception.
To understand the therapeutic goals of estrogen and progestin use in postmenopausal hormone-replacement therapy.

OBJECTIVES
Describe the sites of estrogen synthesis, metabolism and the biological activity of endogenous estrogens
List sites of progesterone synthesis and biological activity
Describe hormonal regulation of menstrual cycle
For each drug in bold be able to describe: (i) the mechanism of action, therapeutic use, adverse reactions & contraindications (ii) adjustments of estrogen/progestin ratio following development of symptoms with oral contraceptives
Describe the use of spermicides in contraception
Describe the use adverse effects, indications and contraindications of estrogen/progestins in menopausal hormonal therapy

I. INTRODUCTION

• Estrogens and progestins are steroid hormones that produce many physiological actions

II. ENDOGENOUS ESTROGEN
A. BIOSYNTHESIS
• Estrogen is formed in ovary, placenta, adrenals, liver & adipose.
• Premenopausal: estrogen is predominantly made by granulosa cells of ovary
• During pregnancy it is the fetoplacental unit.
• Men and postmenopausal women: estrogen synthesis occurs in adipose & hepatic tissue -androstenedione & testosterone converted to estrone
• 17β-estradiol, is the most potent endogenous estrogen
  17β-estradiol >> estrone > estriol
• Hepatic metabolism reversibly converts estradiol to estrone; estrone also converted to estriol

B. SYNTHESIS AND METABOLISM
• All gonadal hormones are synthesized from cholesterol in a series of steps that include shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus.
• Steroidal estrogens arise from androstenedione or testosterone by aromatization of the A ring. This is catalyzed by Cyp450 monooxygenase (aromatase or CYP19)
• Placenta – uses fetal dehydroepiandrostosterone (DHEA) to produce large amounts of estrone and estriol
• All three of the estrogens are **excreted** in the urine along with their glucuronide and sulfate conjugates

**C. PHYSIOLOGICAL ACTIONS OF ESTROGEN**

1. **ON SEXUAL ORGANS**

   Ovaries: stimulate follicular growth, large doses causes atrophy of ovaries
   Uterus: endometrial growth
   Vagina: cornification of epithelial cells with thickening and stratification of epithelium
   Cervix: increase of cervical mucous with a lowered viscosity (favoring sperm access)
   Development and maintenance of internal and external genitalia

2. **OTHERS**

   Skin: increase in vascularization, development of soft, textured and smooth skin
   Bone: increase osteoblastic activity
   Electrolytes: retention of Na⁺, Cl⁻ and water by the kidney
   Cholesterol: hypocholesterolemic effect

**III. ENDOGENOUS PROGESTINS**

A. **BIOSYNTHESIS**

   • The major endogenous progestin is **progesterone**.
   • Synthesis: ovary (corpus luteum), placenta, adrenal cortex and testis

B. **PHYSIOLOGICAL ACTION**

   • Important intermediate in steroid biogenesis
   • Development of secretory endometrium
   • Endocervical glandular fluid: increases viscosity and decreases amount
   • Abrupt decline of progesterone initiates menstruation

**IV. MENSTRUAL CYCLE**

Regulated by a neuroendocrine interaction of the hypothalamus, pituitary and ovaries

A. **FOLLICULAR PHASE**

   • **Gonadotropin-releasing hormone (GnRH)** is released into the hypothalamic-pituitary portal vasculature **in intervals**.
   • **GnRH** stimulates the **pulsatile secretion** of gonadotropins - FSH and LH from the pituitary.
   • LH and FSH regulate the growth and maturation of the graafian follicle in the ovary and the ovarian production of Estradiol (E) and Progesterone (P).
   • The effects of E on pituitary are inhibitory at this time and cause the amount of LH and FSH released from the pituitary to decline (decrease in LH pulse amplitude). So the levels of gonadotropins drop.

B. **MIDCYCLE SURGE**
• Serum E rises above threshold for approximately 36 hours. This exerts a brief positive feedback effect on the pituitary to trigger the preovulatory surge of LH and FSH.
• Progesterone may contribute to the mid-cycle LH surge. This surge is essential for ovulation.
• This surge in gonadotropins, stimulates follicular rupture and ovulation within 1 to 2 days.

C. LUTEAL PHASE
• The ruptured follicle develops into corpus luteum, which produces large amounts of P and less E under the influence of LH during the second half of the cycle.
• P controls the frequency and amplitude of LH
• In the luteal (secretory) phase, elevated P limits the proliferative effect of E on the endometrium by stimulating differentiation.
• P is thus important in preparation of implantation
• If implantation does not occur, there is decrease in P and E
• When Progesterone levels drop it signals the onset of menses, the pulse generator resets and the new ovarian cycle occurs.
• If pregnancy occurs, embryo secretes human chorionic gonadotropin (hCG) which maintains elevated E and P.

V. THERAPEUTIC USE OF ESTROGENS AND PROGESTINS
• Contraception (E & P)
• Postmenopausal Hormone therapy (E & P)
• Osteoporosis (E) (now replaced by other drugs such as bisphosphonates)
• Conditions where there is deficiency of estrogens: lack of development of ovaries, menopause or castration
• Dysfunctional uterine bleeding (P)
• Dysmenorrhea (P)
• Endometriosis (P)

VI. ORAL CONTRACEPTIVES
A. COMBINED ESTROGEN AND PROGESTERONE most common hormonal Contraceptive in the US
1. Monophasic
   Constant amount of Estrogen and Progesterone for 21 days
   estrogen varies from 20 to > 50 µg ethinyl estradiol; low dose ( < 35 µg estrogen)
2. Phasic - Biphasic or Triphasic (21 day dose)
   a) lower levels of hormones to reduce adverse effects
   b) biphasic
      - 2 levels of progesterone + constant estrogen (20/35 µg ethinyl estradiol)
   c) triphasic
      - 3 different progesterone levels with 20, 30 or 35 µg ethinyl estradiol
- 1 level of progesterone and 20, 30 & 35 µg ethinyl estradiol

3. **Alter number of pill free days**
   a) **Mircette**: One 20 µg EE is formulated for 21 days followed by 2 days of placebo and 5 days of 10 µg EE.
      - Limits the number of days of hypoestrogenism after 21 days.
      - 5 days of unopposed estrogen would prevent FSH from rising and prevent early folliculogenesis during the usual placebo period
      - Fewer estrogen-withdrawal headaches.
   
   b) **YAZ**: COC introduced in April 2006. 24 days COC (20 µg EE and 3 mg drospirenone (DSRP)) followed by 4 days of inert placebo pills. (YAZ is FDA approved for improving symptoms of premenstrual dysphoric disorder - PMDD).
      
      **Yasmin**: (30 µg EE + 3 mg DSRP)
      
   c) **SEASONALE**: In 2003, FDA approved levonorgestral-EE (0.6 mg + 120 µg of EE) combination taken continuously for 84 days followed by 7 days placebo tablets. Reduces menstrual bleeding to once every 13 weeks.
      
      **Seasonique** similar to seasonale but has seven days of 10 µg of EE instead of placebo. Seasonique had better follicular suppression and less unscheduled bleeding.
      
   d) **LYBREL** (EE 20 µg, levonorgestrel 90 µg) is the first low dose COC designed to be taken **365 days** a year without placebo or pill free days.

4. **Patch** (Xulane, a generic version of Ortho-Evra Patch)
   - combination of 20 mcg ethinyl estradiol and 0.15mg Norelgestromin
   - apply once weekly for 3 weeks with a 1 week free period
   - high incidence of localized rash at site of patch
   - risk of thrombosis equal or greater to other OC

5. **Vaginal Ring** (NuvaRing)
   - Contains ethinyl estradiol and 120 µg of etonogestrel (active metabolite of desogestrel) **daily**
   - Inserted for 3 weeks with 1 week break period

6. **ESTROGEN COMPONENT (SYNTHETIC ESTROGENS)**
   - Mestranol and Ethinyl estradiol
   - 80 µg of mestranol is equivalent to 50 µg ethinyl estradiol
   - mestranol must be metabolized to ethinyl estradiol to be active

7. **PROGESTIN COMPONENT**
   - Norethindrone
   - Levonorgestrel
-Norgestimate
-Norelgestromin (metabolite of norgestimate)
-Desogestrel
-Ethynodiol diacetate
-Gestodene
-Norgestrel
-Drospirenone (YAZ, Yasmin)

a. Levonorgestrel is 2 times more potent than Norgestrel
   Norgestrel, racemic mixture of Levonorgestrel & inactive isomer

b. Drospirenone, antiandrogen activity and antimineralocorticoid (unique)
   3 mg drospirenone comparable to 25 mg spironolactone
   Must monitor plasma K+ in first month of use
   Less weight gain than levonorgestrel and is beneficial for acne

c. Ethinyl Estradiol – Norelgestromin (Ortho Evra Patch)
   -norelgestromin active metabolite of norgestimate

d. ANDROGENIC ACTIVITY:
   Progestins with higher androgenic activity increase the chances of androgen-related side effects which mainly include acne and hirsutism.
   Progestins with lower androgenic activity have little or no effect on carbohydrate metabolism

   Androgenic activity
   Levonorgestrel & Norgestrel >>
   Norethindrone = Ethynodiol > Desogestrel = Norgestimate = Gestodene, Drospirenone

   Norgestrel and Levonorgestrel have most progestational & androgenic activity

B. MECHANISM OF ACTION FOR COMBINATION PILLS
   1. Inhibit ovulation through a negative feedback on hypothalamus prevents midcycle surge of FSH and LH
      -progesterone GnRH & LH; estrogen inhibit FSH and LH (high doses)
   2. Thicken cervical mucus
   3. Endometrium unsuitable for nidation

C. DOSING AND EFFECTIVENESS
   1. Required for 7 days to become effective for Tri cyclics (Ortho Tri-cyclen) and 21 days for monophasics (ortho cyclen); recommend use of additional
method
2. Emphasize importance of taking doses at same time/day
   - lessens adverse effects
   - better therapeutic success when starting drugs
3. Pack started on first or fifth day of menses

D. ADVERSE EFFECTS and CONTRAINDICATIONS
1. GENERAL: nausea, headache, breast tenderness, weight gain, bleeding,
   migraines, depression & lethargy

2. METABOLIC: decreased HDL, worsens abnormal glucose tolerance
   increase incidence of gall stones
3. CARDIOVASCULAR: increased levels of coagulation factors II, VII, VIII, IX & X
   greater platelet aggregation
   higher incidence of thrombophlebitis and thromboembolism
   higher incidence of hypertension and myocardial infarction
   thrombotic strokes (2-10x higher)
4. OTHER:
   - decreased incidence of ovarian & endometrial cancer
   - increased risk of benign hepatomas

5. Contraindications
   - Pregnancy
   - Thrombophlebitis or thromboembolic disease
   - Breast or estrogen dependent carcinoma (current)
   - Cerebrovascular or coronary artery disease
   - Liver disease
   - Cholestatic jaundice during pregnancy or with OC
   - Estrogen associated benign or malignant hepatic tumors
   - Diabetes with vascular disease
   - Cigarette smoker (> 15 cigarettes/day) over age 35

E. RISKS

- **Venous Thromboembolism**: The rates of VTE in COC users are 3 to 4 fold
  higher than among non-users. The risk of VTE during the first year of use
  appears to be higher than subsequent years of use
- **Myocardial Infarction**: In women taking COC containing > 50 mg of ethinyl
  estradiol, MI rate increased 3 fold
- **Stroke**: Increased risk of stroke in women taking COC containing > 50 mg of EE.
  COC users with hypertension have increased risk of stroke compared to COC
  users who are normotensive
- **Gall bladder disease**: COC use increases the secretion of cholic acid in bile,
  thereby leading to a higher incidence of gallstone formation
- **Breast Cancer**: The risk of breast cancer in COC users is still controversial
F. NON-CONTRACEPTIVE BENEFITS

- Cycle regulation
- Decreased menstrual flow
- **Increased bone mineral density**
- Decreased dysmenorrhea
- Decreased peri-menopausal symptoms
- **Decreased acne**
- Decreased hirsutism
- Decreased endometrial cancer
- Decreased epithelial ovarian cancer
- Decreased risk of fibroids
- Possible fewer ovarian cysts
- Possibly fewer cases of benign breast disease
- Possible less colorectal carcinoma
- Lower incidence of ectopic pregnancy
- COC used off-label to treat polycystic ovarian syndrome

G. ADJUSTMENT OF ORAL CONTRACEPTIVE DOSE

Many side effects can be corrected by adjusting the balance of estrogen:progestin ratio

<table>
<thead>
<tr>
<th>Side effects due to Estrogen excess (lower E2 dose)</th>
<th>Side effects due to too little Estrogen (increase E2 dose)</th>
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</thead>
<tbody>
<tr>
<td>Nausea, bloating</td>
<td>Early spotting and bleeding (Days 1-14)</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>Hypomenorrhea</td>
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<tr>
<td>Cyclic Weight gain</td>
<td>Nervousness</td>
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<tr>
<td>Irritability</td>
<td>Vasomotor symptoms</td>
</tr>
<tr>
<td>Chloasma, hyperpigmentation</td>
<td>Atrophic vaginitis</td>
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<tr>
<td><strong>Hypermorhrea</strong></td>
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<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Breast fullness</td>
<td></td>
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<tr>
<td>Leg Cramps, Edema</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effects due to Progestin Excess (decrease P dose)</th>
<th>Side Effects due to too little Progestin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, fatigue</td>
<td>Late-cycle bleeding (Days 15-21)</td>
</tr>
<tr>
<td>Breast regression</td>
<td>Hypermorhrea</td>
</tr>
<tr>
<td>Hirsutism</td>
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<tr>
<td>Libido change</td>
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</tr>
</tbody>
</table>

**Side effects to excess androgenic activity**

(switch to P with less androgenic activity)

**Noncyclic Weight gain**\(^{a}\)

- Oily skin, acne\(^{ab}\)

\(^{a}\)Superscript indicates androgenic activity

\(^{b}\)Superscript indicates woman with acne may switch to triphasic Ortho Tri-Cyclen
Norgestimate & Ethinyl estradiol or ethinyl estradiol/drospirenone  *Yasmin*

**H. SPECIAL CONSIDERATIONS**

1. Low estrogen preparations will decrease side effects but increase the chance of failure esp. in patients: obese, poor compliance or take pills at different daily intervals (>24 hr)

2. **Missed pills** increase risk of pregnancy esp. in beginning of cycle
   - 1 PILL: take pill immediately and continue pack (can take 2 in one day) if occurs in beginning use other method for 7 days
   - 2 PILLS (missed in first 2 weeks): take extra pill for 2 days, use other method for 7 days
   - 2 PILLS in week 3 or 3 PILLS: stop current cycle of pills; start new cycle and use additional method for 7 days
   - **MISSED PILLS DURING 7 INACTIVE DAYS:**
     - Take remaining pills at regular schedule

   *Check package insert for each individual preparation*

3. **Cigarette smoking & some Drugs increase OC’s clearance** will increase risk of therapeutic failure for example: cigarette smoke, rifampin, barbiturates,

4. Anticonvulsants and OC: Carbamazepine, phenytoin, phenobarbital, primidone induce P450 and enhance clearance of OC’s, must use other contraceptive method or other anticonvulsants

5. **Antibiotics can increase risk of therapeutic failure**, estrogen undergoes enterohepatic recirculation following conjugation and excretion in bile.

   Antibiotics such as **Tetracycline, Penicillin V, erythromycin or ampicillin** decrease the concentration of GI flora which are needed for hydrolysis of conjugates.

   *Should use other method while taking these agents.*

6. Use with caution in patients with: depression, migraine or hypertension

7. Non-nursing mother can begin 4 weeks after delivery
   - not recommended for use during breast feeding
   - during breast feeding use progesterone only (minipill)

**VII. PROGESTERONE ONLY MINIPILLS**

**A. MECHANISM**

1. Decreased frequency of GnRH and LH release; inhibit ovulation in 70-80% of cycles
2. Decrease volume and increase viscosity for cervical fluid
3. Alter endometrium
B. USE AND SPECIAL CONSIDERATIONS
1. Taken throughout the cycle
2. Associated with menstrual irregularities
3. **Used primarily in women who cannot take estrogen**
   - cardiovascular disease
   - migraines
4. Use in nursing mothers

C. AGENTS
   - Norethindrone
   - Norgestrel

D. Higher incidence of ovulation
   - especially first 6 months

VIII. DEPOT PREPARATIONS
A. MEDROXYPROGESTERONE ACETATE (DMPA)
1. **MECHANISM OF ACTION**
   Inhibits ovulation, suppresses midcycle LH surge
   - Thicken cervical mucus;
   - Atrophy of endometrium
2. **EFFECTIVENESS**
   one injection every 3 months; more effective than OC's
3. **ADVERSE EFFECTS**
   - Delay in fertility after withdrawal of drug (1 yr.)
   - Weight gain, insomnia, menstrual irregularities,
   - Risk of loss of bone mineral density, (long term use) (recommended discontinuing their use after 2 years unless no acceptable alternative is available)

Other products:
1. **Nexplanon:** Progestin-based single rod formulated for 3 years continues use. 4cm long, 2mm in diameter. Central core contains 68mg etonogestrel encased by a membrane of ethylene vinyl acetate copolymer (radiopaque). Etonogestrel is slow-released.
2. **PROGESTERONE CONTAINING IUD (Mirena)**
   Intrauterine device (IUD) releases low levels of progesterone 20 mcg/day of levonorgestrel initially which decreases gradually over 5 years to 10 mcg/day. Effective for 5 years. Replace once every 5 years. Affects implantation of egg, sperm migration. High incidence of irregular bleeding in first 6 months. IUD is inserted within 7 days of the onset of menstruation or immediately after first-trimester abortion.
3. **ParaGard T380A:** copper containing IUD, inserted for 10 years. Copper is spermicidal. Alters normal uterine contractions and may lead to decreased sperm transport through the reproductive tract.
4. **Skyla**: (approved in 2013) 30x28 mm T-shaped polyethylene frame with a drug reservoir that contains 13.5 mg levonorgestrel. (releases 14 mcg/day initially and decreases gradually over 3 years to 5 mcg/day). Smallest of the IUDs.

5. **Liletta** (approved in 2015): Similar to Mirena releases 18.6 mcg/day of levonorgestrel which decreases to 12.6 mcg/day over 3 years.

**IX. EMERGENCY CONTRACEPTIVE:**

- Drugs used for the prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure
- to be effective these must be taken within 72 hours of intercourse
- two products are available:
  - **Plan B**: 0.75 mg levonorgestrel
  - **Plan B one Step OTC**: single 1.5 mg tablet taken once
  - Side effects: headache, abdominal pain
  - Efficacy decreases with increasing BMI

**Other ECPs:**

- **Combined ECPs**: Preven: 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol (this product includes a pregnancy test kit)
  - 2 doses 12 hours apart
  - Taken within 72 hours after unprotected intercourse
- **Copper IUD**: Inserted within 5 days after intercourse is most effective
  - Pregnancy rates as low as 0.1%.
  - Most effective method
- **Antiprogestin ECPs**- (Ulipristal acetate –Ella), an antiprogestin FDA approved for ECP.
  - SPRM (selective progesterone receptor modulator)
  - Only available by prescription, approved for use up to 5 days after unprotected

**X. VAGINAL SPERMICIDES** (non-hormonal contraceptives)

- **A. OTC preparations of creams, gels, foams or suppositories**
- **B. Active ingredient is octoxynol-9 or nonoxynol-9**
  - a nonionic detergent that permeabilizes the cell wall of sperm
- **C. Used before intercourse**
- **D. Most effective when combined with diaphragm, condom or cervical cap**
- **E. Perfumes and additives may be irritating**

**XI. METHODS OF CONTRACEPTION**

1. Vary in effectiveness and safety
2. Choice of contraceptive depends on patient
<table>
<thead>
<tr>
<th>METHOD</th>
<th>PREDICTED EFFECTIVENESS (%)</th>
<th>ACTUAL EFFECTIVENESS (%)</th>
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<tbody>
<tr>
<td>oral contraceptive</td>
<td>99.9</td>
<td>97-98</td>
</tr>
<tr>
<td>minipill</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>vaginal spermicide</td>
<td>97</td>
<td>70-98</td>
</tr>
<tr>
<td>condom</td>
<td>97</td>
<td>80-98</td>
</tr>
<tr>
<td>diaphragm</td>
<td>97</td>
<td>80-97</td>
</tr>
<tr>
<td>rhythm</td>
<td>96</td>
<td>70-95</td>
</tr>
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</table>

XII. MENOPAUSAL REPLACEMENT THERAPY

A. Goal is to delay and/or prevent or delay osteoporosis, 
   Reduce risk of cardiovascular disease, 
   Reduce vasomotor disturbances

B. At menopause estrogen levels fall to 10% of premenopausal and progesterone is negligible

C. DRUG REGIMEN

1. Estrogen combined with progesterone
   - unopposed estrogen associated with increased risk of endometrial cancer
2. REGIMENS
   a. Cyclic estrogen 21 days + progesterone for last 10 days + 1 week off
   b. Estrogen + progesterone for first 10-13 days
   c. Continuous estrogen + progesterone
3. Estrogen and progesterone components
   - conjugated estrogen - medroxyprogesterone acetate
   - norethindrone

D. Adverse Effects
   - blood clots
   - hypertension (dose dependent)

E. Contraindications
   - estrogen dependent neoplasia
   - breast cancer
   - thrombophlebitis

2. Conjugated estrogens/selective estrogen receptor modulator
   - Newly approved by FDA (2013)
   - Fixed dose combination of conjugated estrogen and the new selective estrogen receptor modulator (SERM) bazedoxifene (Duavee by Pfizer)
   - Treatment of moderate to severe vasomotor symptoms
   - Prevention of osteoporosis in postmenopausal women with an intact uterus
   - Bazedoxifene is an estrogen agonist/antagonist with estrogen like effects on bone and antiestrogen effects on uterus.
   - Not approved for treatment of vulvovaginal atrophy or dyspareunia
   - Long term effect of VTE and ischemic stroke needs to determined
F. Long Term Hormone Replacement
1. Must weigh benefits with risks in each individual
2. Will reduce hypo-estrogenic symptoms and reduce risk of osteoporosis
3. Greater risk of cardiovascular disease
4. Greater risk of breast cancer
### APPENDIX MATERIALS

#### Oral Contraceptive Preparations

**Monophasic Oral Contraceptives**

<table>
<thead>
<tr>
<th></th>
<th>Estrogen (mcg)</th>
<th>Progestin (mg)</th>
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<tbody>
<tr>
<td>Ortho-Novum 1/50(R)</td>
<td>50 mestranol</td>
<td>1 norethindrone</td>
</tr>
<tr>
<td>Ortho-Novum 1/35(R)</td>
<td>35 ethinyl estradiol</td>
<td>1 norethindrone</td>
</tr>
<tr>
<td>Ovcon-50(R)</td>
<td>50 ethinyl estradiol</td>
<td>1 norethindrone</td>
</tr>
<tr>
<td>Ovral-28(R)</td>
<td>50 ethinyl estradiol</td>
<td>0.5 norgestrel</td>
</tr>
<tr>
<td>Lo/Ovral(R)</td>
<td>30 ethinyl estradiol</td>
<td>0.3 norgestrel</td>
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<tr>
<td>Ortho-Cyclen(R)</td>
<td>35 ethinyl estradiol</td>
<td>0.25 norgestimate</td>
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<tr>
<td>Desogen(R)</td>
<td>30 ethinyl estradiol</td>
<td>0.15 desogestrel</td>
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<tr>
<td>Ortho-Cept(R)</td>
<td>30 ethinyl estradiol</td>
<td>3 drospirenone</td>
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<tr>
<td>Yasmin(R)</td>
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<tr>
<td>Alesse(R)</td>
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<td>0.1 levonorgestrel</td>
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**Biphasic Oral Contraceptives**

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
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<tbody>
<tr>
<td>Jenest-28(R)</td>
<td>0.5 mg norethindrone</td>
<td>1 mg norethindrone</td>
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<tr>
<td></td>
<td>35 mcg ethinyl estradiol</td>
<td>35 mcg ethinyl estradiol</td>
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<tr>
<td></td>
<td>(7 tablets)</td>
<td>(14 tablets)</td>
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<tr>
<td>Ortho-Novum 10/11(R)</td>
<td>0.5 mg norethindrone</td>
<td>1 mg norethindrone</td>
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<tr>
<td></td>
<td>35 mcg ethinyl estradiol</td>
<td>35 mcg ethinyl estradiol</td>
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<tr>
<td></td>
<td>(10 tablets)</td>
<td>(11 tablets)</td>
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<tr>
<td>Mircette(R)</td>
<td>0.15 mg desogestrel</td>
<td>0.01 mg ethinyl estradiol</td>
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<td></td>
<td>20 mcg ethinyl estradiol</td>
<td>(5 tablets)</td>
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<td></td>
<td>(21 tablets)</td>
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**Triphasic Oral Contraceptives**

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<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri-Norinyl(R)</td>
<td>0.5 mg norethindrone</td>
<td>1 mg norethindrone</td>
<td>0.25 mg norgestimate</td>
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<tr>
<td></td>
<td>35 mcg ethinyl estradiol</td>
<td>35 mcg ethinyl estradiol</td>
<td>35 mcg ethinyl estradiol</td>
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<tr>
<td></td>
<td>(7 tablets)</td>
<td>(7 tablets)</td>
<td>(7 tablets)</td>
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<tr>
<td>Ortho-Novum 7/7/7(R)</td>
<td>0.5 mg norethindrone</td>
<td>0.75 mg norethindrone</td>
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<td></td>
<td>(7 tablets)</td>
<td>(7 tablets)</td>
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<tr>
<td></td>
<td>1 mg norethindrone</td>
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<td></td>
<td>35 mcg ethinyl estradiol</td>
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<td>(9 tablets)</td>
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</tr>
<tr>
<td>Ortho Tri-Cyclen(R)</td>
<td>0.18 mg norgestimate</td>
<td>1 mg norethindrone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 mcg ethinyl estradiol</td>
<td>35 mcg ethinyl estradiol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7 tablets)</td>
<td>(7 tablets)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.215 mg norgestimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 mcg ethinyl estradiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7 tablets)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Summary of guidelines for the use of combination estrogen-progestin oral contraceptives

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACOG guidelines</th>
<th>WHO guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker, &gt;35 yr of age</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>&lt;15 cigarettes/day</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>≥15 cigarettes/day</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit if systolic blood pressure is 140-159 mmHg and diastolic blood pressure is 90-99 mmHg</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Risk acceptable; no definition of blood-pressure control</td>
<td>Risk unacceptable if systolic blood pressure is ≥160 mmHg or diastolic blood pressure is ≥100 mmHg</td>
</tr>
<tr>
<td>Blood pressure controlled</td>
<td>Risk unacceptable; no definition of uncontrolled blood pressure</td>
<td>Benefit outweighs risk if no end-organ damage and diabetes is of ≤20 yr duration</td>
</tr>
<tr>
<td>Blood pressure uncontrolled</td>
<td>Risk unacceptable</td>
<td>Benefit-risk ratio is dependent on the presence or absence of other cardiovascular risk factors</td>
</tr>
<tr>
<td>History of stroke, ischemic heart disease, or venous thromboembolism</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit or risk unacceptable, depending on risk factors</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Risk acceptable if no other cardiovascular risk factors and no end-organ damage</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Risk acceptable if LDL cholesterol &lt;160 mg/dL and no other cardiovascular risk factors</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Multiple cardiovascular risk factors</td>
<td>Not addressed</td>
<td>Risk usually outweighs benefit or risk unacceptable, depending on risk factors</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>Risk usually outweighs benefit</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Age ≥35 yr</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Focal symptoms</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Current disease</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Past disease, no active disease for 5 yr</td>
<td>Risk unacceptable</td>
<td>Risk acceptable</td>
</tr>
<tr>
<td>Family history of breast or ovarian cancer</td>
<td>Risk acceptable</td>
<td>Risk acceptable</td>
</tr>
</tbody>
</table>


### Conditions in which a progestin-only contraceptive may be desirable

- Migraine headaches
- Age over 35 years and smoker or obese
- History of thromboembolic disease
- Cardiac disease, especially coronary artery disease or congestive heart failure
- Cerebrovascular disease
- Early postpartum period
- Hypertension with vascular disease or older than 35 years of age
- Systemic lupus erythematosus with vascular disease, nephritis, or antiphospholipid antibodies
- Hypertriglyceridemia

Adapted from the American College of Obstetricians and Gynecologists. The use of hormonal contraception in women with coexisting medical conditions. ACOG practice bulletin #73, 2006.
## Efficacy contraception methods

### Pregnancy rate (percent) during first year of use

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical use</th>
<th>Correct use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical cap</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous births</td>
<td>32</td>
<td>26</td>
</tr>
<tr>
<td>No previous birth</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td><strong>Condom (without spermicide)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Diaphragm with spermicde</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td><strong>Sponge</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous births</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>No previous births</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td><strong>Fertility awareness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Symptothermal</td>
<td>13-20</td>
<td>2</td>
</tr>
<tr>
<td>TwoDay</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Standard days</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Lactational amenorrhea*</td>
<td>5</td>
<td>&lt;2</td>
</tr>
<tr>
<td><strong>Withdrawal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Depot-provera</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>IUD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper T or Mirena</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Patch</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>OCPs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestin only or combination estrogen-progestin</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ring</td>
<td>8</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Emergency contraception</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate decreased by 75 to 89 percent depending on the regimen used (higher pregnancy rate is for combined estrogen-progestin pills, lower pregnancy rate is for levonorgestrel alone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate decreased by 99 percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implanon</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Spermicides</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>No method</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

Data refer to number of pregnancies per 100 women during first year of use.

Typical Use: refers to failure rates for women and men whose use is not consistent or always correct.

Correct Use: refers to failure rates for those whose use is consistent and always correct.

*Rate reflects cumulative pregnancy rate in the first 6 months following birth.

Data adapted from: Contraceptive Technology, 19th edition, 2007
<table>
<thead>
<tr>
<th>Method</th>
<th>Characteristics</th>
<th>Effectiveness</th>
<th>Advantages</th>
<th>Side effects and risks</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined estrogen-progestin contraception</td>
<td>Mechanism of action: inhibition of ovulation; endometrial effects; cervical mucus effects; tubal peristalsis</td>
<td>Perfect use: 99.7 percent</td>
<td>Effective and reversible</td>
<td>Side effects: irregular bleeding or spotting; breast tenderness; nausea; headache</td>
<td>Not associated with weight gain</td>
</tr>
<tr>
<td></td>
<td>1 pill daily: cyclically or continuously</td>
<td>Typical use: 92 percent</td>
<td>Nonconceptive benefits: Cycle regulation; decreased menstrual flow; decreased dysmenorrheal</td>
<td>Risks: Risk of venous thromboembolism: increased 3- to 4-fold; absolute risk is 1 to 1.5 events per 10,000 users per year of use; risk highest in first year of use</td>
<td>Pill free intervals not necessary</td>
</tr>
<tr>
<td></td>
<td>Initiation: first-day start (on first day of menses), Sunday start or &quot;quick start&quot; (at doctor's office)</td>
<td></td>
<td>Increased bone density</td>
<td>No increased risk of myocardial infarction, cerebrovascular accident or gallbladder disease in healthy women</td>
<td>No limit to duration of use in healthy women Final height of adolescent users not affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fewer perimenopausal symptoms</td>
<td>Risk of breast cancer is increased only slightly if at all</td>
<td>Future fertility not affected May be used by healthy, nonsmoking women over age 35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Less acne and hirsutism</td>
<td></td>
<td>Not teratogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased risk of ovarian, endometrial and possibly colorectal cancer; fewer ovarian cysts; decreased incidence or severity of premenstrual symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive pill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal contraceptive patch</td>
<td>Contains ethinyl estradiol and norelgestromin</td>
<td>Perfect use: 99.7 percent</td>
<td>Effective and reversible</td>
<td>Side effects: similar to those of oral contraceptives; local skin irritation in 20 percent</td>
<td>May be less effective in women weighing &gt;90kg Higher overall estrogen dose, but lower peak levels, than with oral contraceptive Effect of avoiding first-passmetabolism in liver uncertain</td>
</tr>
<tr>
<td></td>
<td>Mechanism of action: same as that of oral contraceptive</td>
<td>Typical use: 92 percent</td>
<td></td>
<td>Patch detachment (uncommon)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 patch weekly: cyclically (1 patch weekly for 3 weeks, then 1 patch-free week) or</td>
<td></td>
<td>Once-a-week dosing schedule</td>
<td>Risks: similar to those of oral contraceptive; possibly increased risk of venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48-hour &quot;window of forgiveness&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nonconceptive benefits similar to those of oral contraceptive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Vaginal contraceptive ring | **Mechanism of action:** same as that of oral contraceptive  
1 ring monthly; cyclically (1 ring for 21 days, then 7-day ring-free interval) or continuously | **Effective and reversible**  
**Perfect use:** 99.7 percent  
**Typical use:** 92 percent | **Side effects:** similar to those of oral contraceptive.  
Ring-specific side effects: vaginitis (5.6 percent), leucorrhea (4.6 percent), vaginal discomfort (2.4 percent).  
**Expulsion (uncommon)**  
Uterovaginal prolapsed or vaginal stenosis are relative contraindications  
**Risks:** similar safety profile as that of oral contraceptive  
Vaginal spermicides and antifungals have no effect on ring efficacy  
Use does not worsen low-grade squamous intraepithelial lesions  
Effect of avoiding first-pass metabolism in liver uncertain |}

| Progestin-only contraception | **Mechanism of action:** cervical mucus changes; impaired sperm motility; possible inhibition of ovulation  
1 pill daily: no pill-free interval; must be taken at same time every day (back-up method of contraception required if >27 hours between pills) | **Effective and reversible**  
**Perfect use:** 99.7 percent  
**Typical use:** 92 percent | **Side effects:** irregular bleeding; headache, bloating; acne; breast tenderness  
**Risks:** no apparent increased risk of venous thromboembolism or cerebrovascular accident  
**Although often used by breast-feeding women, it may be used by any woman seeking reliable, reversible contraception** |}