Managing Special Circumstances in Contraceptive Care

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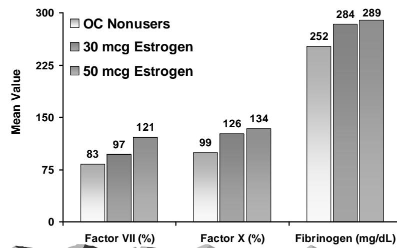
Objectives

- Identify the baseline risks of modern combined hormonal contraceptive methods
- Discuss the interaction of these risks with certain medical conditions
- Discuss the risks and benefits of intrauterine contraception for women with medical conditions

The Estrogen Component of COCPs Is Responsible for Most Current Risks

OC Effects on Clotting Parameters



Meade et al. *Lancet.* 1977;2:948.

Cardiovascular Diseases Affected by OC Use

- Venous thrombosis and embolism
- Thrombotic strokes
- Myocardial infarction

Harlap et al. *Preventing Pregnancy, Protecting Health: A New Look at Birth Control Choices in the United States.* New York: The Alan Guttmacher Institute; 1991:74.

Incidence of VTE in Women of Reproductive Age

	Estimated Incidence of VTE (per 10,000 Woman-Years)
Controls	1
OC users	3
Pregnancy	6

Farmer, Preston. *J Obstet Gynaecol.* 1995;15:195.

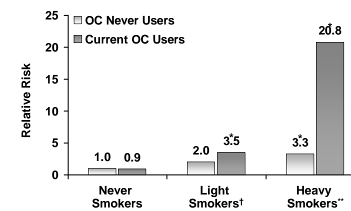
Stroke Risk and Estrogen Dose[1]

Dose Mestranol or EE (mcg)	*Adjusted Odds Ratio*	*95% Confidence Interval*
Never users	**1.0**	**(Ref)**
>50	**5.8**	**1.5–22.8***
50	**2.9**	**1.7–5.0***
30-35	**0.6**	**0.1–2.9**

* $P=0.01$.
† $P<0.01$.
1. No data on 20-mcg EE dose.
Hannaford et al. *Stroke.* 1994;25:935.

Relative Risk of MI

Royal College of General Practitioners' Study: 1968-1987



N=158.
* $P<0.05$.
† <15 cigarettes/day.
** ≥15 cigarettes/day.
Croft, Hannaford. *Br Med J.* 1989;298:165.

OCs, Smoking, and MI Risk

- OC-induced changes in coagulation factors act synergistically with nicotine-induced vasoconstriction and increase in thromboxane
- Effect is especially significant with pre-existing arterial vascular disease
  - Women ≥ age 35
  - Hypertensives
  - Diabetics

Conclusions
Cardiovascular Risk and OC Use

- 3- to 4-fold increased risk of VTE among all low-estrogen dose OC users
- Increased risk of MI only in smokers and those with pre-existing arterial vascular disease
- Probably no increased risk of stroke in healthy, nonsmoking OC users. Risk may be increased in certain populations.

Contraindications to COCPs

- Unexplained vaginal bleeding
- History of venous thrombotic disease*
- History of arterial vascular disease*
- Smoker > 35*
- Untreated hypertension*
- Migraines with focal neurologic signs*
- Impairment of liver function
- Personal history of breast cancer

*Can use POPs, Dep Provera, Implanon

Estrogen in Oral Contraceptives
Ethinyl Estradiol

Positive Effects
- Increase contraceptive efficacy
- Stabilize endometrium (prevent BTB)
- Strengthen bones
- Improve lipids
- Healthy skin

Negative Effects
- Nausea, vomiting
- Headaches (including migraines)
- Increased blood pressure
- Thrombogenicity

Estrogen in Oral Contraceptives

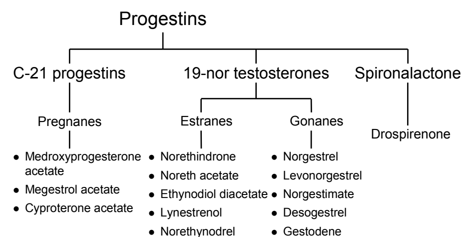
- None – Micronor, Nor-QD, Ovrette
- 20 µg – Loestrin 1/20, Alesse, Mircette, Yaz, Lybrel
- 25 µg – Ortho Tri-Cyclen Lo, Cyclessa
- 30 µg – Loestrin 1.5/30, Ortho-Cept (Desogen), Nordette (Levlen), Lo/Ovral, Estrostep, Yasmin, Seasonale, Seasonique
- 32.4 µg – Triphasil (Trilevlen)
- 35 µg – Ortho-Novum 7/7/7, 10/11, 1/35; Modicon, Norinyl 1+35, Tri Norinyl, Brevicon, Ortho-Cyclen, Ortho Tri-Cyclen, Demulen 1/35, Ovcon 35

The Progestin Component of OCs

Progestins

- No significant immediate risk
- Associated with side effects and metabolic effects
  - Acne, hirsutism, weight gain
  - Insulin resistance
  - Adverse lipid profile
- Adverse effects significantly decreased or reversed with reduced doses and new formulations

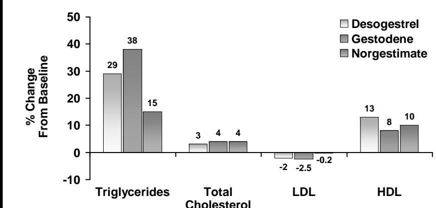
Classification of Progestins



Gonane Progestins
Desogestrel, Norgestimate

Small Changes in Steroid Structure Responsible for Differences in:
- Metabolism
- Androgenic / progestational activity
- Globulin binding
- Metabolic effect
- Clinical profile

Changes in Lipids Associated With OCs Containing Low-Androgenic Progestins



Speroff, DeCherney. *Obstet Gynecol.* 1993;81:1034.

Drospirenone (Yasmin®, Yaz®)

- Binds to progesterone receptors
  - Inhibits ovulation
  - Endometrial effect
- Spironolactone derivative
  - Anti-androgenic effects
  - Antimineralocorticoid/diuretic effects

30-μg EE/3-mg DRSP: Additional Labeling

- Warning to measure serum potassium at first month in patients taking the following medications chronically
  - NSAIDs, including Motrin, Advil, Aleve, etc.
  - Heparin
  - Potassium-sparing diuretics
  - ACE inhibitors
  - Angiotensin-II receptor antagonists
  - Aldosterone antagonists
  - Potassium supplements, including multi-vitamins

Contraceptive Ring and Patch

- Slow release methods – first day of menses start (not Sunday start) is the best approach
- More convenient for many women
- Same hormones as oral contraceptives
  - Similar efficacy
  - Similar side effects
  - SAME CONTRAINDICATIONS

Women of Reproductive Age with Medical Problems

- Risk of pregnancy may be greater than that of effective contraception
- Better to have planned than unintended pregnancy

Hypertension

- All COCPs mildly increase bp (first pass through liver increases angiotensinogen)
- History of PIH not a contraindication to COCPs
- If bp 130/85 – 140/90
  - Consider ↓ E dose
  - Consider drospirenone
- If bp > 140/90, stop COCPs
  - Can use progestin-only method
- If bp treated in nonsmoker age < 35, can try low-dose COCP with careful observation

Diabetes Mellitus

- No evidence that COCPs worsen or accelerate the development of Type I or Type II diabetes
- COCPs contraindicated in smokers, diabetics age ≥35, and in the presence of vascular disease
- History of gestational diabetes
  - On the whole, COCPs do not accelerate the development of Type II diabetes
  - Potent progestins (DMPA, POPs, levonorgestrel) immediately postpartum may increase risk
  - COCPs with norgestimate, desogestrel, norethindrone, or perhaps drospirenone, preferred

Hyperlipidemia

- COCPs increase triglycerides
- Older androgenic progestins increase LDL and lower HDL, newer progestins reverse
- COCPs can be used with lipid-lowering agents and controlled hyperlipidemia
- COCPs contraindicated
  - Triglycerides > 250mg/dl
  - LDL > 160 mg/dl
  - Multiple coronary risk factors

Obesity

- A delicate balance
  - Increased risk of DVT/VTE
  - Decreased efficacy of low-dose methods
- DMPA associated with potential 5-10# per year further weight gain
  - Accumulates at satiety center, ↑ insulin resistance
  - Requires counseling and support re dietary control
- Optimal choices
  - IUD, particularly Mirena
  - Implanon?

Combination OC Use in Women With Coagulation Disorders

Problem	*Ok to Use*	*Contraindicated*
• History of deep vein thrombosis, pulmonary embolism		√*
• Superficial varicosities	√	
• Bleeding disorders	√	
• Sickle cell disease	√	

*unless anticoagulated

Other Factors Related to VTE Risk

- COCPs containing desogestrel
  - VTE risk 1.5-2x greater than with other combination OCs in some, but not all, studies
- Obesity: 5X risk of VTE
- Age > 40 substantially increases risk
- 50% higher risk of VTE after major surgery
- Air travel
- Progestin-only methods considered safe

Thrombophilias

- COCPs contraindicated with known Factor V Leiden or other thrombogenic mutations
  - Risk of VTE 28.5/10,000 women
- WHO recommends against screening all women
  - The mutations occur in 10% of white women
  - Thrombotic events are rare
- Consider screening women with a first-degree relative with history of DVT or VTE
  - APC resistance assay ± prothrombin gene G20210A

Headaches (Non-Migraine)

- If occur during active pills, ↓ estrogen dose
  - Switch to another method if headaches persist or migraines develop
- If occur during pill-free week, probably estrogen-withdrawal headaches
  - Try daily continuous OCs

Migraine Headaches

- E increases risk of CVA in migraineurs
  - Common vs. classic migraine
- COCP contraindicated with neurologic signs
  - Can use progestin-only method
- Can try low-dose COCP in nonsmoker age < 35 with common migraine
  - 40% worsen, must stop COCPs
  - 40% same frequency and severity
  - 20% improve

Thyroid Conditions

- COCPs not contraindicated
- Estrogen increases thyroid binding globulin → ↑ bound thyroxin → ↑ thyroxin production (↑ T4, ↓T3, TSH unchanged)
- In women on levothyroxine, estrogen can increase the dose required
- In women on levothyroxine, check TSH 4-6 weeks after starting COCPs

Systemic Lupus Erythematosus

- Pregnancy can exacerbate SLE
- Estrogen component of COCPs may cause flare-ups
- COCPs contraindicated in SLE patients with
  - Peripheral vascular disease
  - Nephritis
  - Antiphospholipid antibodies
- Appropriate contraception for SLE patients includes
  - Progestin-only methods
  - IUDs
  - COCPs in selected cases with mild disease

Rheumatoid Arthritis

- Meta-analysis of 9 hospital- and population-based studies suggests OC use may prevent progression of rheumatoid arthritis to more severe form
- Case-control study suggests protective effect of OC use
  - OC use for ≥5 years: RR of developing severe disease 0.1 (95% CI, 0.01-0.6)

Mood Disorders

- Not a contraindication to COCPs
- Can worsen, but more often improve
- Add multivitamin and/or B complex
- Monophasic, low-androgenic pill preferred
- Drospirenone pill may be a good choice
- If symptoms appear or worsen
  - Rule out other causes
  - Change to nonhormonal method

Mood Disorders and DMPA

- No evidence for increased depression with DMPA → not a contraindication
- Careful observation
- Can occur anecdotally
  - Consider adding estrogen (no evidence)
  - Don't hesitate to switch methods

Perimenopause

- Benefits
  - Symptom relief
  - Regulation of menses
  - Maintenance of bone density
- Risks
  - Safe for nonsmokers with no CV risk factors
  - Incidence of VTE increases at age 40
    - Exercise caution with high risk, e.g. obesity

Medication Use

Anticonvulsant Use

- Anticonvulsant drugs can induce liver enzymes, leading to lower estrogen levels
- High rate of BTB with concomitant use of OCs and antiepileptic drugs suggests decreased contraceptive efficacy
- Effective contraception essential because
  - Pregnancy increases seizure frequency and risks to mother and fetus
  - Many anticonvulsants are teratogenic

Which anticonvulsants?

- Affect Hormone Levels
  - Phenobarbital
  - Phenytoin
  - Carbamazepine
  - Oxcarbamazepine
  - Felbamate
  - Primidone
  - Topiramate
  - Vigabatrin
- Do not affect
  - Benzodiazepines
  - Ethosuximide
  - Gabapentin
  - Lamotrigine
  - Levetiracetam
  - Tiagabine
  - Valproic Acid
  - Zonisamide

Enzyme-Inducing Anticonvulsants

- Consider use of back-up barrier method or OCs containing 50 mcg EE, especially if breakthrough bleeding occurs
- Consider use of DMPA, which has some anti-seizure activity and is probably unaffected by enzymes
- IUD may also be appropriate
- Do not use low-dose progestin-only methods

Antibiotics

- There is no evidence that common antibiotics affect hormone levels with OCPs or decrease the efficacy of OCPs
- Only rifampin (used for TB and HIV) and griseofulvin (used for significant fungal infections) have been shown to affect efficacy of oral contraceptives

Remember Health Benefits of COCPs

Menstrual Cycle Benefits = Improved Quality of Life

Decreased Risk Of	*Relative Risk*
PMS	**0.7**
Menstrual-Related Problems	
Dysmenorrhea	**0.4**
Irregularity	**0.7**
Menorrhagia	**0.5**
Iron-Deficiency Anemia	**0.6**

Mishell. *Am J Obstet Gynecol.* 1982;142:809.

Other Benefits = ↓ Morbidity and Mortality

Decreased Risk Of	*Relative Risk*
Endometrial cancer[1]	**0.5**
Ovarian cancer[1]	**0.3**
Functional ovarian cysts[1]	**0.4**
PID[1]	**0.5**
Ectopic pregnancy[2]	**0.1**
Benign breast disease[1]	**0.5**

1. Mishell. *Am J Obstet Gynecol.* 1982;142:809.
2. Ory. *Obstet Gynecol.* 1981;57:137.

Intrauterine Contraception

Appropriate Candidates for IUC Use

- IUCs are appropriate for women who seek a method of contraception that is
  - Effective, reversible, long term, and convenient
  - Coitus independent
- Such women are particularly good IUC candidates if they are in a stable, mutually monogamous relationship
- Hormone-releasing IUCs decrease menstrual blood loss
  - Preferred for women with menorrhagia or dysmenorrhea

Conditions for Which IUC Insertion Is Contraindicated

- Might be pregnant
- Unexplained vaginal bleeding
- Acute PID or recent history of PID
- High risk for STIs and PID
- Post-pregnancy or post-abortion infection within 3 mos
- Acute cervicitis, vaginitis, or genital actinomycosis
- Distorted uterine cavity
- Uterine or cervical cancer

Conditions Precluding Use of One but not Both IUCs

- Mirena
  - Breast cancer
  - Acute liver disease
- Paragard
  - Allergy to copper
  - Wilson's Disease

IUCs: Safe for Women With Certain Medical Conditions

- IUCs usually have no impact on either the disease or the drugs used in treatment
- Copper IUCs provide safe and reliable contraception without systemic hormonal effects
- Levonorgestrel-releasing IUC may cause systemic hormonal effects

Cardiovascular Disease

IUCs can be used in women with

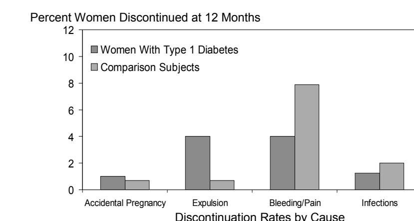
- History of VTE, MI, or stroke
- Valvular heart disease
- Hypertension
- Risk Factors for cardiovascular disease
  - Smokers aged ≥35 years
  - Obesity

Diabetes Mellitus

- Women with diabetes mellitus can use IUCs
- IUCs not associated with increased infection in women with diabetes[1-3]
- Diabetes has no impact on IUC efficacy or adverse event rates[1,2,4]

1. Skouby SO, et al. *Fertil Steril.* 1984;42:568; 2. Mestman JH, Schmidt-Sarosi C. *Am J Obstet Gynecol.* 1993;168:2012; 3. Manufacturer's prescribing information; 4. Kjos SL, et al. *Obstet Gynecol.* 1994;84:1006.

One-Year Discontinuation Rates per 100 Women With Type 1 Diabetes vs Controls



P>0.05 for each comparison.

Hematologic Disorders and Anemia

- Limited data available regarding use of IUCs by women with hematologic disorders (eg, von Willebrand's disease, thrombocytopenia)
- Hormone-releasing IUCs preferred
  - decrease menstrual blood loss[1]
- Iron deficiency anemia is a relative contraindication to copper IUC

1. Treiman K, et al. *Population Reports.* 1995.

Neurologic Disorders: Migraine Headache and Seizure Disorders

- IUCs have no impact on migraine headaches, seizure disorders, or drugs used to treat them
- DMPA may reduce seizure rates and should also be considered for women with seizure disorders

Mattson RH, et al. *Neurology.* 1984;34:1255; Kaunitz AM, Rosenfield A. *Drugs.* 1993;45:857.

Neuropsychiatric Conditions

- IUC are appropriate for many women with depression or other neuropsychiatric disorders
  - Convenient, no impact on mood or drug treatment
  - Eliminates possible difficulties in daily pill-taking or visiting clinicians for scheduled injections
- For women with comorbid substance abuse disorders, clinical judgment—weighing STI risks against risks of unintended pregnancy—is necessary

Gynecologic Conditions that Do Not Contraindicate IUC Use

- Cervical dysplasia or abnormal cervical cytology, once invasive carcinoma has been ruled out
- Leiomyomas not distorting the uterine cavity
- Endometriosis (hormonal methods including progestin-releasing IUC are preferred)
- Irregular menses (hormonal method preferred)
- Cervical stenosis (may require paracervical block and dilatation)
- History of ectopic pregnancy

IUCs for Perimenopausal Women

- Among perimenopausal women who are bleeding normally or less frequently, either the Copper T 380A IUD or the levonorgestrel-releasing IUD is acceptable
- Among women who are bleeding abnormally
  - Preinsertion endometrial evaluation is recommended
  - If no intrauterine pathology, hormone-releasing IUDs may be appropriate

Noncontraceptive Benefits of Mirena (Off-label uses)

- Effective treatment for menorrhagia
  - Increases hemoglobin concentration
  - Acceptable alternative to hysterectomy
- Decreases dysmenorrhea
  - Even in medical conditions
- Provides effective progestin component for Hormone Therapy and possibly tamoxifen
- May decrease incidence of endometrial Ca

Remember contraceptive efficacy of IUC – Same in typical and perfect use ↓ May be of particular benefit to women in special circumstances