Recent Advances in Contraception

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Learning Objectives:

• Describe extended cycle oral contraceptive characteristics including dosing regimen, indications, potential advantages and common adverse effects

• Discuss contemporary issues with hormonal contraceptives including the Ortho Evra® patch, desogestrel-containing products

• Discuss recent changes in the use of emergency contraception
Extended Cycle Oral Contraceptives

• Differ from traditional 21/7 products by decreasing or eliminating the hormone-free interval (HFI)
• Consecutive days of hormone therapy extend to 84 or 365 days
• Add-back regimens
  • HFI is shortened to 0, 2 or 4 days instead of the typical 7 day period
  • The remaining days provide a lower dose of hormone than the dose found during the rest of the cycle

Extended Cycle Products

• 84/7 regimens
  • Seasonale®, Jolessa®, Quasense®
    • 30µg EE + LNG 0.15mg
  • Seasonique™ - 84 tab containing 30µg EE+ 0.15mg LNG followed by 7 tabs of 10µg EE

• 24/4 regimens
  • Yaz® - 20µg EE+ 3 mg drospirenone
  • Loestrin® 24 - 24 tab containing 20µg EE+ 1 mg norethindrone acetate followed by 4 tab containing 75mg ferrous fumarate

EE = ethinyl estradiol; LNG = levonorgestrel
**Extended Cycle Products**

- **21/2/5 regimen**
  - Mircette® - 21 tab containing 20µg EE+ 0.15mg desogestrel followed by 2 placebo tab followed by 5 tab containing 10µg EE
  - Kariva® - 21 tab containing 20µg EE+ 0.15mg desogestrel followed by 2 placebo tab followed by 5 tab containing 10µg EE

- **Continuous regimen**
  - Lybrel® - 365 tab containing 20µg EE+ 90µg LNG

*EE = ethinyl estradiol; LNG = levonorgestrel*

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**Reasons for Switching to Extended Cycle Products**

- Decrease menstrual-related symptoms experienced by women during the HFI
- Improve efficacy in women who forget to restart the pill
- Patient preference to decrease the frequency of menstrual-like bleeding
Decreasing Symptoms During HFI

- Exacerbations of dysmenorrhea, PMS, PMDD are common
- Reduces or eliminates breast tenderness, headache, bloating, cramping, hypermenorrhea and the psychological symptoms typical of hormone withdrawal
- Patients experience less menstrual blood loss on an extended cycle product thereby decreasing the risk of iron deficiency anemia

Improved Efficacy of Extended Cycle Products

- 2006 study in Contraception
  - Continuous regimens are more effective at preventing follicular development and breakthrough ovulation during the HFI
  - Beneficial to patients who forget to take tablets
  - Low dose products are now the norm (20-30µg)
- Are patients more adherent to continuous regimens?
  - Coraliance study in 2004 reported patients remember to take ECPs more easily


Patient and Provider Preference

- 2005 survey by ARHP to determine women’s views of menstrual cycling
  - ~50% reported a preference to have no periods
  - ~25% would continue to have monthly cycles
- Second study – women favor extended cycle products if they are safe, don’t affect fertility and don’t increase ADRs
- 44% of providers surveyed believed that menstrual suppression was a good idea
  - 52% prescribe extended cycle products


Economic Considerations

- Eliminating menstrual cycling is likely to improve work productivity and decrease health care costs
- Menstrual disorders – most common gynecologic complaint
  - 75% of women surveyed had consulted a doctor
  - 30% spent > one day in bed the previous year
- 2002 study - menstrual bleeding costs $1,692 per woman in the workplace

Adverse Effects of Extended Cycle Products

- Unscheduled bleeding and spotting during first few months
- Balance long term benefits vs. short term inconvenience
- Patient counseling issues

Other Candidates for Extended Cycle Products

- Perimenopausal women
- Athletes
- Military women
- Developmentally delayed women
- Adolescents
Is it Safe to Eliminate Menstrual Bleeding?

- Opponents
  - Menstruation is a natural state
  - Bleeding is necessary to cleanse the system
  - Confirms that patient is not pregnant
- Proponents
  - Modern women have ~450 cycles compared to ~160 for pre-industrial revolution women
    - Earlier menarche, later menopause, fewer pregnancies, lack of breast feeding

John Rock's Error

What the co-inventor of the pill didn’t know about menstruation can endanger women’s health (Annals of Medicine March 10, 2000)

- First oral contraceptive developed by Rock, Pincus and Chang
- Approved by FDA in 1960
- Rock, a devout Catholic, sought approval of the pill from the Catholic church
- A 21-day regimen of estrogen followed by estrogen + progestin was developed to appear “natural”
- Rationale was not scientific but rather political
Ortho Evra® Patch
- Matrix system
  - 6mg norelgestromin and 0.75mg EE
- Approved in 2001
- Advantages
  - Improved adherence to regimen
  - Efficacy improved for patients who make errors ≤2 days
  - Avoids first pass metabolism, GI destruction of drug, peaks and troughs in drug levels
  - Patient can verify presence of patch/protection
- Use of patch has declined
  - 9.9 million in 2004
  - 2.7 million in 2007

Ortho Evra® – Changes to Label
- Changes made 9/06
  - Study reported that patch exposes patient to 60% more estrogen than 35µg EE tablet
  - Patients are twice as likely to develop blood clots
  - Peak estrogen level is 25% lower with patch compared to oral tablets

Ortho Evra® – Changes to Label

- Changes made 1/19/08
  - Based on the Boston Collaborative Drug Surveillance Program study.
  - Includes results that found that users of the patch were at higher risk of developing VTE than women using pills.
  - The patch was studied in women aged 15-44.
  - Findings support an earlier study that also said women in this group were at higher risk for VTE

http://www.fda.gov/medwatch/safety/2008/safety08.htm#orthoevrapatch

FDA recommendations for Ortho Evra® Use

- Women with risk factors for VTE should consider use of nonhormonal methods of contraception
  - Risk factors include
    - > 35 years of age
    - Smoking
    - Obesity
    - < 4 weeks post-partum
    - 4 weeks prior to surgery and 2 weeks after surgery
    - Bed rest
    - Personal or family history of heart attack, stroke or DVT
**Desogestrel-containing products**

- 3rd generation progestin
  - Cyclessa®, Ortho-Cept®, Mircette®, Desogen®
- Developed to decrease androgenic effects
- Two 2001 studies reported increased risk of VTE by factor of 1.7 over LNG products
- FDA requires a statement in Warnings section regarding risk of VTE
- At risk patients should switch to 2nd generation product

**Yaz®/Yasmin® Drug Interactions**

- Drosperinone is antimineralocorticoid
- Risk of hyperkalemia is low in most patients
- 2007 study found 17.6% of patients also take another potassium-sparing drug
  - 40% of women ≥ 35 yo were taking an interacting combination
  - Only 40% with a potential interaction were monitored for hyperkalemia
- Reasons for noncompliance include physician decision, patient factors, health plan barriers
Use of COCs in Perimenopausal Women

- Controls vasomotor symptoms and DUB while providing contraception
- May increase BMD and decrease risk of ovarian and endometrial cancer
- Extended cycle products may prevent hot flashes during HFI
- Can be used in healthy nonsmokers women > 35 yo
  - Can continue use until age 55
- Consider Depo Provera® or Mirena® in women who are not candidates for oral contraceptives

Emergency Contraception with Plan B

- equally effective if tablets are taken in a single dose
  - May improve adherence to regimen
- may be effective up to 5 days after unprotected intercourse – not approved use
- Advance provision – purchase to have on hand if needed
  - Does not appear to increase sexual risk-taking behavior
- Issues related to purchase by males
- New thoughts on mechanism – primarily contraceptive
Emergency Contraception

- Regular oral contraceptives can be used
  - 2-5 tablets of LNG containing product per dose
- Copper IUD may be inserted up to 5 days after unprotected sex
  - Impedes fertilization, alters sperm motility and impairs implantation
- Mifepristone (RU 486) – used as abortifacient in US since 2000
  - Single dose of 10-50mg is effective up to 5 days after unprotected sex
  - Delays onset of bleeding

Intrauterine Devices (IUDs)

- Most widely used reversible contraceptive method in the world
- 2% of US women use the IUD
- Advantages
  - Immediately effective
  - Fertility returns upon removal
  - No compliance issues
Two types of IUDs

- Copper IUD (Paragard)
  - Effective for 10 years
  - Can be emergency contraceptive
  - Associated with decrease in endometrial cancer

- LNG-IUS (Mirena)
  - releases 20 µg of LNG into the uterus every 24 hours
  - provides non-contraceptive health benefits including treatment of menorrhagia and anemia

Why Aren't IUDs Used More Often?

- Memory of Dalkon shield and fear of litigation
- Practitioners not trained to insert and remove
- Upfront cost
- Misconceptions about suitability of candidates
**Common Myths and Truths about IUDs**

**MYTH:** IUDs are abortifacients  
**TRUTH:** Primary MOA is to prevent fertilization  
**MYTH:** IUDs cause pelvic inflammatory disease  
**TRUTH:** Risk of PID for first 20 days post-insertion  
**MYTH:** Nulliparous women can’t use IUDs  
**TRUTH:** Failure and expulsion rates are no higher  
**MYTH:** IUDs cause infertility  
**TRUTH:** IUD use is not associated with infertility. Untreated infection is the most common cause of infertility.

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**Take Home Message**

- Extended cycle products appear to be safe and offer several advantages to patients who have menstrual dysfunction  
- Ortho Evra® and desogestrel-containing products increase the risk of thromboembolism and should not be used by patients with other risk factors  
- Emergency contraception options include Plan B taken as two tablets in one dose and copper IUDs for patients who also desire long term contraception