LECTURE NOTES
Advanced Pharmacotherapeutics
CONTRACEPTION
FEMALE (genetically determined at birth) Reproductive system

Learning Outcomes

1. Review Pathophysiology
2. Clinical Pharmacology
3. Mechanism of action (MOA)
4. PK/PD
5. Medication/Interactions
6. ADR's -Adverse drug reactions
7. RBA (Risk Benefit Analysis/Stratification)

FSH & LH trigger

- Ovulation
- Menstrual cycle
    - DAY #1 =first day of menses represents the first day of cycle
    - divided into two phases: follicular and luteal
        - follicular phase =begins with the onset of menses and ends on the day before the luteinizing hormone (LH) surge
        - 14 to 21 days in the follicular phase
        - luteal phase =begins on the day of the LH surge and ends at the onset of the next menses
            - 14 days in the luteal phase

Estrogen	Progesterone

• Estrogen, a steroid hormone, derived from androgenic precursors androstenedione and testosterone by means of aromatization
• Naturally occurring estrogens are (order of potency)
  ○ 17 (beta)-estradiol (E2)
  ○ estrone (E1)
  ○ estriol (E3)
• Effects of estrogen
  ○ Increases bone density
  ○ Results in normal skin and blood vessel structure
	• "Hormone of pregnancy"
	• Maintains thickened endometrium
	• Hypertrophy (thickening) of the myometrium in preparation of labor
	• Relaxing smooth muscle of the myometrium, which prevents pre-mature contractions
	• helps uterus expand
	• promotes growth lobules and alveoli in breast preparing for lactation
	• preventing additional maturation of ova by way of suppressing FSH and LH, thereby stopping the menstrual cycle

○ Affects lipid levels ○ Reduces bowel motility ○ Enhances coagulability of blood ○ Causes edema because of its action on the renin–angiotensin system ○ Maintains stability of the thermoregulatory center	• provides immune modulation of the fetus so the mothers system does not attack the fetus and prevents pre-term labor

Goals of Treatment

1. Effectiveness
2. Statistics show 2 numbers:
   a. Failure rate: # of women per 100 who become pregnant after 1 yr. when using a birth control consistently & correctly
   b. Typical use failure rate--takes into account improper or inconsistent use
   c.
3. Factors that contribute to improper use include lack of partner involvement, forgetfulness, feeling guilty about sex, poor communication w/partner, not wanting to appear "easy
4. About half of all unintended pregnancies occur among women using contraceptives

Hormone-based contraceptives

- Combined estrogen/progestin contraception (COC)
  - pills, patch, or vaginal ring
- Progestin-only contraception (POP)
  - pill, injection, implant, or progestin intrauterine device

PROGESTRIN containing names	ESTROGEN containing names
progestogen norethisterone Norgestrel Levonorgestrel medroxyprogesterone	ethynediol diacetate gestodene desogestrel estrogen Ethinyoestradiol (EE) mestranol

Clinical Pharmacology

- Mechanism of action:

- Progestins:
  - inhibit secretion of FSH, LH - inhibit ovulation
  - Cause atrophy of the endometrium – preventing implantation
  - additional actions on endometrium tubal motility, cervical mucosa
- Estrogens:
  - Improves efficacy by suppressing FSH release
  - Provides cycle control

First-generation progesterone(s)	Norethindrone, norethindrone acetate, and ethynediol diacetate
Second-generation progesterone (s)	Norgestrel and levonorgestrel
Third-generation progesterone	Desogestrel and norgestimate
Fourth-generation progesterone	19-nor testosterone derivative, Dienogest
Spironolactone derivative	Drospirenone

- Bioavailability –ALL PO preparations undergo FIRST PASS metabolism
- Clinical Pharmacology
- absorption
- well absorbed orally
- distribution
- bound to plasma proteins

- CTP3A4 -system caution with inducers
  - increased clearance, lower plasma estrogen concentrations
  - Induce failure

- Antibiotics (fact or myth??)
  - ***Rifampin only concern
  - Caution due to may impaired absorption
  - Drugs that interfere with liver enzymes:
    - rifampicin, Griseofulvin, anticonvulsants, St John's Wort

Pharmacodynamics

- Two formulations of estrogen are available in contraceptive preparations: ethinyl estradiol and mestranol.

Rational Drug Selection

- Start with absolute contraindications!!! (must know these)
  - They include
    - ________________________
    - ________________________
    - ________________________
    - ________________________
- Delivery method should be of patient's choice.
- Fine tune based on:
  - Menstrual pattern
  - Side-effect profile ****
- Consider:
  - Patient's desire for discretion
  - Timing of subsequent pregnancy
- ALL types of oral contraception (OC) have similar effectiveness.

Cost

- Retail cost of OC is $30 to $100 per cycle.
- Generic OC is available on $4 retail lists.
- Intrauterine device (IUD) or implant: upfront cost is expensive but may have lower overall cost.
- Patient variables

Mechanisms of Pregnancy Prevention

- Progestins
  - are primarily responsible for the contraceptive effect.
  - Progestins exhibit a negative effect in the hypothalamic-pituitary-ovarian axis.
  - Progestins cause atrophy of the endometrium, preventing implantation.
  - The estrogen component improves efficacy by suppressing FSH release.
- Estrogen provides cycle control.
  - Estrogen: Need to Know
    - Estrogen-only products are contraindicated in women with an intact uterus

Precautions and contraindications:

  - Pregnancy (unless specialist directed low hormone level)
  - Breast cancer
  - Estrogen-dependent neoplasia
- Active deep vein thrombosis or pulmonary embolism
- History of stroke or myocardial infarction (within 1 yr.)
- Liver dysfunction
- Smokers (>15 per day age >35) caution(<15 per day age >35)

Progesterones

- Progesterones
- Progesterone (Promethrium, Progesterone in Oil, Crinone, Prochieve)
- Medroxyprogesterone acetate (Provera, Depo-Provera)
- Norethindrone (Aygestin)
- Megestrol acetate (Megace)

Androgen-derived progestins

- Norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, desogestrel, levonorgestrel, and norgestimate
- Drospirenone: a progestin developed as a derivative of spironolactone

Progesterones: Need to know

- Precautions and contraindications
  - Thromboembolic disease
  - Breast cancer
  - Impaired liver function
  - Depression
  - Disorders that worsen with fluid retention
  - Progesterone
    - Old pregnancy category D.
  - Norethindrone acetate
    - Old pregnancy category X.
- Adverse Events:
  - Irregular bleeding
  - Amenorrhea
  - Acne

Injectable and implanted progesterone

1. Weight gain
2. Irregular menstrual bleeding
3. Osteoporosis risk with 2+ year use

Progesterones: Clinical Use

- Postmenopausal hormone replacement
  - Combined with estrogen when uterus is intact
- Progestin-only contraception
  - Progestin-only pills (norethindrone)
  - Medroxyprogesterone acetate (Depo-Provera)
- Progestin implanted intrauterine device (Mirena)

- Monitoring
    - Depression
    - Increased risk of seizures
    - In diabetes, monitoring of blood glucose

Dosing Regimens
- "Traditional"
    - 21 days active drug + 7 days inactive tablets with withdrawal bleed during inactive tablets
- Extended cycle: 84 days of active drug, then 7 days off
    - Withdrawal bleed once every 3 months
- Monophasic: same dose of estrogen and progestin for full cycle
- Biphasic: vary the dose of progestin
- Triphasic: vary the dose of estrogen, progestin, or both

Doses
- monophasic
- estrogen - up to 50 mg/day
- progestogen - up to 1 mg/day

Biphasic
- estrogen: constant
- progestogen:
    i. example: 11 days @50 mg, 10 days @125 mg

Triphasic
- estrogen 30/40/30
- progestogen 50/75/125

Starting Methods
1. First-day start
    a. Pills started on first day of menstrual cycle
    b. No back up method needed
2. Sunday start
    a. First pill taken on the Sunday following the start of menses
    b. Back up method for first 7 days
    c. Menses only occur during the week

3. Quick or "same day" start
    a. First pill taken on the day of the office visit
    b. Back up method for first 7 days

Non-Contraceptive Benefits

1. Decreased dysmenorrhea, menstrual irregularities, and menstrual blood loss
2. Lessening of acne and hirsutism
3. Fewer ovarian cysts
4. Significantly reduced endometrial and ovarian cancer risk
5. Lower incidence of benign breast conditions such as fibrocystic changes and fibroadenoma
6. Reduced risk of hospitalization for gonorrheal pelvic inflammatory disease
7. Suppression of endometriosis for women who do not currently desire pregnancy
8. other risks
9. thromboembolic disorder
10. high dose estrogen - Inman, dose response relationship
11. worse with other risk factors (age, smoking)
12. ? third generation progestogens
13. differentiating effects on VTE and other cardiovascular disease

MAJOR teaching points: How to use oral contraceptives

- Different types of OCs will differ in how to begin, and other instruction
- Don't skip pills, regardless of whether having sex
- Take pill at the same time each day
- If you miss 1 pill:
    - take missed pill as soon as you remember, and then take next pill at the regular time
- If you miss >1 pill:
    - consult health care practitioner for advice; use a backup method for remainder of your cycle

Patient education

1. Taking birth control pills can increase your risk of blood clots, stroke, or heart attack
2. You are even more at risk if you have high blood pressure, diabetes, high cholesterol, or if you are overweight
3. Your risk of stroke or blood clot is highest during your first year of taking birth control pills
4. Your risk is also high when you restart birth control pills after not taking them for 4 weeks or longer

Causes of Adverse Reactions of Hormone Contraception			
Too Much Estrogen • Heavy bleeding • Cystic breasts • Breast enlargement • Breast tenderness • Dysmenorrhea • Premenstrual edema • GI symptoms • Premenstrual H/A • Premenstrual irritability	**Too Little Estrogen** • Bleeding (spotting) early in cycle • Too light bleeding • Bleeding throughout the cycle • Amenorrhea	**Too Much Progestin** • Increased appetite • Candidiasis • Depression • Fatigue • Cervicitis	**Too Little Progestin** • Bleeding (spotting) late in cycle • Heavy bleeding • Delayed withdrawal bleeding • Bloating • Dysmenorrhea • Premenstrual edema • GI Symptoms • Premenstrual H/A • Premenstrual irritability

progestogen excess
amenorrhea
acne/oily skin
weight gain
mood changes
depressed libido
breast tenderness

Oral contraceptives

possible side effects & health issues
Rare but serious side effects of OCs—CALL to clinic/health care practitioner ASAP

Oral contraceptives
possible side effects & health issues

• Rare but serious side effects of OCs—CALL to clinic/health care practitioner ASAP

Sign/symptom	Concern for Outcome
A – abdominal pain	Blood clot in pelvis or liver(mesenteric or pelvic vein thrombosis)
C- chest pain & SOB	Blood clot in lungs or heart vessels (PE or MI)
H- headaches	Stroke
E- eye problems	Stroke or retinal vein thrombosis
S-swelling (thighs/ankles)	DVT

http://www.contraceptivetechnology.org/wp-content/uploads/2015/06/ACHES-figure.pdf

Other hormonal methods
(contain both estrogen and progestin)

- NuvaRing is a soft, flexible plastic ring that releases 15 mcg of estrogen and 120 mcg of etonogestrel daily.
- Ring is placed in the vagina, left in place for 3 weeks, and then is left off for 1 week.
- Better cycle control and decreased breakthrough bleeding are achieved compared with OC.
- Systemic exposure to estrogen is lower.

Transdermal patch (Ortho Evra)

- Patch is placed on buttock, abdomen, outer upper arm, or upper torso
- Replaced weekly for 3 weeks, then a patch-free week
- Cost per year: $420
- Pros: no daily pill
- Cons: no STD protection, skin irritation
- Women weighing > 198 lbs. – increased failure rate

Contraceptive injection

- Depot medroxyprogesterone acetate
- Depo-Provera is a long-acting, injectable progestin-only contraceptive.
- One injection is effective in suppressing ovulation for 12 to 13 weeks.
- Advantages
  - Once every 12-week dosing
  - Effective
- Disadvantages
  - Spotting, followed by amenorrhea; Weight gain; Depression
- ***Black Box warning: decreased bone density with longer-term use***

Contraceptive Implants

- Implanon (progestin- only)
- 1.5” rod is inserted under skin of upper arm
- Effective for up to 3 years
- Pros:
  - no daily pill; spontaneity
- Cons:
  - no STD protection, weight gain, bleeding, mood change, surgical procedure

Intrauterine Devices (IUDs)

- Small plastic objects inserted into uterus
- 2 types
  - Hormone-releasing (progesterone)

    - Copper-releasing
- Have fine plastic threads attached that hang slightly out of cervix into vagina for removal
- Very high continuation rate (how many women are still using it one year after starting) compared w/other methods
- Mechanisms of Action
    - Levonorgestrel-Releasing IUD (LNG-IUS, Mirena®)
        - Inhibits fertilization
        - Thickens cervical mucous
        - Inhibits sperm function
        - Thins and suppresses the endometrium
    - Copper
        - Inhibits fertilization
        - Release of copper ions reduce sperm motility
        - May disrupt normal oocytes and the formation of fertilizable oocyte
- Costs, pros, & cons of IUDs
    - Copper: $550 (good for up to 10 years)
    - Hormone: $500-$700 (good for up to 6-7 years)
- Advantages
    - Very effective (essentially no "user error")
    - Long-term protection
    - No interruption of sexual activity
    - Don't have to remember to use
    - Can be used during breast-feeding
- Disadvantages
    - No STI protection
    - Risk of PID (usually within first 1-2 months following insertion)
    - Rare incidence of perforating uterine wall
- Copper-T IUD
    - 99% effective if inserted within 5 days

Monitoring

- Routine female screening
    - History
    - Breast and pelvic examinations
    - Papanicolaou ("Pap") test and sexually transmitted infection testing
    - Blood pressure (BP)
    - Specific to contraception: history and BP
- Physical examination, breast examination, pelvic examination, and PAP testing not required for contraception prescription
- BP and ADRs monitored at 3 months, then annually

Emergency Contraception

- Works mainly by preventing ovulation or fertilization
- In theory, can also interfere w/implantation
    - Evidence suggests this is not primary mechanism of action
    - If it was, efficacy should not decrease w/short-term delay, as long as EC was administered some time before implantation
    - However, EC is increasingly less effective w/delay
- Oral contraceptive pills
    - 95% effective within 24 hrs; 75% effective within 72 hrs
        - Preven: 2 doses of combined estrogen & progesterone
        - Plan B: 2 doses of progesterone

Resources
Arcangelo. (2020). Pharmacotherapeutics for Advanced Practice – 4th ed.
Dipiro, T., & Talbert, R. (019). Pharmacotherapy-A pathophysiological Approach 10th ed.
Epocrates (various topics)
Familypracticenotebook.COM (various topics)
Up to date (various topics)
Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers -5th ed.