Emergency Contraception Update: Preventing Unintended Pregnancy

Update on Emergency Contraception

Association of Reproductive Health Professionals
www.arhp.org

Faculty Disclosure

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• No Disclosure

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Learning Objectives
At the conclusion of this program, participants should be able to:
• Describe emergency contraceptive (EC) products, including progestin-only EC pills (ECPs), regimens, and ease of access, to ensure more consistent usage by patients
• Outline and discuss ECPs’ mechanism of action with patients in order to dispel myths surrounding ECPs
Learning Objectives (continued)

- Respond to patients’ concerns about the safety and efficacy of ECPs, according to FDA guidelines
- Provide evidence-based EC information, and appropriate counseling and care to patients to insure improved patient health care outcomes.

Emergency Contraception Outline

What is EC?
- Methods
- Effectiveness
- Mechanisms of Action
- Safety

What is the Impact of EC?
- Risk Taking
- Impact on Unintended Pregnancy
- Barriers to Use

Counseling Points
- Access to Emergency Contraception
- What to Say to Patients

What If…?
- the condom broke or slipped off...
- you forgot your regular birth control...
- you were forced to have sex...
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Unintended Pregnancy in the U.S.

- 6.3 million pregnancies
- 51% Intended
- 49% Unintended
  - 22% Birth
  - 20% Abortion
  - 7% Miscarriage

Impact of Tough Economic Times

- Poor women more likely to face unintended pregnancy
- 1 in 4 women
  - Delayed gynecology or birth control visit
  - Having harder time paying for birth control


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EC Available in the United States: Progestin-only Pills

Dedicated products

Plan B® One-Step

Plan B One-Step
• One 1.5mg levonorgestrel pill
• Taken within 72 hours after intercourse (product label)
• Can be effective up to 120 hours after intercourse
• Most effective when taken as soon as possible
• Cost: $35-$60 retail; prescription prices vary

Next Choice™

Next Choice (generic)
• Two 0.75mg levonorgestrel pills
• Both pills taken at the same time
• Can be effective up to 120 hours after intercourse
• Most effective when taken as soon as possible
• Cost: 10-20% lower than Plan B brand


www.not-2-late.com

www.rhtp.org
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Combination oral contraceptives (Yuzpe method)

- Ethinyl estradiol 0.1 mg + DL-norgestrel 1.0 mg
- TWO (2) doses: 12 hours apart
  - Ovral: 2 white tablets
  - Lo-Ovral: 4 white tablets
  - Nordette: 4 light orange tablets
  - Levlen: 4 light orange tablets
  - Alesse: 5 pink tablets
  - Trilevlen: 4 yellow tablets
  - Triphasil: 4 yellow tablets
  - Others...

New option approved 8/3/2010
ulipristal acetate

- Approved and marketed in Europe by HRA Pharma for treatment up to 120 hours after UPI
- Will be marketed in the US by Watson as ella®

EC Available in the United States:
Copper-T IUD

ParaGard®

 Trudeau J, Raymond EG. 2009.
When is EC needed?

- When any method of birth control fails
- No birth control is used
- A woman misses 2 or more birth control pills in a row or starts a pack 2 or more days late
- A woman is more than 2 weeks late for a Depo-provera® injection
- A woman is sexually assaulted

Newer Indications:

- Ortho Evra® Patch (transdermal patch)
  - Patch off for ≥ 24 hours during patch-on weeks
  - Left patch on more than 9 days straight
  - More than 2 days late putting patch back on

Newer Indications:

- NuvaRing® (vaginal ring)
  - Taken out for > 3 hours during ring-in weeks
  - Left in more than 5 weeks in a row
  - More than 2 days late putting ring back in
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**Effectiveness of EC Methods**

Preventing Pregnancy

<table>
<thead>
<tr>
<th>Method</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-T IUD</td>
<td>99%</td>
</tr>
<tr>
<td>Progestin-only pills</td>
<td>89%</td>
</tr>
<tr>
<td>Combined pills</td>
<td>74%</td>
</tr>
</tbody>
</table>

Progestin and combined pills EC effectiveness rates are most likely overestimated


**Current Estimates**

- ECP efficacy conveys the reduction in pregnancy risk after a single coital act
- Plan B package (LNg regimen): 89%
- Published literature:
  - LNg regimen: 60% - 94%
  - Yuzpe regimen: 56% - 89%

**Methodology**

In a group of ECP users, compare:
- observed number of pregnancies
- expected number of pregnancies (number that would have occurred without ECPs)

Calculate the reduction due to the ECPs
Example
WHO 1998 trial of LNG vs. Yuzpe regimen
- 1001 women using LNG regimen
- Pregnancies observed: 11
- Pregnancies expected without EC: 75.3
- Pregnancies prevented: 75.3 - 11 = 64.3
- Efficacy: \( \frac{64.3}{75.3} \times 100 \% = 85\% \)

Expected Pregnancies
- Determine the day of the menstrual cycle when the coital act occurred
- Estimate that day relative to day of ovulation
- Use published probabilities of pregnancy by cycle day to estimate expected pregnancies

Calculation of effectiveness:
- Many assumptions
- Dependent on accurate recording of timing of intercourse and cycle day
Do Any of the Charts Apply?

- Another study found that 99 women were between days -5 and +1 when the day of ovulation was estimated as usual cycle length minus 13.
- Hormonal data indicated that only 51 of these 99 (56%) were in fact between days -5 and +1.

Espinós et al. Contraception 1999

Efficacy: Conclusion

Numbers of expected pregnancies reported by studies are probably too high.

Most published efficacy figures are probably overestimates.

Don’t Give Up…

ECPs do work!

- Physiology studies show effects incompatible with pregnancy.
- LNG regimen proven to be more effective than Yuzpe → it must be more effective than nothing.

Raymond et al. Contraception 2004
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**Efficacy of LNG Regimen**

![Graph showing efficacy of LNG regimen](image)

**Efficacy of LNg Regimen**

![Graph showing efficacy of LNG regimen](image)

**How MIGHT ECPs Work?**

- Inhibit or delay ovulation
- Prevent sperm and egg from meeting
- Prevent implantation by disrupting the uterine lining

Clinical Evidence: LNG ECPs

- Can inhibit ovulation, though not always
  - May be only mechanism of action
- Have no effect on the quality of cervical mucus or on the penetration of spermatozoa in the uterine cavity
- Can shorten the luteal phase
- Do not alter endometrium


ECP Mechanism of Action

- Levonorgestrel (LNG):
  - Lowers LH surge levels
  - Delays LH surge
  - Suppresses LH surge
  - Even if follicle ruptures, fertilization is impaired if LH timing or level is changed
  - These events occur in 79-86% of women taking LNG before LH surge (same as rate of effectiveness of Plan B™)
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ECP Mechanism of Action

- Levonorgestrel (LNG): (Plan B™)
- No evidence of endometrial changes leading to prevention of implantation
- Single dose (0.75mg x 2) as effective as 2 doses

Enhancing the Efficacy of Plan B

- Pilot study in 41 women
- Adding meloxicam 15 mg significantly increased the proportion of cycles with no follicular rupture or ovulatory dysfunction (88% versus 66%, p=0.012)
- Adding a Cox-2 inhibitor can disturb the ovulatory process after onset of the LH surge
- Trial regarding optimal dosing is under way

What should women be told about how EC works?

- The evidence strongly suggests that EC works primarily by stopping or delaying ovulation.
- It cannot be proved that LNG ECPs have no post fertilization effect
- The best available evidence is consistent with the hypothesis that LNG’s ability to prevent pregnancy can be fully accounted for by mechanisms that do not involve interference with post-fertilization events

Massai et al. Human Reprod 2007

Ulipristal acetate
Mechanism of action:

• selective progesterone receptor modulator (SPRM)
• antagonistic and partial agonistic effects at the progesterone receptor
• Inhibition or delay of ovulation
• Possible endometrial changes

Ulipristal Dose:

• 30mg tablet taken with 120 hours of UPI or contraceptive failure
• Dose repeated only if vomiting within 3 hours
• Not recommended more than once per cycle

Restrictions on use

• Pregnancy or suspected pregnancy
• Severe hepatic impairment
• Severe uncontrolled asthmatics
• Breastfeeding: unknown—advise not to breastfeed for 36 hours post treatment
### Side effects
- Abdominal pain and menstrual irregularities, dysmenorrhea
- Headache, nausea

### Drug Interactions
- Metabolized via cytochrome P450—mainly Cyp3A4
- Reduced plasma concentrations of ulipristal and possibly reduced efficacy with Cyp 3A4 inducers
- Possible increased levels with Cyp 3A4 inhibitors—significance is uncertain
- PPI, H2 antagonists and antacids—may decrease absorption and decrease efficacy

### Drug Interactions
- Other progestin containing contraceptives
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Do we need another emergency contraceptive?

- Another option
- Longer window of time (120 hours vs 72 hours)
- No decrease in efficacy with greater time lapse from UPI

Barriers to ulipristal

- Prescription only
- Cost??
- Confusion with mifepristone

Efficacy data: Ulipristal Acetate

- Randomized trial up to 72 hours after UPI found pregnancy rates of 0.9% for UPA and 1.7% for LNG, OR = 0.53 (95% CI, 0.18-1.45)
- Randomized trial up to 120 hours after UPI found pregnancy rates of 1.6% for UPA and 2.6% for LNG, OR = 0.57 (95% CI, 0.29-1.09)

Creinin MD et al. Obstet Gynecol 2006;108:1089-97
Glasier AF et al. Lancet 2010;375:555-62
Ulipristal Acetate

- Meta-analysis of two randomized studies found UPA superior to LNG
  - 0-24 h: OR=0.35 (95% CI, 0.11-0.93)
  - 0-72 h: OR=0.58 (95% CI, 0.33-0.99)
  - 0-120 h: OR=0.55 (95% CI, 0.32-0.93)
- But only after other factors were controlled (study, BMI, time from UPI to ovulation, expected probability of conception, further UPI)

Glasier AF et al. Lancet 2010;375:555-62

Ulipristal Acetate

- Levonorgestrel is no more effective than a placebo in preventing ovulation when the leading follicle reaches 15-17 mm
- By the time the leading follicle reaches 18-22 mm, ulipristal acetate prevents follicular rupture within 5 days of administration in 59% of cycles (versus 0% for the placebo)

Croxatto HB et al. Contraception 2004;70:442-50
Brache V et al. Hum Reprod, in press

Ulipristal Acetate

- In the UK, the cost of ellaOne is >3 times that of Levonelle 1500 in family planning clinics (£16.95 versus £5.37)
- In the UK, recommended for use in the 73-120 hour window

http://www.nyrdtc.nhs.uk/docs/nnde/NDE_97_Ulipristal_a.pdf
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**ECP Safety**

- Benefits outweigh risks for all situations
- Breastfeeding women may use ECPs
- Short duration of exposure and low total hormone content
- Safer than pregnancy
- No increased risk of birth defects
- No increased risk of ectopic pregnancy

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**ECP Side Effects**

- Nausea and vomiting
- Abdominal pain
- Breast tenderness
- Fatigue
- Headache
- Short-term cycle changes

Trussell J, Raymond EG. 2009.

Progestin-only EC pill side effects are mild

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**Case Study**

- Age 37
- Hx of DVT
- On Coumadin
- Uses condoms because has been told “birth control is not safe for her”
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Do ECPs Increase Risk Taking?

Studies conducted around the world: Scotland, San Francisco, Los Angeles, Pittsburgh, Nevada, China, North Carolina, Hong Kong

Studies of ECP Use & Risk Taking

Women randomized to receive either:

1. Counseling and ECPs on demand
2. ECPs in advance for later use

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Findings from ECP Use Studies: Effect on risk taking unclear

Women who received ECPs in advance were not more likely to:

- Use ECPs repeatedly
- Have unprotected sex
- Change to less effective contraception
- Use contraception less consistently
- Acquire an STI

but...

- reanalysis of one trial suggests easier access to ECPs:
  - may have increased frequency of coital acts with potential to lead to pregnancy
  - led to more substitution of ECPs for other contraceptives


Impact of Advance Provision of ECPs

Advance provision of ECPs has not been shown to reduce rates of unintended pregnancy.

Schwarz EB, Gerbert B, Gonzales R. J Gen Intern Med 2008

Impact of Advance Provision of ECPs (continued)

However, women who receive ECPs in advance:

- Take ECPs sooner after sex
- Use other methods of contraception equally well
- Advance provision is recommended

Schwarz EB, Gerbert B, Gonzales R. J Gen Intern Med 2008
**Why No Reduction in Pregnancies?**

Among women who received ECPs in advance

- 50% of women who had unprotected sex did not use ECPs
- 80% of pregnancies occurred to women who did not use ECPs in that cycle
- 77% of pregnancies occurred to women who did not use ECPs in that cycle

San Francisco | China | Nevada/NC


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**Why No Reduction in Pregnancies?**

Community intervention in Scotland

- Women ages 16-29 received ECPs in advance
- ~50% used ECPs at least once

**Results**

| 78% of women with advance supplies who got pregnant did not use ECPs |
| Women most at risk probably did not get ECPs |
| No effect on abortion rates |


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**Use and underuse of ECPs**

- Women underestimate their risk of pregnancy
- Education is needed to encourage women to use ECPs every time they are needed
- ECPs are not used frequently enough
- Underuse of ECPs means major public health impact is unlikely

[Raymond EG, Trussell J, Pols C. Obstet Gynecol. 2007.]
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Barriers to EC Access

- Political
- Marketing of EC
- Lack of clinician discussion

Barriers to EC Access: US Department of Justice


- STI counseling, testing, prophylaxis
- Pregnancy risk evaluation, care


Barriers to EC Access: US Department of Defense

Basic Core Formulary
- List of medications required to be on all Military Treatment Facility formularies

- Plan B®

April 3, 2002: Added
May 8, 2002: Removed
February 3rd, 2010: Added

American Civil Liberties Union. 2006; Maze R. Marine Corps Times. 2007;
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Barriers to EC Access: Marketing

Where are the ads?

Kavunagh ML, Schwarz EB. 2008.
Trussell J, Raymond EG. 2009.

Barriers to EC Access: Clinician Discussion

• Clinicians neither prescribe EC nor provide EC information frequently

Kavunagh ML, Schwarz EB. 2008.
Trussell J, Raymond EG. 2009.

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ECPs Available Over-the-Counter in US

<table>
<thead>
<tr>
<th>ECP</th>
<th>Availability for 17 yos</th>
<th>Availability for &lt; 17 yos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plan B® One-Step</td>
<td>behind counter ≥ 17</td>
<td>by prescription for &lt; 17 yos</td>
</tr>
<tr>
<td>Next Choice™ two pills</td>
<td>behind counter ≥ 17</td>
<td>by prescription for &lt; 17 yos</td>
</tr>
</tbody>
</table>


ECP Counseling Points

• How to obtain them
• Why it is a good idea to keep them on hand
• How they work
• They are safe and benefits always outweigh risks
• There are more effective long-term and reversible methods of contraception

Case Study

• Age: 25
• Primary care visit for birth control options
• Brings a prescription to your pharmacy for oral contraception
EC Hotline and Website

www.not-2-late.com
888-NOT-2-LATE

Case Study: Pharmacy

* Missed 1st 3 doses of OCs
* Wonders if she needs EC

Case Study: Pharmacy

* Can he buy EC for his girlfriend?
Case Study: Pharmacy

- Young-looking person asks for EC
- Was raped
- Age 15

Other counseling points to consider:

Beginning Contraception after EC

- **Oral contraceptives:**
  - Regular start: use backup until next period, then begin pills according to regular patient instructions
  - Quick start: take ECP. Start a new pack of OCs on the next day (use backup for first seven days)
  - Important Precaution: Be sure to have a pregnancy test if you do not have a normal period after completing your first package of pills.
When to Expect Menses after ECP Use

- Time to resumption of menses similar for combined and progestin-only regimens
- Compared with anticipated onset of next menses:
  - 13% have a delay of 8+ days
  - 15% have a delay of 4-7 days
  - 61% have menses within ± 3 days
  - 11% have early onset (>3 days early)
- A follow-up visit is warranted if menses do not return within three weeks following treatment

Source: WHO 1998

Best Available Evidence

- Levonorgestrel (LNG) does not disrupt an existing pregnancy
- Primary mechanism of action is prevention or delay of ovulation
- No evidence to support LNG post-fertilization effects
- ECPs do not work if a woman doesn’t recognize that she’s at risk for pregnancy

Role for Pharmacists

- Changes in status allows for greater involvement and counseling opportunities
- Reliable sources of information
- Unique position to offer education to patients, providers and improve access in the community