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POST-COITAL PREVENTION: NEW DEVELOPMENTS TO REDUCE STI AND PREGNANCY RISK

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Commercial Disclosures

- Michael Policar, MD, MPH is a senior author of *Contraceptive Technology*, 22nd edition

- He has no financial relationships to disclose relative to content of this presentation

Who Is This Famous ObGyn Physician?

Primary Prevention of Sexually Transmitted Infections

Intervention	Strategy
Behavior change • Take a sexual history • Risk reduction counseling	Practice safer sex • External and internal condoms • Dental dams for receptive oral sex • Partner selection, partner screening, abstinence
Partner treatment	Expedited Partner Therapy (EPT) • Patient delivered partner therapy (PDPT)
Vaccination	HPV, Monkey pox, and hepatitis A and B infections
Pre-exposure prophylaxis	**HIV**: PrEP **HSV:** daily antivirals
Post-exposure prophylaxis (PEP)	• **HIV**: oPEP (occupational), **nPEP** (non-occupational) • **Bacterial STIs:** DoxyPEP

Doxycycline Post-Exposure Prophylaxis (DoxyPEP)

The “Morning After Pill” for bacterial STIs

DoxyPEP: Post-Exposure Prophylaxis for Bacterial STI Prevention

- RCT using a *single dose* of doxycycline (doxy) 200mg < 72 hours after condomless oral, anal, or insertive vaginal sex in men who have sex with men (MSM) and transgender women
- Of 501 participants, *reduction* in STIs per follow-up quarter

	Using HIV PrEP	People living with HIV
GC	55 percent	57 percent
Chlamydia	88 percent	74 percent
Syphilis	87 percent	77 percent
# needed to treat (all 3 STIs)	4.7	5.3

What about cisgender women?

DoxyPEP for Cisgender Women

Methods: DoxyPEP vs. Standard of Care among Women

Design: Open-label randomized trial	• 200 mg doxy (within 72 hours of sex) vs. standard of care (quarterly STI screening/treatment)
Population: 18-30-year-old women, Kisumu, Kenya	• All pts taking daily oral HIV PrEP • Contraception not required (doxy stopped if pregnancy occurred)
Adherence	• Weekly SMS surveys to assess doxy use w/sex
Endpoint: Incident CT, GC, or syphilis infection	• Measured quarterly x 1 year, at study visits (Q3 months)

Stewart J, et al. Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. N Engl J Med 2023 Dec 21;389(25):2331-2340

dPEP Results: No Difference In STIs by Study Group

- Overall: Incident STIs detected @ 109 follow-up visits
  - 50 STIs in DoxyPEP group vs. 59 STIs in standard group
    - RR 0.88 (95% CI 0.60-1.29; p=0.51)
    - *No significant difference*

- Findings unchanged in additional analyses
  - Analysis of each STI separately
  - Subgroup analyses (age, contraception, transactional sex, STIs at baseline)

- No serious adverse events; no incident HIV infections

Slide adapted from: K. Johnson, CAPTC.

Adherence: Hair Sampling

- Proximal 1.0 cm of hair corresponds to about 4 weeks of growth
- Results for DoxyPEP group
  - 56% of participants had doxy detected at least once
  - *44% may not have taken any doxy*

"Differing results between trials among MSM and this trial among cisgender women are likely explained by low use of DoxyPEP"

Stewart et al., Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. N Engl J Med. 2023 Dec 21;389(25):2331-2340.

CDC DoxyPEP Recommendations (October 2023)

As the Centers for Disease Control & Prevention (CDC) and others work quickly to evaluate data to inform clinical guidance, there are those who are already engaged in the off-label use of DoxyPEP or considering it:

- Current efficacy data applies only to gay and bisexual men and transgender women
- Other antibiotics should not be considered for PEP
- Counsel on adverse effects: phototoxicity, GI symptoms, and esophageal ulceration
- Providers should continue to screen, test, and treat for bacterial STIs even among people who may be using doxy as PEP or PrEP

https://www.cdc.gov/std/treatment-guidelines/clinical-primary.htm

Initial and Follow Up DoxyPEP Visit

Initial Visit	Follow Up Visits
GC/CT (all sites), syphilis	Every 3-6 months
HIV screen (if using PrEP, per CDC HIV PrEP guidelines)	Every 3-6 months
Risk reduction counseling: condoms, reducing partners, HIV PrEP, nPEP, or HIV treatment	Same
Counsel re: side effects: photosensitivity, esophagitis, GI intolerance, potential for antibiotic resistance	Assess side effects
Counsel no antacids or supplements with Ca, Fe, Mg, or Na bicarb within 2 hours of dose	Same
Doxy may reduce efficacy of combined contraceptives, use backup method **(this is incorrect advice!)**	
Provide enough doses until next follow up visit	Reassess need for DoxyPEP

https://www.regulations.gov/document/CDC-2023-0080-0002

Prescribing DoxyPEP

- Prescribe doxy 200 mg (two 100 mg tablets) ideally < 24 hours, but no later than 72 hours, after condomless oral, anal, or vaginal sex
- Can be taken daily, but no more than 200 mg every 24 hours
- Screen for GC and CT at sites of exposure; test for syphilis and HIV
  - At initiation of DoxyPEP and every 3 months
- Doxy should not be taken during pregnancy
- Consider hematopoietic, renal, and hepatic lab monitoring as clinically indicated
- Counsel patients on standard precautions and warnings while taking DoxyPEP (e.g., sun sensitivity, pill esophagitis, and rarely intracranial hypertension)

DoxyPEP for Prevention of Syphilis, CT & GC (April 28, 2023)

1. Recommend DoxyPEP to MSM or transgender women who have had ≥1 bacterial STI in the past 12 months

2. Offer doxy-PEP using shared decision-making to all non-pregnant individuals at increased risk for bacterial STIs and to those requesting DoxyPEP, even if not previously diagnosed with an STI or have not disclosed their risk status

3. Sexual health counseling and education to all sexually-active individuals to include HIV/STI screening, DoxyPEP, HIV PrEP, HIV PEP, vaccinations (e.g., HPV, Mpox, Hepatitis A/B), EPT, and contraception

DoxyPEP for Prevention of Syphilis, CT & GC (April 28, 2023)

Offer DoxyPEP using shared decision-making to all non-pregnant individuals at increased risk for bacterial STIs and to those requesting DoxyPEP, even if not previously diagnosed with an STI or have not disclosed their risk status

CDPH Rationale:

1. Studies show that oral doxy is secreted into vaginal fluid
2. PrEP studies show equal efficacy in various populations, including cis-females
3. Equity problem arises when withholding DoxyPEP from females

Options for Emergency Contraception (EC)

- Emergency contraceptive pills (ECPs)
  - Levonorgestrel (LNg)
  - Ulipristal acetate (UPA)
- Copper T-380A (Cu) IUD
- ? Levonorgestrel (LNg) IUD

What Are The Specific Indications For EC?

- As desired within five days of unprotected intercourse
- As a component of a “quick start” regimen for off-cycle initiation of hormonal contraception, if a person has had unprotected intercourse in the last 5 days
- People who have been sexually assaulted
- Share with a friend
- SPR: Consider EC and use a barrier back-up for the next 7 days
  - People who have missed multiple pills
  - Patch detachment for more than 48 hours
  - Ring removal for more than 48 hours in the five days prior to intercourse

Levonorgestrel ECPs

- Single dose 1.5 mg LNg tablet
  - Labeled for use within 72 hours of unprotected intercourse
  - Efficacy is good 0-72 hours; “moderate” 72-120 hours
- Products
  - Plan B One-Step®
  - Generic one-dose tablets
  - Two-tablet products now obsolete

Ulipristal Acetate (UPA)

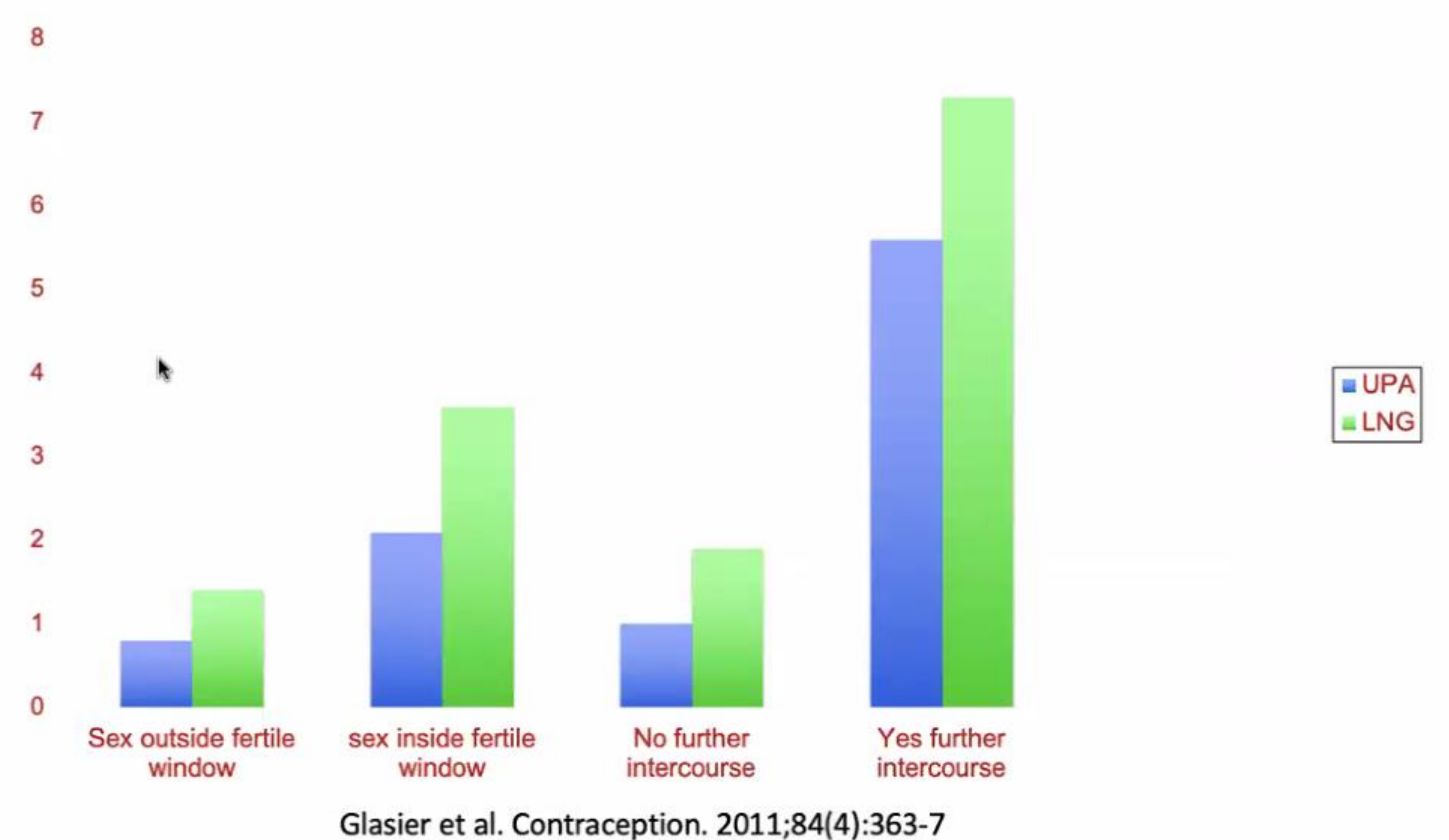
- Selective progesterone receptor modulator
- Mechanism of action
  - Prevents ovulation, with follicles up to 18-20 mm
  - Inhibits implantation, but higher dose required
- Taken orally in single 30 mg dose
- Labeled for use up to 5 days from last unprotected intercourse

Efficacy of UPA vs. LNg ECPs

- Trial of UPA 30 mg vs. LNG 1.5 mg
  - 1,696 women used *within 72 hours* of unprotected intercourse
    - Failure rates: UPA 1.8% vs. LNG 2.6% (OR=0.68)
  - 203 women used *within 72-120 hours* of unprotected intercourse
    - Failures: UPA - none vs. LNG - 3 pregnancies
- Conclusion
  - UPA is “not inferior” to LNG
  - UPA is effective for up to 5 days after exposure

Glasier AF, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010 Feb 13;375(9714):555-62.

Percent of Pregnancies Among UPA & LNG EC Users



Glasier et al. Contraception. 2011;84(4):363-7

EC Failure and Body Weight

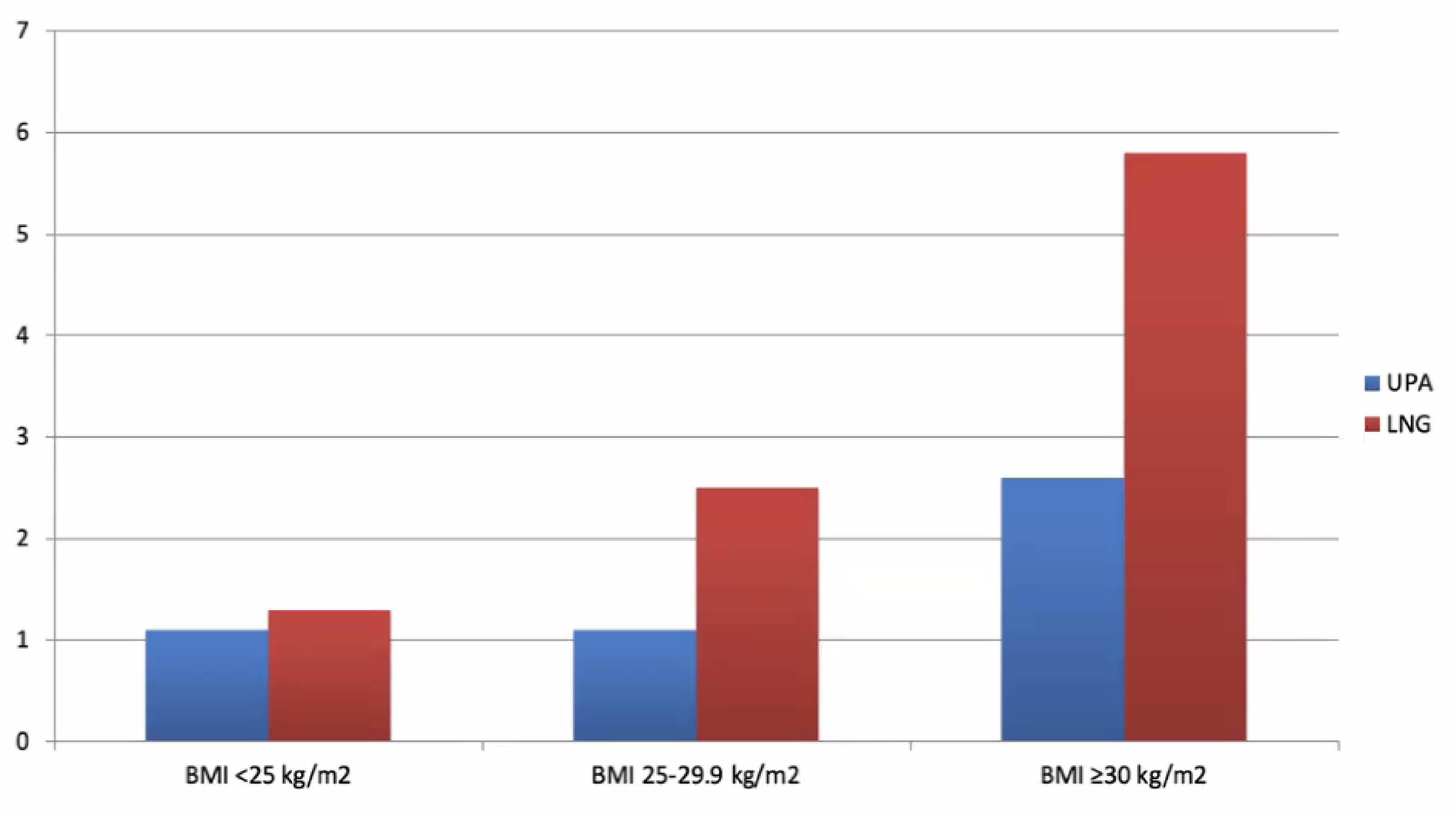
- Compared with people with BMI <25 kg/m^2
  - BMI 25–29 had a risk of pregnancy 1.5 times greater
  - BMI ≥30 had a three times greater risk of pregnancy

Why?

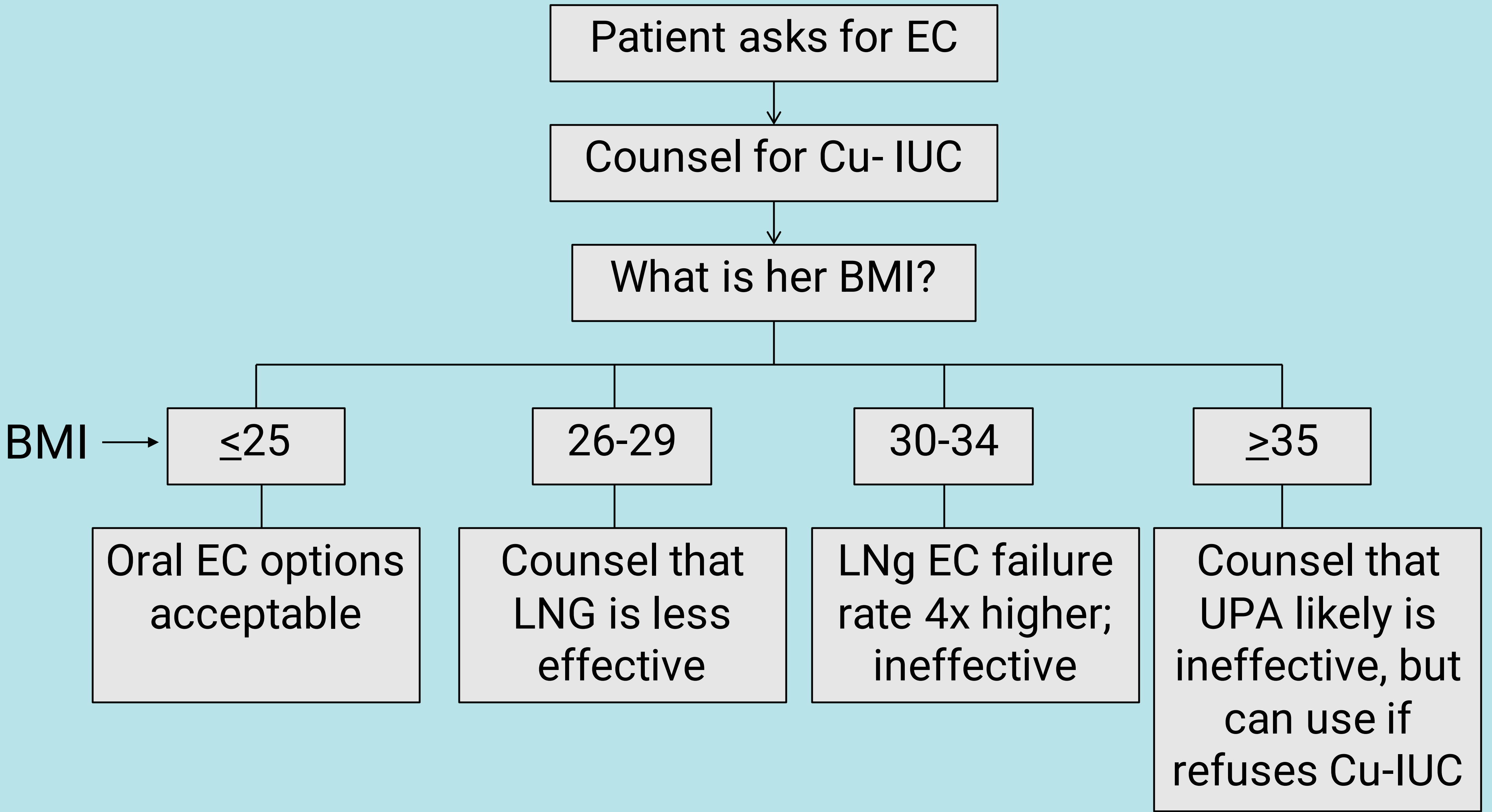
- Two recent have demonstrated that OC hormone absorption is slower in larger women than in women of normal weight

Glasier A, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception. 2011 Oct;84(4):363-7.

Percent of EC Pregnancies Among Ulipristal Acetate & LNG EC Users by BMI



Glasier et al. Contraception. 2011;84(4):363-7



EC: Challenges and Choices. Algorithm for Dispensing Emergency Contraceptives Rapkin RB, Creinin M. OBG Management 2011; 23(8): slides 16-24: http://www.ctcfp.org/wpcontent/uploads/EC-Challenges-Choices1.pdf

National Family Planning & Reproductive Health Association

Quickstarting Hormonal Contraception After UPA

"After using UPA, if a woman wishes to use **hormonal contraception**, she should do **so no sooner than 5 days after the intake of UPA**, and she should use a reliable barrier method until the next menstrual period."

FDA change to UPA label (March 2015)

National Family Planning & Reproductive Health Association

For women starting or continuing OCs, the Patch or the Ring:

For women who	Offer this ECP	For ongoing contraception	Days of backup required after ECP intake
Need EC because of missed pills, patch or ring	LNG	• For pill users: Continue pill pack *or* start new pack if on last week of pills • For patch/ring users: Start new patch or ring • If missing pills is an ongoing concern, counsel on methods that are easier to use consistently and correctly	7 days (2 days for POP)
Want to start OCs, Patch or Ring	UPA	• Provide method • Counsel patient to set a reminder to start 5 days after unprotected sex	7 days

Effectiveness of Simultaneous Use of LNg ECPs and Piroxicam

- RCT of LNg + piroxicam 40 mg PO or LNg + placebo
  - 860 women (430 in each group) recruited in Hong Kong 2018-2022
- Piroxicam: NSAID (COX-2 inhibitor) used for arthritis; $1.53 per 40 mg dose in US
  - Prostaglandins play a role in ovulation; blockade has a sound physiologic basis
- Results
  - Piroxicam: 1 pregnancy/418 subjects; failure rate= 0.2%
  - Placebo: 7 pregnancies /418 subjects; failure rate = 1.7% (odds ratio 0·20).
- LNg *plus* piroxicam prevented 95% of expected pregnancies vs. 63.4% for LNg + pbo
- Co-treatment did not seem to be associated with an increased disturbance to menstrual patterns or adverse events profile

Li R, Lo SST, et al. Oral EC with levonorgestrel plus piroxicam: a randomised double-blind placebo-controlled trial. Lancet 2023; 402: 851–58. https://doi.org/10.1016/S0140-6736(23)01240-0.

Advance Provision of EC: *The Hope*

- Widespread use of ECPs could prevent HALF of all unintended pregnancies and abortions in the US each year

  —*Trussell, Stewart et al. 1992*

Trussell J, Stewart F, Guest F, Hatcher RA. Emergency contraceptive pills: a simple proposal to reduce unintended pregnancies. Fam Plann Perspect. 1992; 24:262-264.

The Reality – 32 Years Later

- Fifteen studies have examined the impact of increased access to ECPs on pregnancy and abortion rates
- Only one has shown any benefit

- Rodriguez MI, Curtis KM, Gaffield ML, et.al. Advance supply of emergency contraception: a systematic review. Contraception. 2013 May;87(5):590-601.
- Polis CB, Raymond EG, Trussell J. Facing the facts on advance provision of emergency contraception. Contraception. 2010 Dec;82(6):579-80.
- Polis CB, Schaffer K, et.al. Advance provision of emergency contraception for pregnancy prevention: a meta-analysis. Obstet Gynecol. 2007 Dec;110(6):1379-88.
- Shen J, Yan C et.al. Interventions for emergency contraception. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324. Meyer JL, Gold MA, Haggerty CL. Advance provision of emergency contraception among adolescent and young adult women: a systematic review of literature. J Pediatr Adolesc Gynecol 2011 Feb;24(1):2-9.

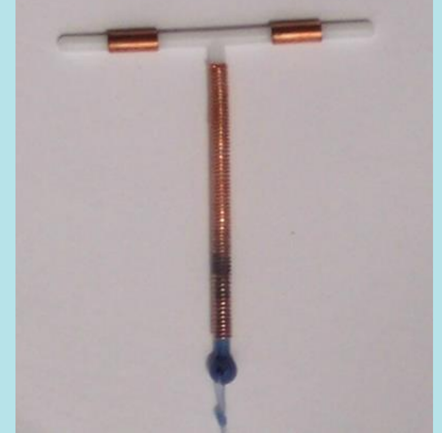
Does Advance Provision of EC Impact Clinical Outcomes?

- Advance provision increases ECP usage
  - No decrease in ongoing use of contraception
  - No increase in STIs

- Advance provision of EC *does not reduce* pregnancy rates when compared to conventional EC use
  - Either EC wasn't used or was used incorrectly

The Copper IUC as EC

- Efficacy[1]: pregnancy rate is 0.1%
  - Based on 35 years of experience; 7,034 women; 8 types of IUDs
- Use as EC[2]
  - Effective when placed up to 5 days from ovulation
  - If can't determine ovulation, insert ≤ 5 days from unprotected intercourse
  - Off label use
- Most cost effective when continued long term (10 years)
  - Duration of use similar to routine Cu IUD placement



1. Shen J, Che Y, et. al. Interventions for EC. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324.
2. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65(No. RR-4):1-66.

The LNG IUD as Emergency Contraception

- Randomized Controlled Trial Assessing Pregnancy for IUDs as EC (RAPID EC) trial
- Participant blinded non-inferiority trial
  - August 2016 - December 2019 at 6 Planned Parenthood of Utah sites
  - $\geq$ 1 episode of unprotected intercourse within 5 days and desires an IUD
  - Desire to prevent pregnancy for 1 year or more
  - Regular cycles and known LMP; negative urine pregnancy test
- Randomized to either LNG 52-mg IUD or Cu T380A IUD

Turok DK, Gero A, Simmons RG, Kaiser JE, Stoddard GJ, Sexsmith CD, Gawron LM, Sanders JN. Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception. N Engl J Med. 2021 Jan 28;384(4):335-344.

The NEW ENGLAND JOURNAL of MEDICINE

Levonorgestrel vs. Copper IUDs for Emergency Contraception

RANDOMIZED NONINFERIORITY TRIAL

Women seeking emergency contraception (unaware of group assignment)	Levonorgestrel 52-mg IUD (N=317)	Copper T380A IUD (N=321)
Pregnancy 1 mo after IUD insertion Noninferiority margin, 2.5 percentage points	**1 Participant** 0.3%; 95% CI, 0.01 to 1.7	**0 Participants** 0.0%; 95% CI, 0 to 1.1
	Difference, 0.3 percentage points; 95% CI, −0.9 to 1.8	
Adverse events resulting in participants seeking medical care ≤1 mo after IUD placement	**5.2%**	**4.9%**

The levonorgestrel IUD was noninferior to the copper IUD for emergency contraception.

D.K. Turok et al. 10.1056/NEJMoa2022141

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An Earlier Study: LNg IUD + LNg ECPs

- 188 women given option of Cu IUD vs. oral LNG 1.5 mg + LNG 52 IUD: 67 (36%) chose Cu IUD; 121 (64%) chose oral LNG + LNG IUD
- Pregnancy rate after oral LNG + LNG IUD EC: 0.9% (95% CI 0.0-5.1%)
  - Multiple episodes of unprotected intercourse, with an episode > 5 days prior
- No pregnancies in the Cu IUD group
- Implications:
  - Consideration should be given to LNG IUD plus oral LNG 1.5 mg for EC
  - Use of this combination may increase the number of women initiating highly effective contraception at the time of their EC visit

Turok DK, et al. Preference for and efficacy of oral levonorgestrel for emergency contraception with concomitant placement of a levonorgestrel IUD: a prospective cohort study. Contraception. 2016 Jun;93(6):526-32.

A Counter Argument

- SFP 2/2023: "We recommend that the LNG 52 mg IUD be offered as a first-line EC an option, along with other EC methods (Grade 1B)"
- "The results of the [Turok] study received considerable attention and have brought about changes to practice guidelines without critical review. We do not find these recommendations to be supported by the available data"
- No studies documenting mechanism of action
- Cited other issues related to randomization, selection bias, and varied pregnancy risk of the participants

Ramanadhan S, Jensen J. LNG IUD as EC: Re-examining the Data. Obstet Gynecol. 2024 143(2):189-194.

More Counter Arguments: Cochrane Review

- Authors' conclusions:
  - Review is limited in its ability to provide definitive evidence regarding the LNG IUD's equivalence, superiority, or inferiority vs. Cu-IUD for EC
  - *Only one study* was identified in the review, which had possible risks of bias related to randomization and rare outcomes
  - Additional studies are needed to provide definitive evidence related to the effectiveness of the LNG IUD for EC

Ramanadhan S, Goldstuck N. et al. Progestin IUDs versus copper IUDs for EC. Cochrane Database Syst Rev 2023 Feb 27;2(2):CD013744.

Emergency Contraception: Take it Home

- The Cu IUD provides superior EC
  - Within 5 days of ovulation
  - *Also* provides long term contraception
- UPA is preferred for unprotected intercourse 72-120 hours and for people with a BMI >25 m^2
  - LNG and UPA equivalent in other cases
- Body weight is an important determinant of ECP efficacy
- Advance provision *doesn't* impact efficacy compared to "as needed" use
- In *one study*, the efficacy of the LNg IUD is not inferior to the Cu IUD
- In *one study*, there were no pregnancies with Cu IUD or LNG IUD + LNG ECPs
- In *one study*, LNG ECPs + piroxicam was more effective than LNG ECPs alone

Case Study: Jenny

- 25-year-old G_o P_o cis-female who is seen with a request for STI screening
- Was at a party 2 days ago and hooked up with male, had unprotected vaginal intercourse and receptive oral sex
- LMP started 6 days ago and was on time
- She considers condoms to be her method of contraception
- History of cervical chlamydia 18 months ago; picked up by screening while asymptomatic
  - Treated with doxy for 7 days
  - PDPT provided
  - Rescreening 3 months later was negative
- Tests today: GC, Ct, VDRL for syphilis, HIV serology
- Reviewed safer sex practices

Case Study: What *Else* Would You Do?

- ☐ Discuss and offer ECPs
- ☐ Discuss and offer a Cu IUD for EC
- ☐ Discuss and offer a LNg IUD for EC
- ☐ Discuss and offer DoxyPEP for STI prevention
- ☐ Discuss and offer PrEP for HIV prevention
- ☐ Discuss and offer n-PEP* for HIV prevention

* n-PEP: non-occupational post-exposure prophylaxis for HIV

Case Study: What *Else* Would You Do?

Yes	Discuss and offer ECPs
Yes	Discuss and offer a Cu IUD for EC
Maybe	Discuss and offer an LNG IUD for EC
Maybe	Discuss and offer DoxyPEP for STI prevention
Maybe	Discuss and offer PrEP for HIV prevention
No	Discuss and offer n-PEP for HIV prevention

What Would David Grimes Do?

EBM: What Is It?

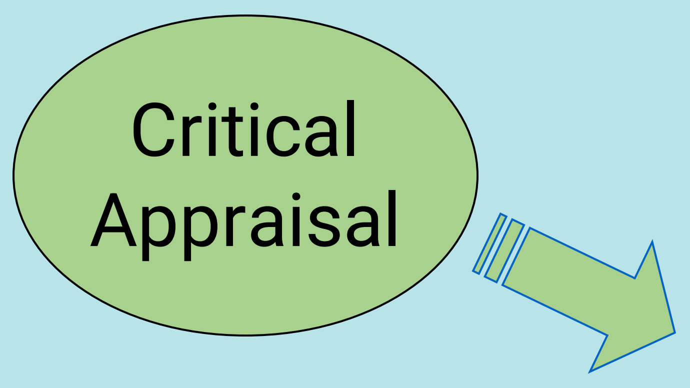
"Evidence based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research."

–David Sackett, MD

Sackett D L, Rosenberg W M C, Gray J A M, Haynes R B, Richardson W S. Evidence based medicine: what it is and what it isn't *BMJ* 1996; 312 :71.

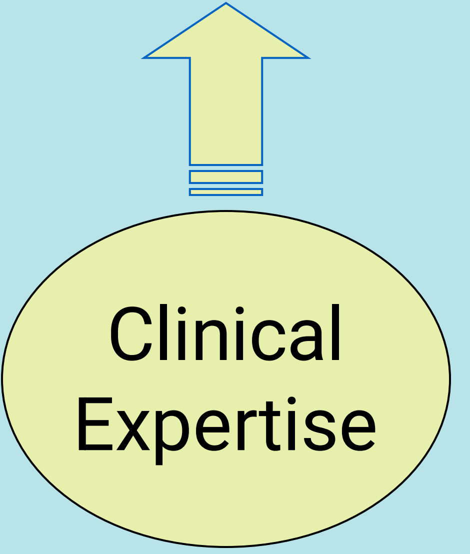
The EBM Paradigm



Clinical Decision

Patient

- Preferences
- Concerns
- Expectations



Sackett, DL, et al. Evidence-based medicine: How to practice and teach EBM, Second Ed. Philadelphia: Elsevier Churchill Livingstone, 2000.

Framework of EBM

- See a patient
- Ask a question
- Seek the best evidence for that question
- Appraise that evidence
- Apply the evidence
- Monitor the change

What Would Dr. David Grimes Do?

Probably remind us that…

- From a *public health* (population-based) perspective, DoxyPEP and LNG IUDs for EC are not “ready from prime time” until more is known
- When caring for an *individual patient*, the three fundamentals of EBM should be applied
  - Clinical evidence, especially from RCTs
  - Clinician experience
  - Patient preference