OCPs for PCPs

Kate Debiec, MD
Associate Professor
University of Washington and Seattle Children's Hospital
Pediatric and Adolescent Gynecology

September 22, 2019

UW Medicine

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Hat Tip: Lyndsey Benson, MD and Anne-Marie Amies Oelschlager, MD

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Disclosure

I am a Merck certified trainer for Nexplanon.

I do not have any financial relationships with the pill brands that I may reference; I will be using the specific drugs because familiarity with the brand names is clinically relevant. Most pills have between 3-6 trade names.

I have no other disclosures to report.

Objectives

- At the end of the talk, participants will be able to:
  - -Name helpful OCP resources
  - -List indications for OCPs
  - -Describe the mechanism of action of OCPs
  - -Discuss the components of OCPs
  - -Decide on which pill to begin
  - -Troubleshoot common pill complaints

There’s an app for that

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

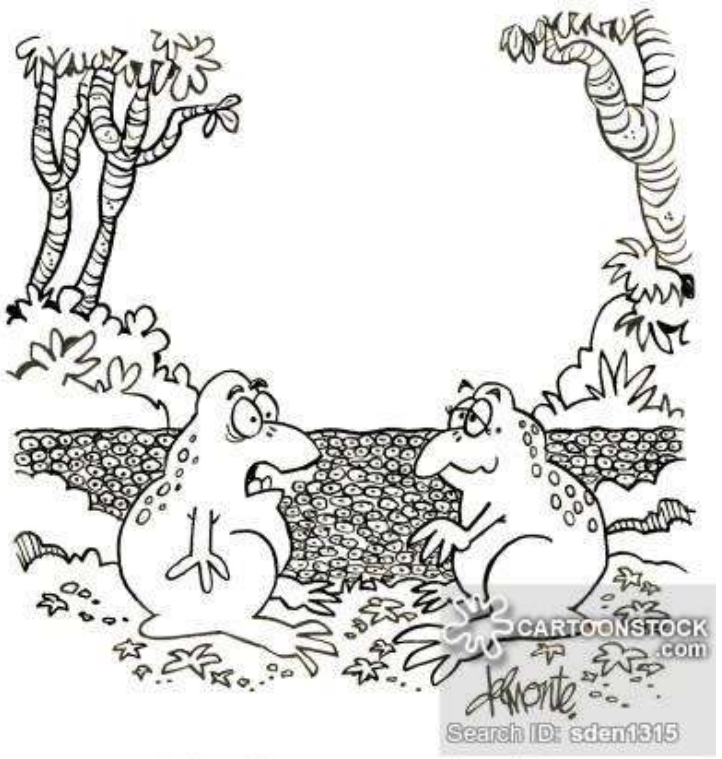
Summary

- Indications for OCPs: contraception + non contraceptive benefits
- Pill I like to start with: 30 mcg EE/norgestrel
- Side effect management:
  - Nausea/breast tenderness/headaches: decrease estrogen
  - BTB: increase estrogen or change progestin
  - Acne: chose third or fourth generation progestin

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Indications for OCPs

- Contraception (↓ pregnancy, abortion, ectopic pregnancy)
- Menstrual regulation or suppression
- Acne, hyperandrogenism
- Ovulation Suppression



"I thought you were on the pill!"

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

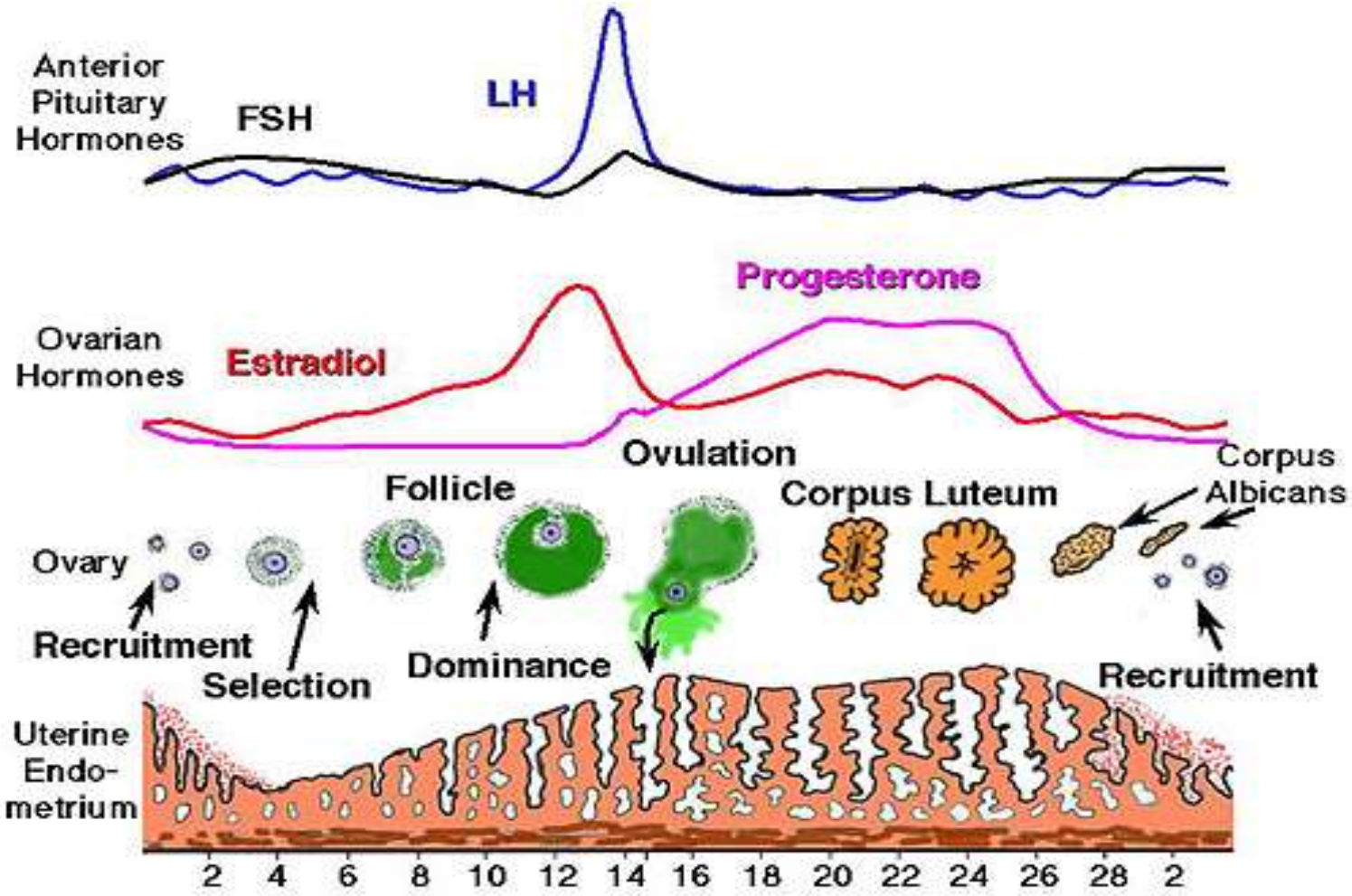
Contraception

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

How I counsel about contraceptives

Estrogen + Progestin	Progestin Only	Non-Hormonal
Pill	Progestin only pill	★ **Condoms**
Patch	Depo Provera	★ **Copper IUD**
Ring	★ **Lng IUD**	
	★ **Nexplanon**	

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION



Menstrual Cycle

Mechanism of Action

Estrogen
- Suppression of FSH
- Endometrial stability
-↑ intracellular progestational receptors
- Inhibition of ovulation

Progestin (synthetic progesterone)
- Inhibition of LH surge
- Causes thin, atrophic endometrium
- Thickens cervical mucous
- ↓ cilia activity in fallopian tubes

Estrogen Component

Ethinyl estradiol (EE)
- Potent
- Orally active metabolite of mestranol in most OCPs, ring, patch

Estradiol valerate (E2V)
- Metabolizes to estradiol, no clear benefits over EE

Estrogen Component

-Original OCPs had EE >50 mcg

-Doses decreased to 20-35 mcg in the 1970s

-More breakthrough bleeding with 20 mcg versus 30-35 mcg, but no difference in discontinuation

-Only one pill with 10 mcg EE, but may be less effective and not typically prescribed for adolescents

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Progestin Component

First generation

Norethindrone, norethindrone acetate

- Excellent potency, well-tolerated
- More unscheduled bleeding due to shorter half-life

Second generation

Levonorgestrel, Norgestrel

- More potent with increased half-life
- More androgenic

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Progestin Component

Third generation

Desogestrel, Noregestimate, Norelgestromin

- Increased progestational activity
- Decreased androgenic activity

Fourth generation

Drosperinone

- Derived from spironolactone
- Antiandrogenic & antimineralocorticoid effects

Which Progestin should you choose?

Cochrane review:
-Less discontinuation with 2nd generation vs 1st generation progestins

-Less unscheduled bleeding and possibly less discontinuation with 3rd generation

-Some evidence for increased VTE risk with 3rd and 4th generation progestins (desogestrel and drosperinone)

A tale of two progestins

- Levonorgestrel (2nd gen) vs Desogestrel (3rd gen)
  - both 30 mcg EE
- Significant differences in SHBG
  - ↑60% with levonorgestrel and ↑280% with desogestrel
- Associated with prothrombotic changes
  - FDA label of these products indicates increased risk of thrombosis 1.7 times over "older progestins"
- Pregnancy is also a high SHBG state

Van Rooijen M, Silvera A, Hamsten A, Bremme K. Sex hormone binding globulin. A surrogate marker for the prothrombotic effects of combined oral contraceptives. Am J Obstet Gynecol 2004;190:332-7.

Thrombosis risk with COCs

- **Slight ↑risk of non-fatal VTE may be present with low-dose COCs**
- **Incidence per 100,000 woman-years:**
  - COCs 10-30
  - Pregnancy 60
  - Non-users 4-8
- **2-4 fold increased risk following elective surgery**

Jick et al. Contraception. 2006 Jun;73(6):566-70. Epub 2006 Mar 29.
Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel.

VTE rate with different progestins

Incidence rates of VTE per 100,000 women years

- Norgestimate 30.6 (95% CI, 25.5-36.5)
- Desogestrel 53.5 (95% CI, 42.9-66.0)
- Levonorgestrel 27.1 (95% CI, 21.1-34.3)

Jick et al. Contraception. 2006 Jun;73(6):566-70. Epub 2006 Mar 29. Risk of nonfatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel.

Drosperinone? Is it better?

Approved for PMDD

Drospirenone

- 21- carbon low potency progestin
- Equivalent to Spironolactone 25mg dose
- Decreased weight at one year
- Possibly higher VTE rate than second generation OCP
- No more likely to develop hyperkalemia unless predisposed

BMJ 2002;324:869 (13 April 2002)Parsey KS, Pong A. An open-label multicenter study to evaluate Yasmin.

Contraception 2000;61:105-11. BMJ 2002;324:869. Dutch GPs warned against new contraceptive pill.

Which OCP?

- Friend or family with personal positive experience?
- Often start with 30 mcg pill
- Typically start 2nd generation, but can switch if significant androgenic side effects
- Learn names of “go to” OCPS

. Sullivan, *Fertil Steril*, 1999; 2. Endrikat, *Contraception*, 2001

Choosing a COC-by patient history

- **Estrogen sensitivity?**
  - 20mcg estrogen
- **Acne or other androgenic excess?**
  - 3rd gen. progestin or norethindrone <1mg
- **Endometriosis?**
  - High progestational activity, continuous
- **Functional ovarian cysts**
  - Higher estrogen dose? 50mcg EE (RARELY USED)

Choosing a COC-Mono-Bi-Tri?

- Multiphasic introduced to reduce total hormone exposure and attempt to mimic menstrual cycle
- No clinical advantage
- More confusing
- Greater potential for incorrect use
- SUMMARY: Monophasic preferred

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Regimens

- Traditional (21-7)
  - Designed to mimic cycle
  - Longer placebo needed with early higher dose pills; with lower EE, withdrawal bleed occurs ~2-3 days after last pill
- Shorter pill free interval (24-4)
- Extended cycling (>28 days active hormones)
- Continuous regimens

Reducing the Pill-Free Interval

- Reduce the possibility of ovulation
  - Decreased follicular development in extended cycles[1]
  - Shorter withdrawal bleeds[2]
  - No difference in break through bleeding[2]

- Combination oral contraceptive pills with reduced pill-free interval
  - 0.15 mg desogestrel/20 mcg EE x 21 d + 10 mcg EE x 5 d + 2 d placebo
  - 3 mg drosperinone/20 mcg EE x 24 d + 4 d placebo
  - 1 mg norethindrone acetate/20 mcg EE x 24 d + 4 d ferrous fumarate placebo

1. Sullivan, *Fertil Steril*, 1999; 2. Endrikat, *Contraception*, 2001

Extended Use Pills (>28 days of active hormones)

- Decreased scheduled bleeding
- Initial increase in unscheduled bleeding/spotting, decreases over time
- Improved ovulation suppression

<u>Pill choices:</u>

- Combination oral contraceptive brands with reduced pill-free interval
  - 0.15 levonorgestrel/EE 30 mcg x 84 d
  - 0.15 levonorgestrel/30 mcg EE x 84 d + 10 mcg EE x 7 d
- ANY MONOPHASIC PILL

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Continuous pills

- Same as extended regimens, but further ovulation/menstrual suppression

- Treatment of unscheduled bleeding with continuous use:
  - Hormone-free interval for 3-4 days (provided OCP has been used continuously for 21 days prior)

Starting pills

- Screen for contraindications to estrogen use using CDC's medical eligibility criteria
- Follow CDC's Selected practice recommendations (SPR)
  - Check BP before starting
  - Document weight/BMI
  - Assess BP yearly/at follow up visits
- If >5 days since LMP, use a back-up method or abstain for 7 days (2 weeks if obese as there is a longer delay for ovulation suppression)

1. Sullivan, *Fertil Steril*, 1999; 2. Endrikat, *Contraception*, 2001

WHO Medical Eligibility Criteria

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

WHO Level 4 Absolute Contraindications

- Migraines with focal symptoms
- Risk of Thromboembolism
- Vascular disease or ischemic heart disease
- Complicated valvular disease
- Complicated solid organ transplant
- HTN with BP $\geq$ 160/100
- Severe liver disease (cirrhosis, hepatitis, tumors)
- Current breast cancer
- Breastfeeding and <21 days post partum
- Major surgery with prolonged immobilization
- Smokers of $\geq$ 15 cigarettes/day, $\geq$ age 35
- Breast cancer

WHO Level 3 Relative Contraindications

- Diabetes or vascular disease x 20 years
- Multiple CAD risk factors
- Controlled HTN or BP=140-159/90-99
- Mild cirrhosis
- Current or treated symptomatic gallbladder disease
- History of cholestasis with COC use
- History of breast cancer w/o recurrence x 5 years
- Migraine
- Hyperlipidemia
- 21-30 days postpartum (or up to 42 days if other risk for VTE) and breastfeeding
- Smoking < 15 cigarettes/day at age > 35
- Drug interactions

Clinically Important Drug Interactions

- Anticonvulsants
  - Oxycarbazepine
  - Phenobarbital
  - Carbamazepine
  - Phenytoin
  - Primidone
  - Topiramate
  - Lamotrigine
  - OK: gabapentin, levetiracetam, tiagabine*
  - Benzodiazepines
- Theophylline
- St. John's Wort
- Vitamin C
- Antibiotics
  - Rifampin
  - Griseofulvin

Contraceptive Efficacy

- Efficacy
  - Perfect use vs. actual or typical use
  - **Combined oral contraceptive pill**
    - **99.7% perfect use, 92% actual use**
    - 10 million women using the pill:
      - 1% ↓ efficacy = 100,000 unintended pregnancies in 1 year
- Adherence (Compliance)
  - Critical and usually over-reported

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

OCP Use Patterns

- 16% of all OCP users are inconsistent in pill taking
- Continuation rates
  - 18% of all OCP users discontinue by 6 months
  - 32% discontinue by 1 year
    - 9 to 40 % continue in free urban community and hospital-based clinics
    - 75 % continuation rate at one year in suburban practice

- Teens using OCPs are 55% more likely to have a contraceptive failure

Trussell, J. Fam Plann Perspect. 1999;31:64-72&93

Patient Education

- Efficacy, mechanism of action
- Benefits / risks (common and serious side effects)
- Lack of STI protection
- Compliance hints (get an app or a timer, schedule with another activity like teeth brushing)
- Potential drug interactions
- When to use back-up
- How to get refills

Common Side Effects

- Breakthrough bleeding
- Weight gain
- Nausea
- Headache
- Breast tenderness
- Acne

Management of Common Side Effects

- Breakthrough Bleeding or Spotting
  - Within first 3 months:
    - Before 10th pill
      - ↑ estrogen dose
    - After 10th pill
      - ↑ progestin potency or dose
  - New onset after several months:
    - D/C for 3-7 days, then start new pack
    - Add short course of Premarin
    - Increase estrogen dose

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Management of Common Side Effects

- Weight gain
- Mean and median weight gains at 1 year
  - DMPA 3.0 and 2.4 kg
  - OC 1.3 and 1.5 kg
- More than 10% baseline weight?
  - 25% of DMPA users
  - 7% of OC users
  - Of adolescents who gained > 5% of baseline weight at 3 months, 93% gained even more weight at 12 months

Risser et al. VJ Adolesc Health. 1999 Jun;24(6):433-6.
Weight change in adolescents who used hormonal contraception

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Management of Common Side Effects

- Nausea
  - Avoid double dosing
  - Take with food or at bedtime
  - Take another pill if vomiting occurs within 1 hour of dose
  - Switch to pill with less estrogen

Management of Common Side Effects

- Acne
  - All combination oral contraceptives should improve acne
  - ↓ androgenicity of pill (not 2nd gen)
  - ↑ estrogen dose
  - Treat acne with labeled products

Management of Common Side Effects

- Headache
  - Discontinue combination oral contraceptive if headache severe or associated with focal neurologic symptoms
  - ↓ estrogen or progestin dose or try continuous use

Management of Common Side Effects

- Breast Tenderness
  - NSAIDs/tylenol
  - Good support bra
  - ↓ estrogen dose
  - Therapies not proved in randomized trials:
    - Low fat diet
    - Elimination of caffeine (helps some women)
    - Evening primrose oil or gamma linoleic acid
    - Vitamin E

Management of Common Side Effects

- Leg Cramps / Swelling
  - Consider pill with less estrogen or ↓ androgenic profile
  - Recommend more dietary calcium and less sodium

Counseling Patients Taking Progestin Only Pills

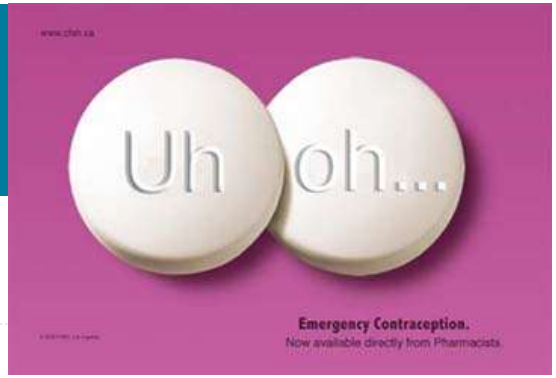
- Start first day of bleeding or anytime in cycle with 1 week of back-up
- Missed pills (use back-up for 2 days)
  - >3 hours late or missed 1 pill – take as soon as remembered or usual time
  - Missed ≥ 2 pills – discard missed pills and take next one usual time

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

Advantage and Disadvantages of Oral Progestin Only Methods

Advantages	Disadvantages
-↓Menstrual disorders	-Menstrual irregularity
-Immediate return to fertility	-Few options
-Avoid estrogen-related side effects	-Timing of dose critical
-May be started sooner post-partum and after abortion or miscarriage	-Loss of positive estrogen effects
-Safe in breastfeeding	-↑risk persistent ovarian follicles & ectopic pregnancy
	-Less effective than combination oral contraceptives

Emergency Contraception



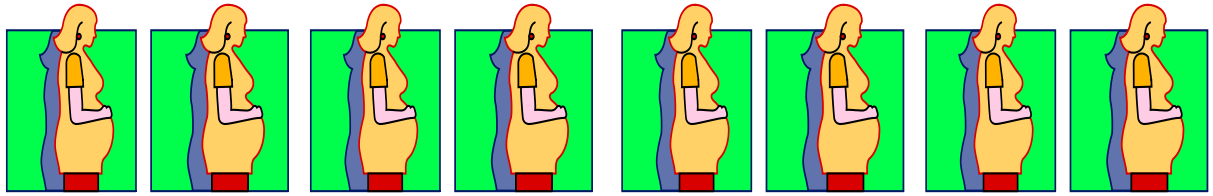
- Mechanism of action similar to OC's
- Estimated efficacy 75-90%
- Efficacy demonstrated up to 120 hours post coitus
- Side effects similar to new-start OC's
- No teratogenicity demonstrated
- Dosing: take both pills at once
- Several OC regimens endorsed by FDA

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

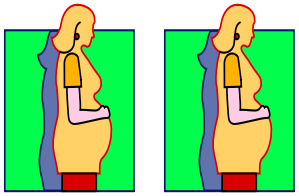
Emergency Contraception Efficacy (use after one act of unprotected intercourse)

If **100** women have unprotected sex in the 2nd or 3rd week of their cycle…

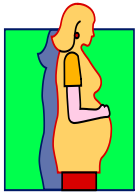
…**8** will become pregnant without EC



…**2** will become pregnant using **combined** EC (75% reduction)



…**1** will become pregnant using **progestin** EC (89% reduction)



Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

THANK YOU!

Please feel free to call or email with questions

kdebiec@uw.edu

Adolescent Clinic 206.987.3005 (nurse line)

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

OCs and Hyperandrogenemia Mechanisms of Action of Estrogen and Progestin

- **Estrogen**
- Increases level of sex hormone-binding globulin (SHBG)
- Results in decreased circulating free testosterone
- Inhibition of adrenal androgen secretion
- *not well understood: possibly due to ↑ in serum cortisol-binding globulin concentrations which ↑ serum cortisol concentration which ↓ pituitary ACTH secretion

- **Progestin**
- Inhibits luteinizing hormone (LH)
- Reduced LH → decreases synthesis of androgens by theca cells in the ovary
- Decreases 5α-reductase activity in skin