Emergency Contraception: New Methods

Alison Edelman, MD, MPH
Professor, OB/GYN
Director, Division of Complex Family Planning (CFP) & Fellowship in CFP
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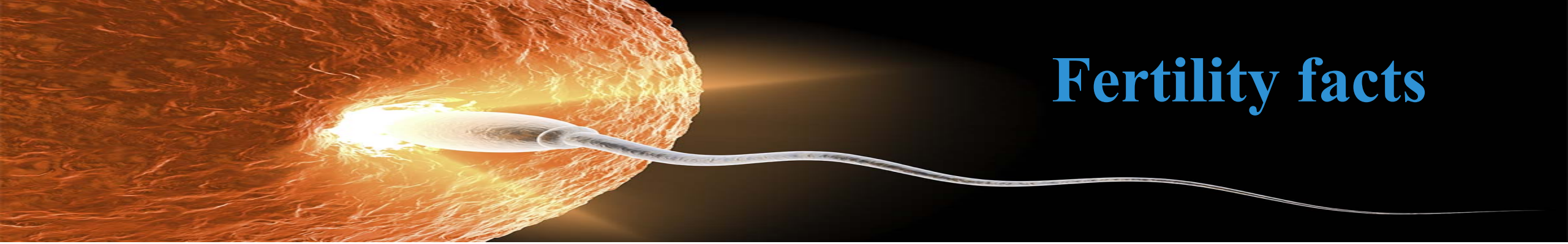
OHSU



Fertility facts

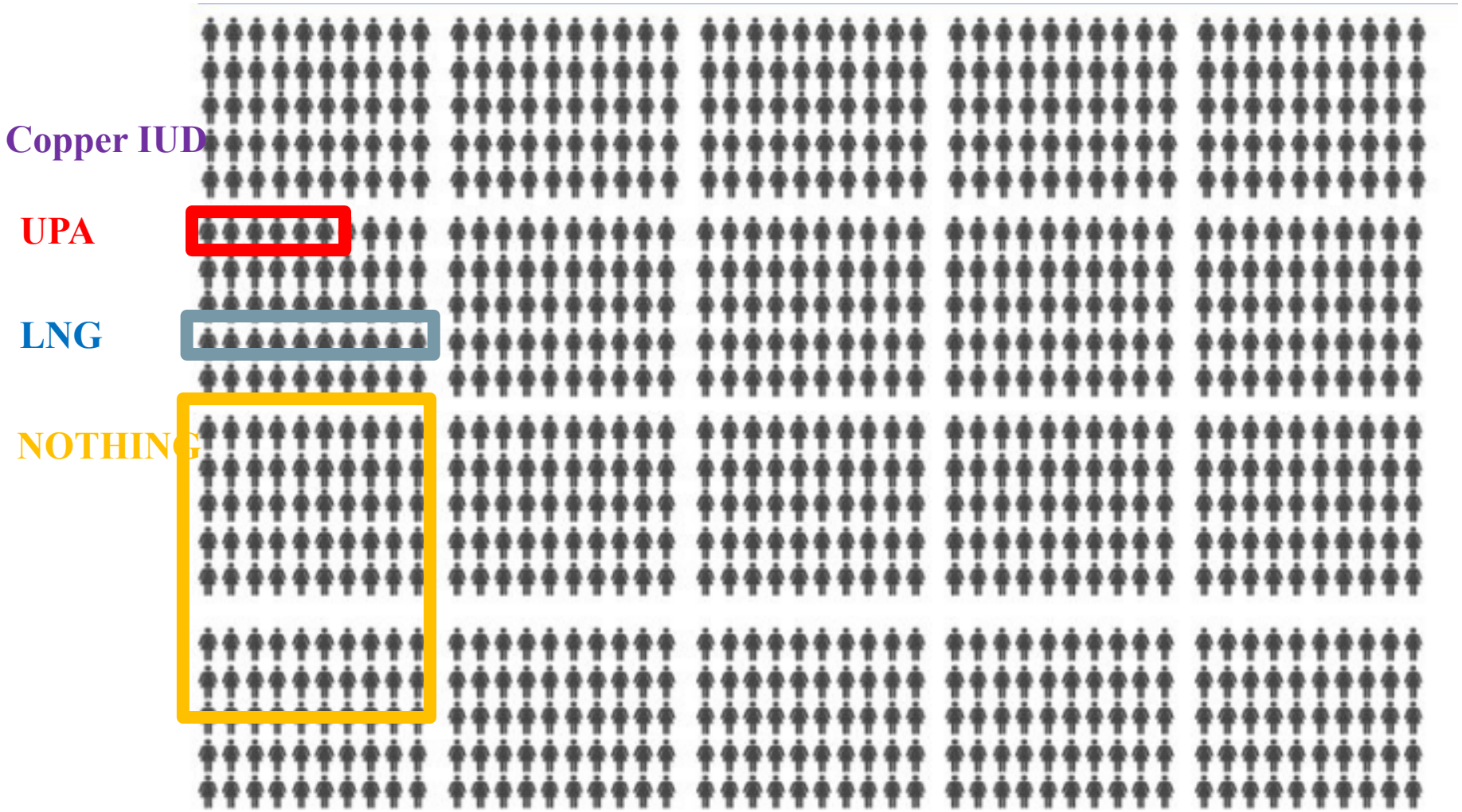
- Fertile period of time in a cycle is ~6 days
- Sperm is viable in the reproductive tract for ~5 days
- An egg is capable of fertilization for 12-24 hours
- Implantation occurs 6-10 days after fertilization
- Pregnancy risk after a single act of intercourse around the most fertile time is estimated to be up to 30%

Evidence-based EC basics

- Copper IUD is the most effective method of EC
- UPA EC demonstrated more effective than LNG EC
- Oral EC & Timing
  - UPA EC effective up to 120 hours after unprotected sex
  - LNG EC effective up to 72 hours after unprotected sex
    - Some evidence that after 96 hours it is ineffective
    - Oral EC, LNG or UPA, given after ovulation is ineffective
- Other impacts on effectiveness
  - Hormonal contraception interferes with UPA EC
  - Higher BMI/weight impacts LNG EC

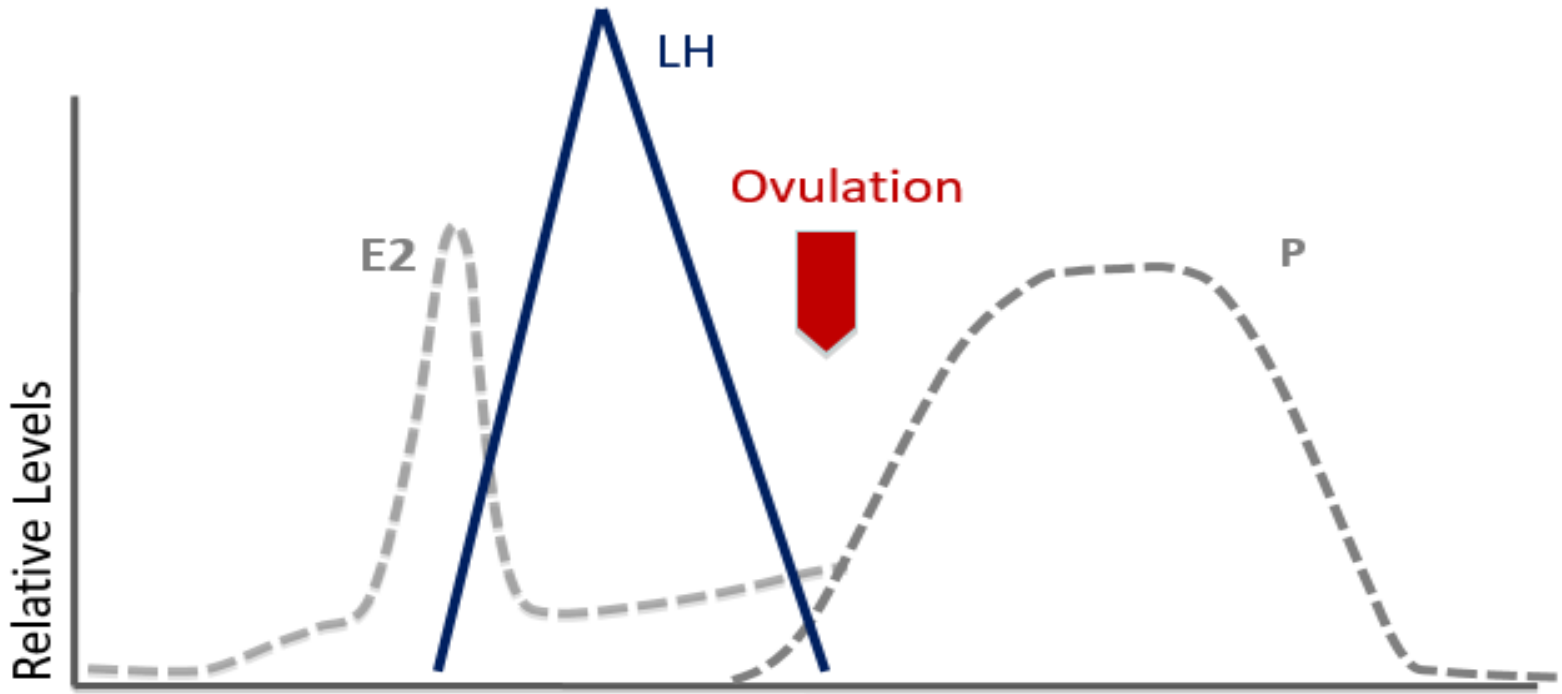
Cochrane Shen 2017; Glasier 2011

Pregnancies per 1000 Women after Unprotected Intercourse



Cochrane Shen 2017; Cleland 2012; Glasier et al Lancet 2010

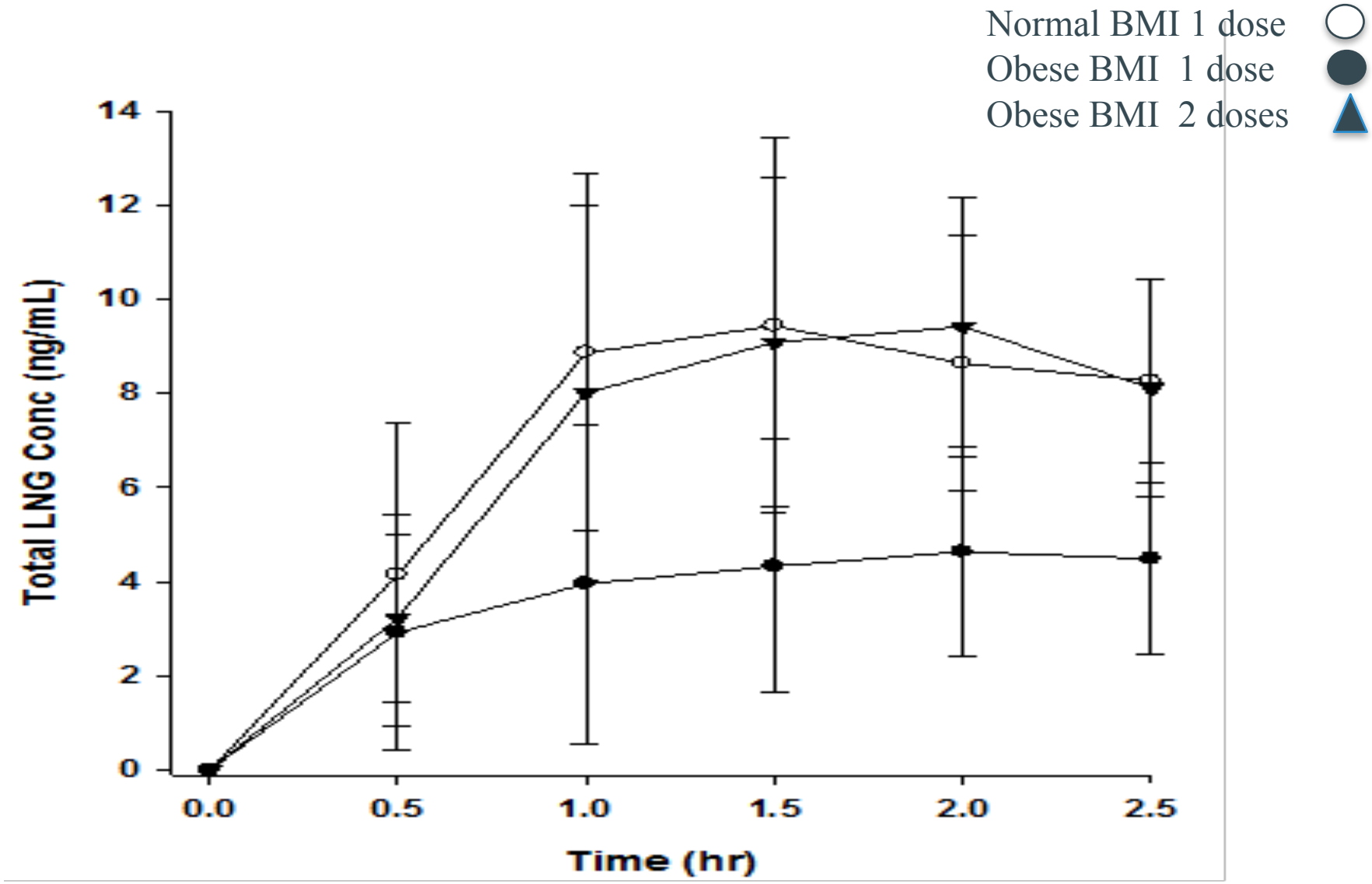
Mechanism of action



Pre-LH surge	LH rise	Post-LH surge
•LNG •UPA	•UPA	

Glasier 2011*; Festin 2017

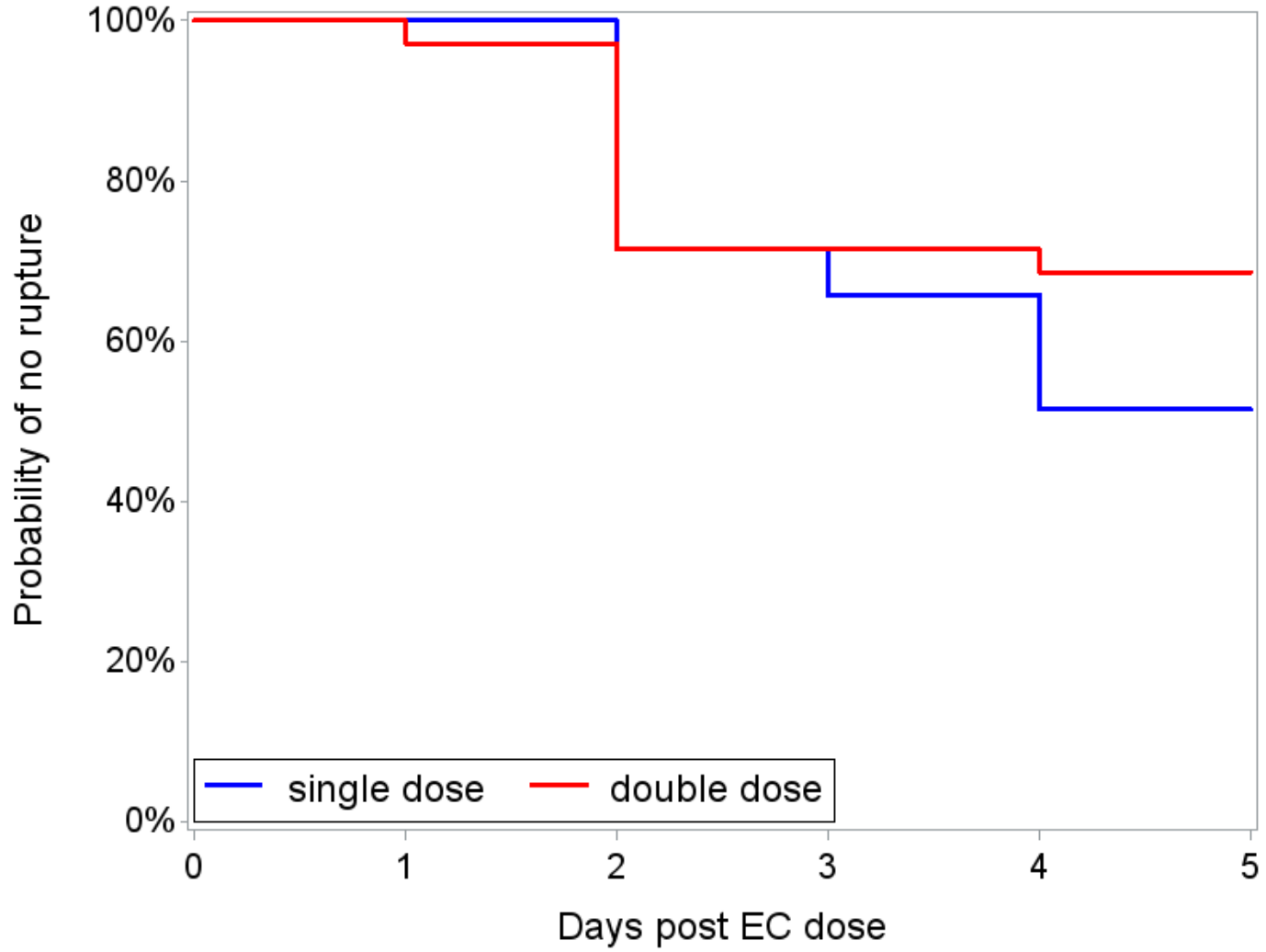
Pharmacokinetics of LNG-EC
Single & Double Dosing



Edelman et al 2016 Contraception; OHSU MRF Funding

Randomized Control Trial of 1.5mg vs 3mg LNG EC

Time to rupture



p value = 0.2
Log-rank test

Per Protocol Analysis. Censored at day 5
75% probability of no rupture is day 2 for both groups

2022 Edelman Obstet Gynecol

Single vs Double Dosing LNG EC

- LNG EC dose escalation had no demonstrated impact on delay or timing of rupture for individuals with obesity.

Strengths

- Randomized design
- Objective outcome
- Directly observed ingestion

Limitations

- Pre-screen ovulatory status by progesterone only
- Luteal phase normalcy not assessed
- Power analysis to determine 30% difference

LNG-IUD for EC?

- **Prospective cohort study (2016)**
  - Those seeking EC could choose
    - Cu-IUD (n=67) v. LNG EC plus 52mg LNG-IUD (n=121)
      - 1 pregnancy LNG group

- **Randomized controlled study (2021)**
  - Those seeking EC randomized
  - Cu-IUD (n=327) v. 52mg LNG-IUD (n=317)
    - 1 pregnancy LNG group
  - Noninferiority methodology
  - Mid-cycle at risk unknown
  - Unbalanced study groups
    - More contraceptive use prior to LNG IUD arm

Quick start? YES
EC? Too early to know

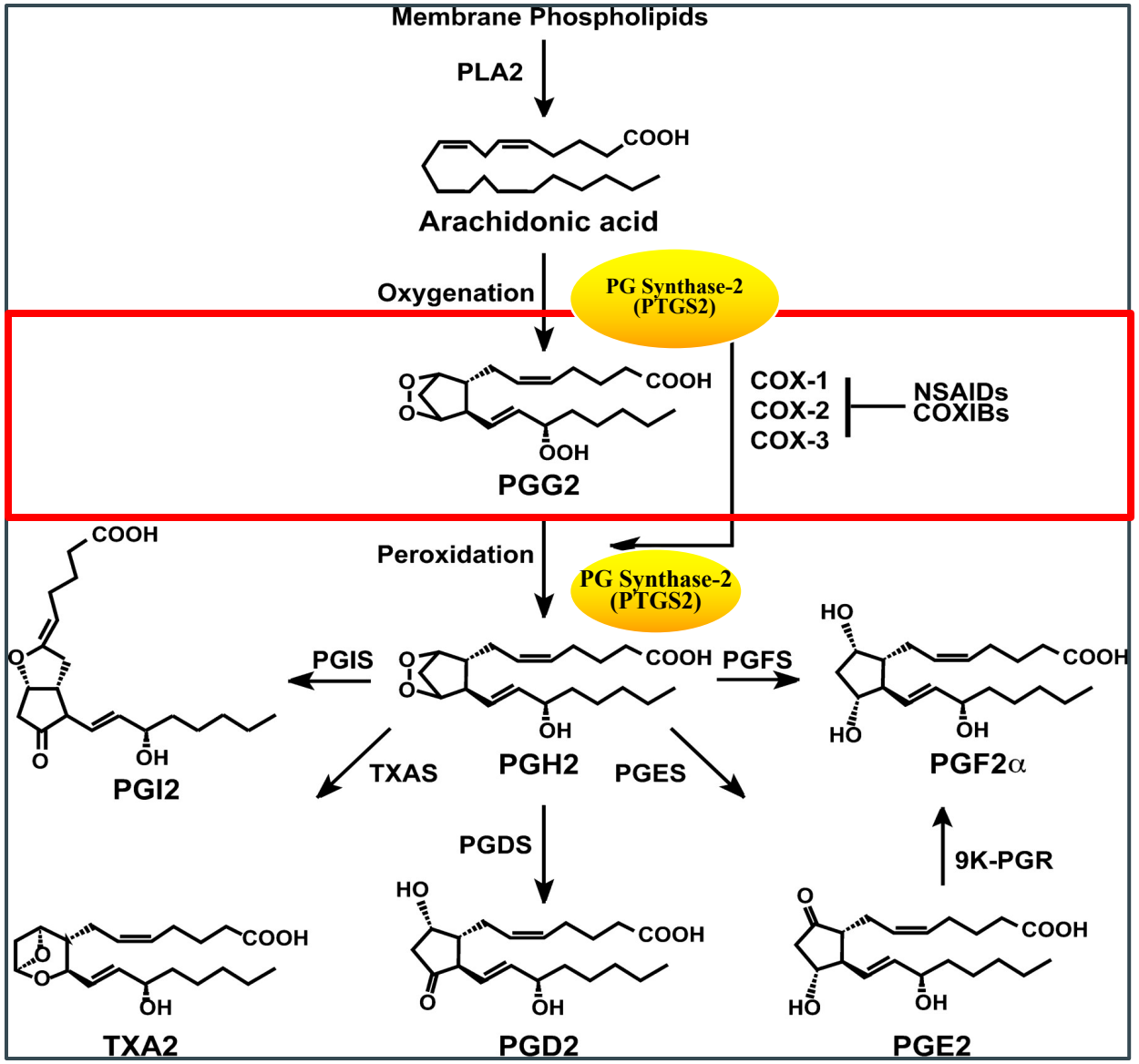
Askalani 1987; CDC SPR 2016; 2016 Turok Contra; 2021 Turok NEJM

Prostaglandins & Fertility

- Follicle rupture
- Cumulus expansion
- Oocyte maturation
- Luteal function
- Fertilization

Armstrong and Grinwich,1972; Orczyk and Behrman, 1972;
Duffy D M , Stouffer R L Mol. Hum. Reprod. 2001;7:731-739

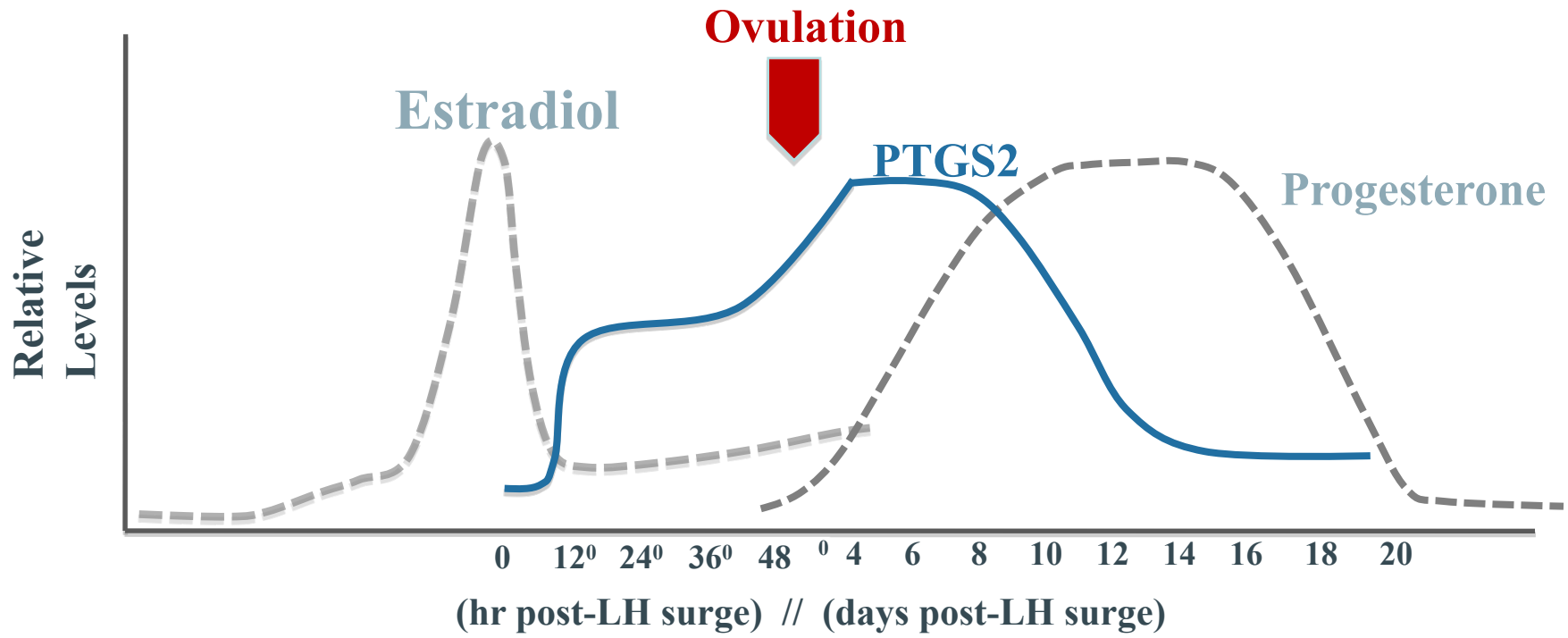
Prostaglandin Pathway



Sirois J et al. Hum. Reprod. Update 2004;10:373-385

Prostaglandins: Post-LH peak effects

PTGS2 is a precurser of PGE2

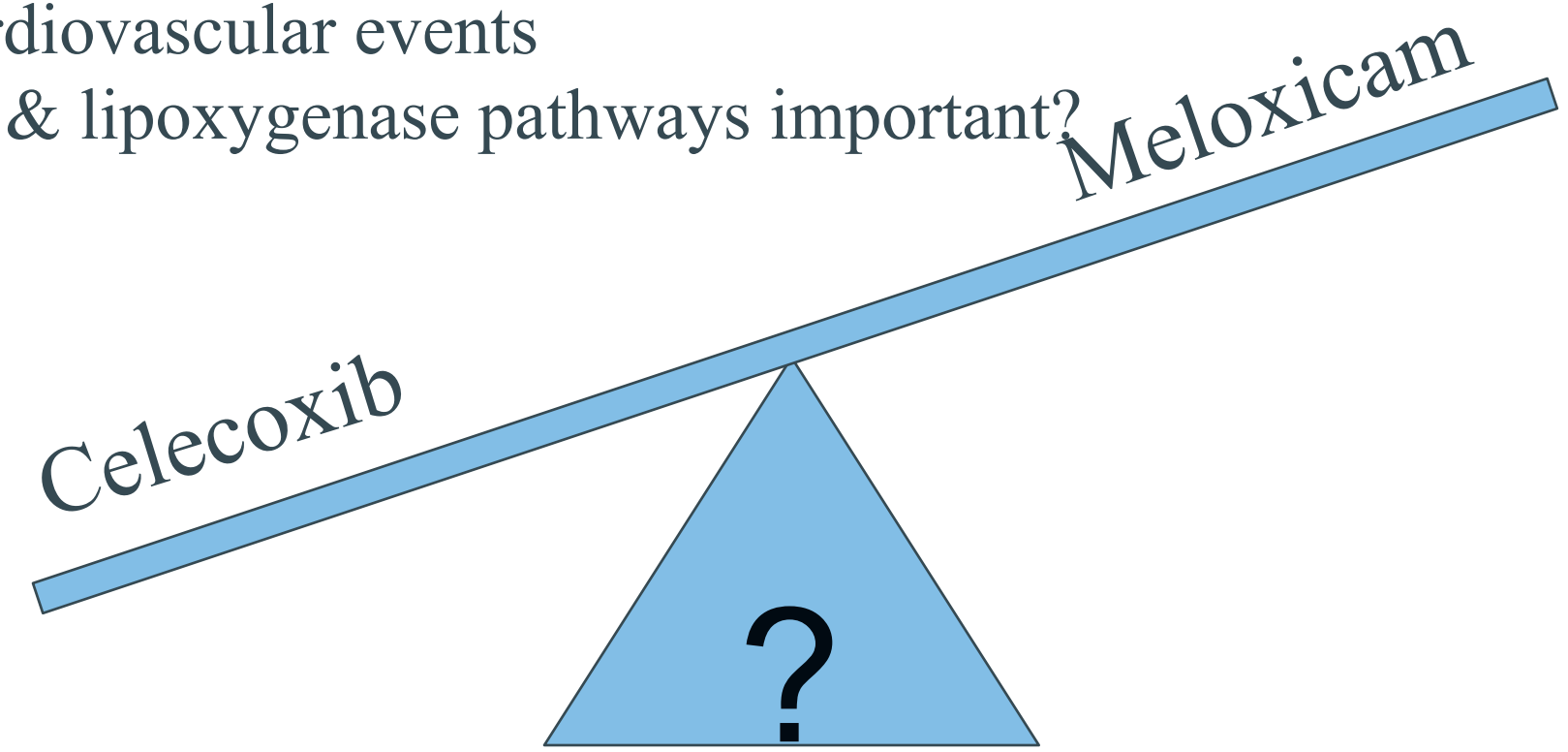


Cox 2 Inhibitors: Meloxicam v Celecoxib

Celecoxib more COX-2 specific (7 fold more specific to PTGS2 than Meloxicam

- Less GI effects
- More cardiovascular events

Are COX-1 & lipoxygenase pathways important?



Meloxicam: Ovulatory dysfunction

HUMAN	Meloxicam 15 mg/day	Meloxicam 30mg/day
Ovulation	11/22 (50%)*	2/22 (9%)
Dysfunctional ovulation	6/22 (27%)	10/22 (45.5%)*
Unruptured follicles	5/22 (23%)	10/22 (45.5%)

Jesam, C., A. M. Salvatierra, et al. (2010). Hum Reprod 25(2): 368-373.

Celecoxib: Ovulatory dysfunction

Cycle type	Normal	Ovulatory dysfunction	Unruptured	Both
Control	19 (95%)	1 (5%)	0 (0%)	5%
Before LH surge	14 (70%)	2 (10%)	4 (20%)	30%
After LH surge	16 (80%)	3 (15%)	2 (10%)	25%

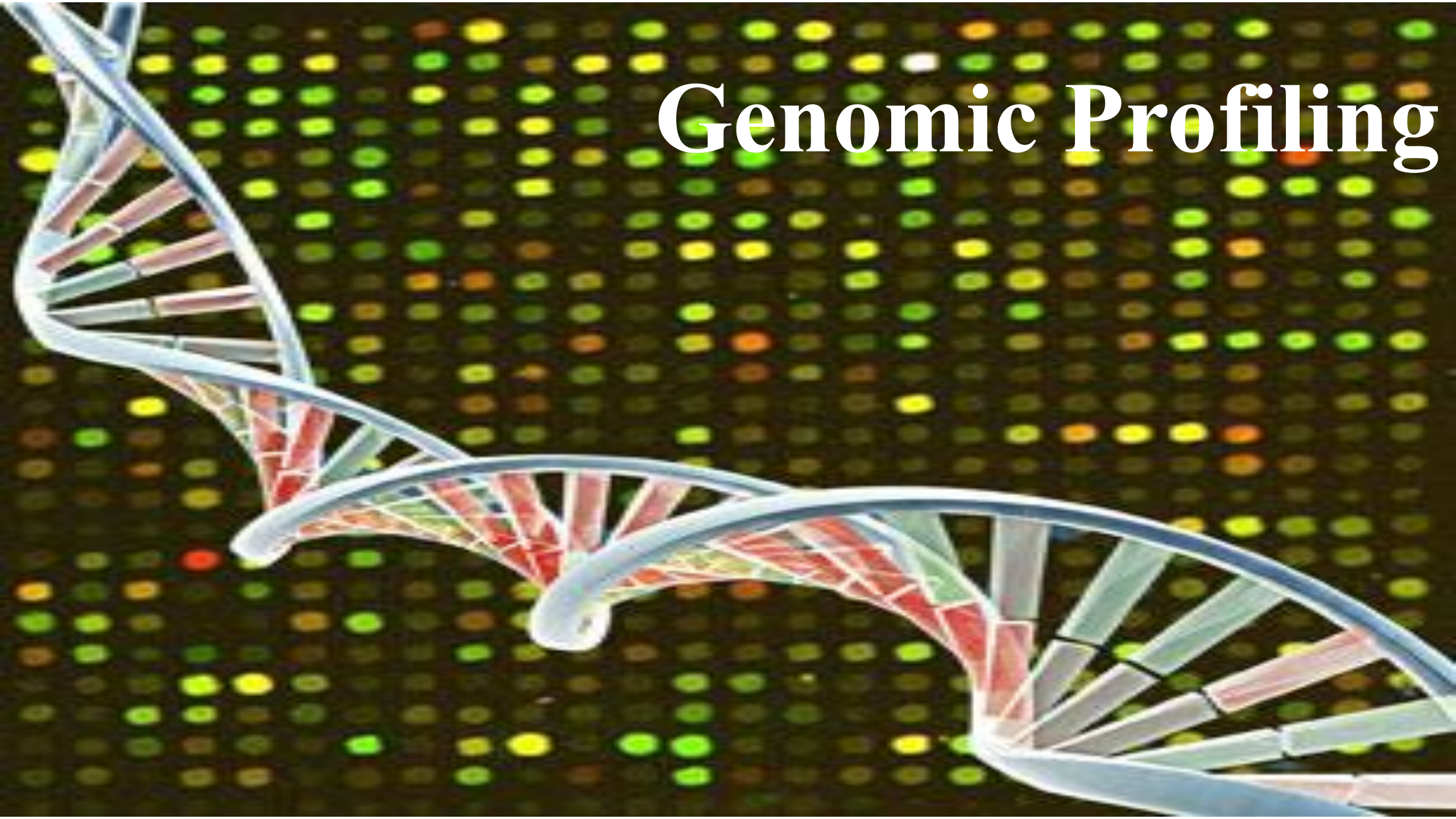
A.B. Edelman, J.T. Jensen, J.D. Hennebold. Impact of the prostaglandin synthase-2 inhibitor celecoxib on ovulation and luteal events in women. *Contraception* 87:352-357, 2012.

Combination EC: Cox 2 plus oral EC

- Meloxicam 15mg plus LNG EC 1.5mg
  - No rupture or follicle dysfunction 66% LNG only vs 88% combo
  - Sample size: 41 paired cycles

- Meloxicam 30mg plus UPA EC 30 mg (single arm study)
  - Only 2 individuals dosed post-LH surge; only 1 ovulated
  - Sample size: 9 participants

Massai 2007 Human Reprod; Cahill 2022 BMJ SRH


Genomic Profiling

Evolution of EC

- Non-use of contraception drives unplanned pregnancy rates
- Unmet need for an on demand/peri-coital method
- Method characteristics differ from EC
  - Impact on cycle cyclicity
  - Side effects

OHSU, Portland, Oregon
Jeff Jensen, MD, MPH
Jeong Lim, PhD
Kise Bond
Women's Health Research Unit

OHSU/ONPRC
Jon Hennebold, PhD

EVMS, Norfolk, VA
David Archer, MD

Consultants
Vivian Brache, Profamilia, DR
Ganesh Cherala PharmD, PhD

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