Understanding the Options: A Guide to Oral Contraceptives

Katie McKinney, MD

Clinical Instructor, Internal Medicine, University of Kentucky
Patient Safety Fellow, Veteran's Administration Medical Center, Lexington, Kentucky

Objectives

- Review estrogen and progestin pharmacology
- Contrast and compare oral contraceptive options
- Overview risks and benefits associated with oral contraceptives
- Discuss common clinical questions related to oral contraceptive use

Contraceptive Methods

1. Abstinence
2. Sterilization
3. Natural methods (periodic abstinence, withdrawl)
4. Barrier methods (condom, diaphragm, spermicide, cervical cap)
5. Intrauterine Devices
6. **Oral contraceptives**
7. **Other pharmaceautical options (injection, patch, implant, vaginal ring)**

US Women 15–44 Years of Age and Contraceptive Use

Contraceptive Status and Method	YEAR OF SURVEY		
	1982	1995	2002
	NUMBER IN THOUSANDS		
All Women	54,099	60,201	61,561
	PERCENT DISTRIBUTION (WITH STANDARD ERROR)		
Total	100.0	100.0	100.0
Using Contraception (Contraceptors)	55.7 (1.0)	64.2 (0.6)	61.9 (0.8)
Female sterilization	12.9 (0.6)	17.8 (0.4)	**16.7 (0.6)**
Male sterilization	6.1 (0.4)	7.0 (0.3)	**5.7 (0.4)**
Pill	15.6 (0.8)	17.3 (0.4)	16.9 (0.7)
Implant, Lunelle, or Patch[c]	NA	0.9 (0.1)	0.8 (0.1)
3-month injectable (Depo-Provera)	NA	1.9 (0.1)	**3.3 (0.3)**
Intrauterine device (IUD)	4.0 (0.4)	0.5 (0.1)	1.3 (0.2)
Diaphragm	4.5 (0.4)	1.2 (0.1)	0.2 (0.1)
Condom	6.7 (0.6)	13.1 (0.4)	**11.1 (0.5)**
Periodic abstinence-calendar rhythm	1.8 (0.3)	1.3 (0.1)	0.7 (0.1)
Periodic abstinence-natural family planning	0.3 (0.3)	0.2 (0.1)	0.2 (0.1)
Withdrawal	1.1 (0.3)	2.0 (0.2)	2.5 (0.3)
Other methods[d]	2.7 (0.3)	1.1 (0.1)	0.6 (0.1)

Katz: Comprehensive Gynecology, 5th ed. Table 14-1

History of Oral Contraceptives

1960

First generation of pills contained
150 µg mestranol (estrogen), 9.85 mg norethynodrel

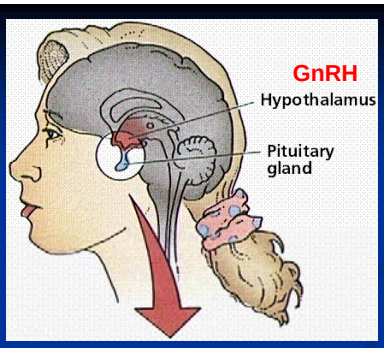
1975

All pills contain ≤ 50 µg ethinyl estradiol, ≤ 3 mg progestin

2009

35 FDA approved oral contraceptives
All pills composed of synthetic steroids

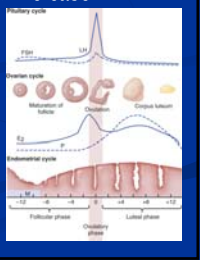
Estrogens and Progestins: Physiology and Pharmacology



www.cartage.org.lb/.../NervousEndocrine.htm

Oral Contraceptives Mechanism of Action

- Primary effect: prevent GnRH release
- Secondary effect: inhibit FSH/LH release
- Possible effect: alter ovarian response to FSH/LH



Pharmacologic Actions of Progestin and Estrogen

Progestin	Estrogen
Ovarian and pituitary inhibition	Ovarian and pituitary inhibition
Thickening of cervical mucus	Thinning of/increase in cervical mucus
Endometrial atrophy/transformation	Endometrial proliferation
Cycle control	Cycle control

Types of Oral Contraceptives

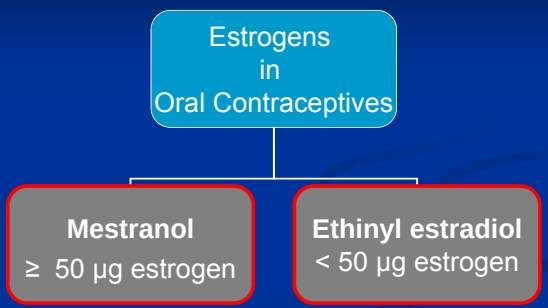
- **Estrogen and progestin combinations**
  - **Fixed** estrogen dose or "monophasic"
  - **Phasic** estrogen and/or progestin dose
- **Progestin only pills**

Oral Contraceptive Pharmacology

Combined oral contraceptives differ by:

- **Level of estrogen**
- **Length of estrogen and progestin or number of "hormone free days"**
- **Type of progestin**

Estrogen Pharmacology



Monophasic Contraceptives: Level of Estrogen

- Estrogen doses: 20, 30, 35, 50 µg
- 35 ug has been the traditional "start dose"
- **Lowest dose of estrogen is preferable**
- Insufficient evidence for 20 ug pills differing in contraceptive effectiveness
- Higher incidence of breakthrough bleeding associated with 20 ug pills

Monophasic Contraceptives: Hormone Free Days

- Most common formulation: 21 days estrogen and progestin, 7 days placebo
- 21/7 formulation associated with hormone withdraw symptoms
- Other formulations decrease hormone free days to alleviate withdraw

Approved Regimens that Shorten the Hormone-Free Interval

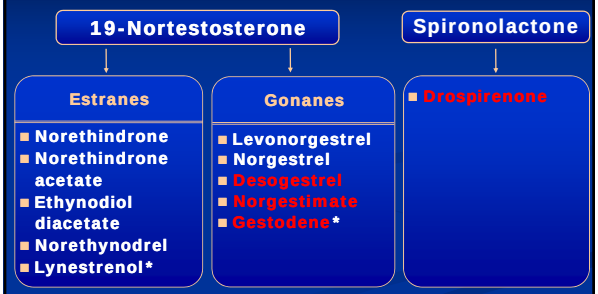
Brand Name	Estrogen Dose	Progestin Dose	Regimen
Seasonale®	30 µg EE	150 µg levonorgestrel	84/7
Seasonique™	30 µg EE	150 µg levonorgestrel	84/7* *7 days 10 µg EE
LoSeasonique™	20 µg EE	100 µg levonorgestrel	84/7
Yaz	20 µg EE	3 mg drospirenone	24/4
Loestrin 24 Fe	20 µg EE	1 mg norethindrone acetate	24/4* *4 days of iron
Lybrel	20 µg EE	90 µg levonorgestrel	365 days (non-cyclic daily dosing)

EE= ethinyl estradiol

Biphasic and Triphasic Oral Contraceptives

- Contain varying doses of estrogen and/or progestin throughout a pill pack
- In theory, more closely mimic "natural" ovarian cycle
- Total lower dose of steroid/month
- No increase in breakthrough bleeding
- No evidence for fewer adverse effects

Progestins in Oral Contraceptives



*Not available in the United States.

Adapted from Sulak PJ. *OBG Management.* 2004;Suppl:3-8.

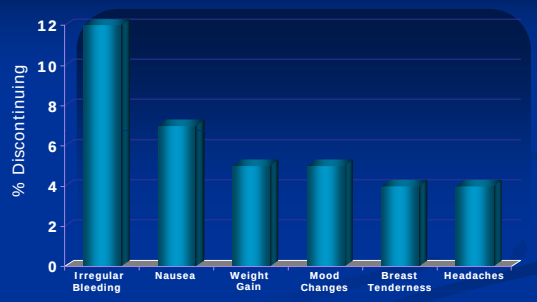
Progestin Only Oral Contraceptive

- Indications: lactation, estrogen contraindications
- Formulation: same dose progestin, taken daily, no steroid free period
- Not as consistent in inhibition of ovulation as combination pills
- Higher incidence of breakthrough bleeding

Oral Contraceptive Risks and Benefits

I'm on my second pack and I'm having some spotting even before my period starts…what should I do?

Side Effects Cited for Discontinuation of Oral Contraceptives

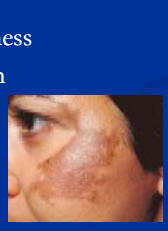


Rosenberg MJ, et al. *Am J Obstet Gynecol.* 1998;179:577-582.

Oral Contraceptive Side Effects

Estrogen mediated

- Nausea
- Breast tenderness
- Fluid retention
- Melasma



http://www.twolia.com/blogs/daily-beauty-break/files/2009/06/melasma.jpg

http://www.blisstree.com/articles/miracle-skin-a-perception-shift-28/

Oral Contraceptive Side Effects

Progestin mediated

- Acne
- Nervousness/depression
- Amenorrhea/breakthrough bleeding
- Weight gain ?

Weight Gain and Oral Contraceptives: Controlled Studies Do Not Show Link

Goldzieher et al., 1971	Placebo-controlled double-blind crossover (N=380)	Weight gain (≥5 lb) in ~ 25% of women; no significant difference between the placebo group and the users of oral contraceptive (≥ 50 µg ethinyl estradiol [EE])
Reubinoff et al., 1995	Prospective, randomized (N=49)	No statistical difference in weight gain (>0.5 kg) between users of oral contraceptives (30 µg EE) and nonusers
Gallo et al., 2006	Systematic review of randomized controlled trials	No association between combination oral contraceptives and weight gain

Goldzieher JW, et al. *Fertil Steril.* 1971;22:609-623; Reubinoff BE, et al. *Fertil Steril.* 1995;63:516-521; Gallo MF, et al. *Cochrane Database Syst Rev.* 2006;(1):CD003987.

Oral Contraceptive Adverse Effects

- Vascular
  - Venothromboembolic disease
  - Arterial embolic disease
  - Hypertension
- Metabolic
- Oncologic

Vascular Adverse Effects

Venous Thromboembolism

- Primary association with estrogen dose
- Secondary association with type of progestin
  - levonorgestrel lowest risk (4 x)
  - less androgenic progestins higher risk (6-7 x)
- Risk highest in first year of oral contraceptive use, peaking in first 3 months of use
- **Lowest risk: lowest estrogen with less androgenic progestin (levonorgestrel)**
- **Don't test for thrombophilic states, but if known, combined OCP contraindicated**

Vascular Adverse Effects

Myocardial Infarction and Stroke

- Risk related to arterial thrombosis NOT atherosclerosis
- Studies showing increased risk done on patients taking >50ug dose of estrogen
- Increased risk for nicotine users >35 years
- Current nicotine use confers increased risk
- **Combined OCP's contraindicated in women >35 who use nicotine**

Vascular Adverse Effects

Hypertension

- Primarily due to estrogen
- Elevated blood pressure in 1/200 women even on low dose estrogen
- Advisable to recheck BP on follow-up
- Carefully consider oral contraceptive use in hypertensive patient

Metabolic Adverse Effects

- Gallbladder disease: no increased incidence, but accelerated progression
- Diabetes: no increased risk
- Cholesterol: may increase TG, increase HDL, decrease LDL

Oncologic Risks

- Breast Cancer: no increased risk, even in with history of breast cancer/high risk
- Cervical Cancer: perhaps increased risk, unclear whether progression from dysplasia
- Endometrial Cancer: protective effect
- Ovarian Cancer: protective effect

Contraindications

- Pregnancy
- Nicotine user age >35
- History of arterial or venous thromboembolism
- Systemic disease affecting vasculature (SLE)
- Inherited thrombophilia
- Uncontrolled hypertension
- Diabetes with vasculopathy
- Classic migraines or migraines with neurologic sequelae
- Undiagnosed uterine bleeding
- Cardiomyopathy
- "Active" liver disease

- *? history of breast cancer*
- *? history of endometrial cancer*

Considerations

- Heavy nicotine use < 35 yrs of age
- Undiagnosed amenorrhea
- Depression
- Hypertension
- Diabetes
- Elevated triglycerides

Non-contraceptive Benefits

- **Primarily due to progestin**

- **Decreased:**
  - menstrual flow
  - benign breast disease
  - menstrual "irregularities"
  - number of functional ovarian cysts

- **Other:**
  - lower risk of rheumatoid arthritis
  - protective effect on bone mineral density

Troubleshooting Common Clinical Senarios

Beginning Oral Contraceptives

- **When to start?**
  - Conventional approach: first Sunday or first day of menses
  - "Quick start": first pill in the office/immediately

- **Backup contraception?**
  - Conventional approach: none
  - Quick start: 7 days

- **Physical exam?**
  - Blood pressure, weight
  - Pap smear not necessary prior to starting

How to Pick a Pill ?

1. Level of estrogen:
- Lowest!

2. Hormone free days:
- 7 hormone free days most widely available option
- Decrease "hormone free days" for menstrual cycle complaints
- Extended cycle for decreased menstrual cycles or amennorrhea

3. Type of progestin:
- Lowest risk for VTE from levonorgestrel
- Less androgenic effect desired pick desogestrel, norgestimate or drosperinone

Mono, Bi or Triphasic?

Mono versus Bi and Tri phasic contraceptives?

- Only 1 randomized controlled trial has compared mono versus biphasic pills
- No differences in breakthrough bleeding
- Many more monophasic generic options $$$

Bottom line: little evidence to support bi or triphasic over monophasic as first choice

Follow-up Considerations

- Clinic visit at 3 months
- Recheck blood pressure
- Evaluate for side effects/need to switch formulations
- No evidence for routine lipid panels or other labs
- Pap smears per preventative guidelines

Troubleshooting Side Effects

- **Breakthrough bleeding:** increase estrogen dose or estrogen/progestin ratio
- **Nausea:** take pill earlier in the evening, eat breakfast, switch to a lower dose of estrogen
- **Weight gain and acne:** switch to less androgenic progestin (3rd generation OCP's, Yaz, Yasmin)
- **Amenorrhea:** change progestin or decrease dose
- **Melasma:** try different OCP or stop
- **Mood changes:** try different OCP, suspect progestin
- **Headaches:** try different OCP

Oral Contraceptives and Drug Interactions

- **Drugs that affect steroid conversion by liver enzymes:**
  - Rifampin: well documented
  - Anticonvulsants: consider IUD
  - Antibiotics: no conclusive evidence
- Anticonvulsants: consult a pharmacist and/or neurologist
- Antibiotics: most conservative approach is to recommend barrier contraception during and for 1 week after taking

Missed Pills

Miss 1 pill:
- take missed pill immediately, continue with pack

Miss 2 pills:
- for > 20 microgram pills, take 1 active pill immediately, continue with pack
- For <20 microgram pills, same as for > 2 missed pills

Miss > 2 pills:
- take 1 active pill immediately, continue with pack
- backup contraception x 7 days
- If in week 3, as above, then start new pack instead of placebo pills

Stopping Oral Contraceptives

- Longterm use of oral contraceptives is safe but may not be most cost effective option
- ~1 month delay to return of ovulatory cycles
- Can continue oral contraceptives in perimenopausal years
- No clear evidence for when to stop and/or switch to hormone replacement therapy
- Typically, age to switch is ~50-51 years

A Final Note: Prescription Alternatives to Oral Contraceptives

Contraceptive Injection

- Tradename: Depo-Provera
- Progestin only (medroxyprogestrone acetate)
- Intramuscular or subcutaneous injection every 12 weeks
- Pro: safe for women with contraindications to estrogen, seizure d/o
- Con: reversible decrease in bone mineral density, higher incidence of weight gain, mood changes than oral contraceptives

Contraceptive Patch

- Tradename: Ortho Evra
- Contains estrogen and Progestin
- Apply to upper arm x 3 weeks, off x 1 week
- Compared to Combined OCPs containing 35 ug estrogen: 2 x increased risk of venous thromboembolism
- However, still lower risk of venous thromboembolism from patch than from pregnancy
- Pro: no daily pills, easy to use
- Con: estrogen bioavailability variable, higher average levels of estrogen than oral contraceptive or Nuva Ring

Vaginal Ring

- Tradename: NuvaRing
- Contains estrogen and progestin
- Intravaginal x 3 weeks, remove x 1 week
- Local relase of hormones: serum estrogen and progestin levels 30-40% of oral contraceptives
- Risk for venous thromboembolism probably similar to oral contraceptives with less androgenic progestins
- Pro: no daily pills, easy to use
- Con: usually more expensive than oral contraceptive options, remembering to take out/reinsert

Implanon

- Progestin only contraceptive surgically inserted in upper arm
- Active for 3 years
- Pro: low maintenance, can be inserted in the office
- Con: high incidence of breakthrough bleeding, little information about adverse effects, therefore contraindicated if patient has other risk factors for venous thromboembolism