Objectives

1. Discuss the emergency contraceptive Ella (ulipristal acetate) and compare to existing emergency contraceptives on the market.

2. Describe the unique characteristics of new contraceptive agents.

3. Utilize the U.S. Medical Eligibility Criteria for Contraceptive Use to identify safe contraceptive choices for women with chronic medical conditions.

Outline

- Review Emergency Contraception
- Updates in Emergency Contraception
- Update on New Contraceptive Products
- Update - U.S. Medical Eligibility Criteria
Emergency Contraception

American College of Obstetrics and Gynecology definition:

“A therapy for women who have had unprotected sexual intercourse, including sexual assault.”


Indications

- Unprotected intercourse in the past 72 hours (120 hours)
- Contraceptive failure
  - Condom breaks
  - Missed oral contraceptive pills
  - Expulsion of IUD or vaginal ring
  - Patch fell off for long period of time
  - Displacement of barrier method (diaphragm)
- Sexual assault
- Exposure to teratogen


EC Methods

- Yuzpe Regimen
- Levonorgestrel
- Copper IUD
  - Up to 5 days after intercourse
- Mifepristone
  - Off label use, up to 5 days after sexual intercourse
- Ulipristal acetate (Ella)
  - Selective Progesterone Receptor Modulator (SPRM)
  - Up to 5 days after sexual intercourse
  - Prescription only

Pharmacologic Actions of Progestin and Estrogen

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Estrogen</th>
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<tbody>
<tr>
<td>Ovarian and pituitary inhibition</td>
<td>Ovarian and pituitary inhibition</td>
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<tr>
<td>Thickening of cervical mucus</td>
<td>Thinning of/increase in cervical mucus</td>
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<tr>
<td>Endometrial atrophy/transform</td>
<td>Endometrial proliferation</td>
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<tr>
<td>Cycle control</td>
<td>Cycle control</td>
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</tbody>
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Yuzpe Regimen

- High dose estrogen (ethinyl estradiol 100 mcg) + High dose progestin (levonorgestrel 0.5 mg) x 2 doses
- Used within 72 - 120 hours to prevent pregnancy
- Does not harm fetus if already conceived
- Not an abortion pill

Yuzpe Regimen

- Efficacy approximately 75% (range 63-79%)
- Side effects:
  - Nausea reported approximately 30-60% (likely due to estrogen component)
  - Vomiting approximately 20% due to estrogen component
  - Heavy menses/breast tenderness
Emergency Contraceptive Pills

One dose listed, two doses required

- Ovral
  - 2 white tabs = 100 mcg EE 0.50 mg LNG
- Alesse
  - 5 pink tablets = 100 mcg EE 0.50 mg LNG
- Nordette
  - 4 light-orange = 120 mcg EE 0.60 mg LNG
- Levlen
  - 4 light-orange = 120 mcg EE 0.60 mg LNG
- Levitate
  - 5 pink tablets = 100 mcg EE 0.50 mg LNG
- Lo/Ovral
  - 4 white tablets = 120 mcg EE 0.60 mg LNG
- Triphasil
  - 4 yellow tablets = 120 mcg EE 0.60 mg LNG
- Tri-Levlen
  - 4 yellow tablets = 120 mcg EE 0.60 mg LNG
- Ovrette
  - 20 yellow tablets = 0 0.75 mg LNG
- Plan B 1-step 1 white tablet = 0 1.5 mg LNG** (**1 dose only)
- Next Choice
  - 2 peach tablets = 0 0.75 mg LNG

Levonorgestrel - progestin only

- Plan B (Generic: Next Choice)
  - Levonorgestrel 0.75 mg, 2 tablets in package
  - Tablets may be taken 12 hours apart or together at one time
  - Recommended use within 72 hours of unprotected intercourse, in practice up to 120 hours
  - OTC for 17 years and older
- Plan B One-Step
  - Levonorgestrel 1.5 mg, 1 tablet
  - Taken as soon as possible after unprotected intercourse within 72 hours, in practice up to 120 hours
  - OTC for 17 years and older

EC Mechanism of Action

Not clear: depends on time of administration, best prior to ovulation time

1. Prevents or delays ovulation
2. Traps sperm in thickened cervical mucus
3. May interfere with fertilization
4. May interfere with implantation (controversial)
   - May causes endometrial changes
   - Probably acts prior to implantation

Does not cause an abortion

ACOG Practice Bulletin No. 112, May 2010

http://ec.princeton.edu/questions/dose.html#dose
Accessed June 9, 2011
**Effectiveness**
(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 (74% reduction, Range: 56-89%)
- 1 will become pregnant using progestin EC (88% reduction, Range: 52-100%)

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**Emergency Contraceptive Pills: Management Concerns**

- May take antiemetics 1 hour before first dose
- If patient vomits within 1 to 2 hours of first dose, need to repeat dose.

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**EC and Behavior**

- Looked at 2117 women ages 15-34 over 2 years (2001-2003)
- 3 arms of study
  - Given 3 packs of EC in advance
  - Pharmacy access
  - Clinic access (control)
- Outcomes: Pregnancies, STIs, and EC use
  - Secondary outcomes: condom use, changes in sexual behavior, and contraceptive use
- Advance provision group twice as likely to use EC than other two groups
- Frequency of unprotected intercourse similar 39.4% vs. 41%, p=0.46
- No differences in condom use, STI, and pregnancy between groups

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Emergency Contraception
Patient Counseling

- Make certain that the patient does not want to get pregnant
- Explain that emergency contraception does not protect from STDs
- Recommend an at home pregnancy test and medical follow up if the patient does not have a normal period within 3 weeks
- Side effects include nausea and vomiting. Headaches, breast tenderness, and dizziness have been reported

Emergency Contraception
Patient Counseling

- As a pharmacist, if a woman comes in for EC, take the opportunity to counsel on the following:
  - Proper contraception techniques and methods available
  - Risk of sexually transmitted infections and regular examinations by a physician or health care provider

States Providing Pharmacist Initiated EC

- Nine States
  - Alaska
  - California
  - Hawaii
  - Maine
  - Massachusetts
  - New Hampshire
  - New Mexico
  - Vermont
  - Washington
Other alternatives

- Mifepristone (RU 486)
  - Stops follicle maturation
  - Interrupts midcycle LH surge
  - Disrupts endometrial support

- Copper IUD
  - Stops fertilization
  - Alters sperm motility
  - Prevents implantation

Prescription EC

- Ulipristal acetate – Selective Progesterone Receptor Modulator (SPRM)
  - Marketed as Ella 30 mg
  - One tablet taken as soon as possible after unprotected intercourse
  - Labeled for 120 hours after unprotected intercourse
  - Prescription-only

Ella (ulipristal acetate)

- Mechanism of action
  - Progesterone agonist/antagonist
  - Inhibits or delays ovulation
    - When given prior to ovulation, prevents follicle rupture and decreases estradiol levels
    - If given during LH surge, may delay ovulation up to 5-9 days
  - May affect endometrial lining, thus affecting implantation

- Side Effects
  - Headache, nausea, abdominal pain, pain during menstruation, fatigue and dizziness
Ella (ulipristal acetate)

- Thought to be most effective EC pill option
- Reported to have 42% more effectiveness in preventing pregnancy than levonorgestrel at 72 hours post coitus and 65% more at 24 hours post coitus
- Thought to be more effective in delaying ovulation when it is imminent

Contraceptive Product Updates

Recent Updates

- Natazia (estradiol valerate/dienogest)
- Beyaz (20 mcg EE/3 mg DSRP/ 0.451 levomefolate calcium)
- Safyral (30 mcg EE/3 mg DSRP/ 0.451 levomefolate calcium)
- Lo Loestrin Fe (10 mcg EE/ 1 mg norethindrone/ 75 mg ferrous fumarate)
Natazia

- Approved May 2010
- Approved uses – Pregnancy prevention
- Unique properties:
  - Contains estradiol valerate/dienogest
  - First quadriphasic formulation
  - Varies in back-up method recommendations 9 days vs. 7 days with other products
  - Missed pill considered 12 hours late
  - Missed pills recommendations vary based on day missed
  - Not studied in women with BMI > 30

Natazia package insert, Bayer Healthcare Pharmaceuticals Inc. Wayne, NJ; 2010

Natazia

- Formulation - 28 tablets
- Does not have a full placebo week
  - 2 tabs – 3 mg of estradiol valerate
  - 5 tabs - 2 mg estradiol valerate/2 mg dienogest
  - 17 tabs – 2 mg estradiol valerate/ 3 mg dienogest
  - 2 tabs – 1 mg estradiol valerate
  - 2 tabs - placebo

Beyaz

- Approved September 2010
- Approved indications:
  - Pregnancy prevention
  - Treatment of Acne
  - Treatment of PMDD
  - Raise folate levels in women
- Monophasic oral contraceptive
  - 24 tabs ethinyl estradiol 20 mcg/drospirenone 3 mg
  - levomefolate calcium 0.451 mg
  - 4 tabs of levomefolate calcium 0.451 mg
- Unique properties
  - Contains 0.451 mg levomefolate calcium (metabolite of folic acid) in each pill
  - Secondary indication – to raise folate levels in women who conceive while on product or shortly after discontinuing
Safyral

- Approved December 2010
- Approved indications:
  - Pregnancy prevention
  - To raise folate levels in women who oral contraceptive for pregnancy prevention
- Monophasic oral contraceptive
  - Contains ethinyl estradiol 30 mcg / drospirenone 3 mg
- Unique properties
  - Contains 0.451 mg levomefolate calcium (metabolite of folic acid) in each pill

Lo Loestrin Fe

- Approved October 2010
- Approved indication – pregnancy prevention
- Contains 28 tablets
  - 24 tablets – ethinyl estradiol 10 mcg and norethindrone acetate 1 mg
  - 2 tablets – ethinyl estradiol 10 mcg
  - 2 tablets – ferrous fumarate 75 mg (instead of placebo)
- Unique properties
  - Lowest estrogen product available
  - Iron for placebo pills
  - Only 2 days non-hormonal tablets
  - Claims decreased menstrual bleeding, <4 days
  - Studied in women 45 years of age and up to 260 lbs.

U.S. Medical Eligibility Criteria for Contraceptive Use 2010

Available at:
http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm
Background

- Adapted from World Health Organization Medical Eligibility Criteria for Contraceptive Use, 4th Edition
- Recommendations based primarily on extrapolations from studies of healthy women, theoretical considerations of risks and benefits, and expert opinion

Contraceptives included in the document
- Combined hormonal contraceptives
  - Oral, patch, vaginal ring
  - Progestin-only contraceptives
  - Oral, depot injection, implant
- Emergency contraceptive pills
  - Levonorgestrel, combined oral contraceptives
- Intrauterine devices
  - Levonorgestrel, copper
  - Copper IUDs for emergency contraception
- Barrier methods
  - Condom, spermicides, diaphragm, cervical cap
- Fertility-awareness based methods
  - Symptom-based, calendar-based
- Lactational amenorrhea method
- Coitus interruptus method
- Sterilization

Structure

- Categories of medical eligibility criteria
  1= A condition for which there is no restriction for the use of the contraceptive method
  2= A condition for which the advantages of using the method generally outweigh the theoretical or proven risks
  3= A condition for which the theoretical or proven risks usually outweigh the advantages of using the method
  4= A condition that represents an unacceptable health risk if the contraceptive method is used
Select Conditions

- Age
- Tobacco use
- Thromboembolism
- Headaches

Patient Case #1

- DT is a 38 y.o. female who has used various combined oral contraceptives (ethinyl estradiol 30-35 mcg) for the past 15 years. She has smoked ½ ppd on and off since she was 17 y.o. She had most recently quit smoking for 5 years, but has restarted in the last 2 months due to the stress of losing her job. She is satisfied with her current contraceptive method.

Age

- Combined hormonal contraceptives
  - Concern regarding cardiovascular risk
    - < 40 yrs = category 1
    - ≥ 40 yrs = category 2
  - Progestin-only minipills = category 1 at all ages
- Depot medroxyprogesterone
  - Concern regarding bone health
    - < 18 yrs = category 2
    - 18-45 yrs = category 1
    - ≥ 45 yrs = category 2
- Implant = category 1 at all ages
- Levonorgestrel and copper IUDs
  - Concern regarding risk for expulsion and STIs
    - < 20 yrs = category 2
    - ≥ 20 yrs = category 1
**Tobacco Use**

- Pertinent to combined hormonal contraceptives (estrogen component)
  - Concern regarding risk for myocardial infarction
    - Age < 35 yrs = category 2
    - Age ≥ 35 yrs
      - < 15 cigarettes/day = category 3
      - ≥ 15 cigarettes/day = category 4

**Thromboembolism**

- Thromboembolism appears highest with estrogen-containing contraceptives
  - History of DVT/PE (not on anticoagulant therapy)
    - Category 3 or 4
  - Acute DVT/PE
    - Category 4
  - DVT/PE on anticoagulants for at least 3 months
    - Category 3 or 4 (higher risk for recurrence)
    - Category 1 – 4 (lower risk for recurrence)

**Thromboembolism**

- Patients with known thrombogenic mutations should not receive estrogen-containing contraceptives (Factor V Leiden, prothrombin mutation, protein C/S/antithrombin deficiencies)
  - Category 4
Thromboembolism

- Role of progestins in thromboembolic risk
  - Progestin-only contraceptives are predominantly category 2
  - Clinical controversy: Are all progestins in combined hormonal contraceptives equal?
    - "Third generation" progestins (desogestrel, norgestimate, etonogestrel, norelgestromin)
      - Oral contraceptives
      - Ortho Evra contraceptive patch
    - "Fourth generation" progestin

- Other recommendations
  - American Congress of Obstetricians and Gynecologists ACOG (formerly "College")
      - Desogestrel associated with higher rates of venous thromboembolism than levonorgestrel oral contraceptives
      - The contraceptive patch results in increased estrogen exposure, possibly increasing risk for thromboembolism
      - Consider discontinuation of combined hormonal contraceptives around high risk surgeries
      - Possible contraceptive options in women on warfarin include: combined oral contraceptives, depot medroxyprogesterone, levonorgestrel IUD

Patient Case #1

- What risk factors are exhibited by DT?
  - Tobacco use
  - Age 35 and older
  - Need to assess other possible factors (weight, heart disease, family history, etc.)

- How should her contraceptive needs be addressed going forward?
  - If continues to smoke, consider non-estrogen based method
  - Utilize contraceptive as motivation to help her quit smoking
Patient Case #2

- GK is a 22 y.o. female who has received Depo-Provera injections for contraception since age 19. She wants to discontinue use of the injections because of mood changes and weight gain. She is interested in an alternative contraceptive option. She experiences approximately 1 migraine every 2-3 months, which she treats with sumatriptan and naproxen. She is taking propranolol daily for migraine prevention.

Headache

- Non-migrainous
  - All progestin-only products = category 1
  - Combined hormonal products = category 1 (initiation) and category 2 (continuation)

- Migraines
  - Factors include age and presence of "aura"
  - Aura: symptoms occurring before or with the onset of headache
    - Visual (flickering lights, spots, lines or vision loss)
    - Sensory (pins/needles or numbness)
    - Speech (dysphasic speech)
  - Associated with increased incidence of ischemic stroke

Headache

- Migraine without aura
  - Progestin-only products
    - Category 2 for initiation/continuation
    - Category 1 for progestin-only minipill
  - Combined hormonal products
    - Age < 35 yrs
      - Category 2 for initiation/Category 3 for continuation
    - Age ≥ 35 yrs
      - Category 3 for initiation/Category 4 for continuation
Headache

- Migraine with aura
  - Progestin-only products
    - Category 2 for initiation/Category 3 for continuation
  - Combined hormonal products
    - Category 4 for initiation/continuation (no age differentiation)

- Menstrual migraines
  - Linked to drop in estrogen levels during the placebo pills/bleeding phase (estrogen withdrawal headache)
  - Occur with a cyclical pattern (usually 2 days prior to menses through 3rd day of bleeding)
  - Options
    - Utilize NSAIDs/triptans prior to hormone therapy
    - Reducing hormone-free interval (24/4 regimens)
    - Continuous use
    - Estrogen supplementation during bleeding phase

- Other recommendations for estrogen-containing contraceptives
  - ACOG
    - Avoid use in patients with focal neurologic signs, smokers, age 35 and older
  - International Headache Society
    - Migraine with or without aura
      - Assess individualized risk (ischemic heart disease, DM, family history of premature heart disease, hyperlipidemia, HTN, obesity, tobacco use, sickle cell disease)
      - Avoid tobacco use; treat HTN and hyperlipidemia prior to use
Patient Case #2

- What is the recommended approach to GK’s contraceptive needs?
  - Clarify her migraine diagnosis, with or without aura
  - Weigh benefits/risks of remaining progestin-only options
  - Consider estrogen-containing option only after determination of aura and evaluating additional stroke risk factors
  - Provide careful monitoring to determine effect on migraine frequency