

# Impact of sex hormones in migraine

5th Nordic Migraine Symposium

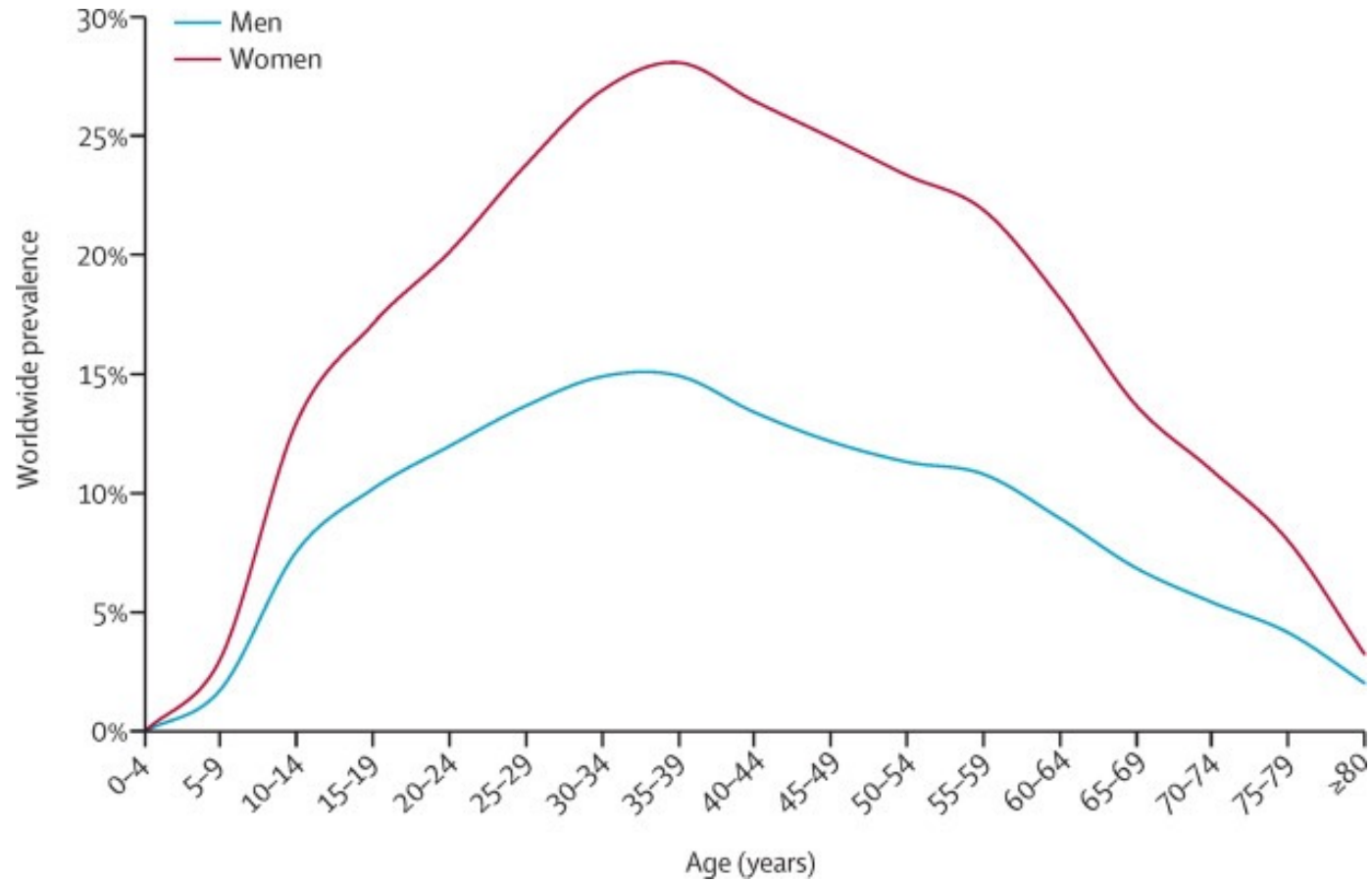
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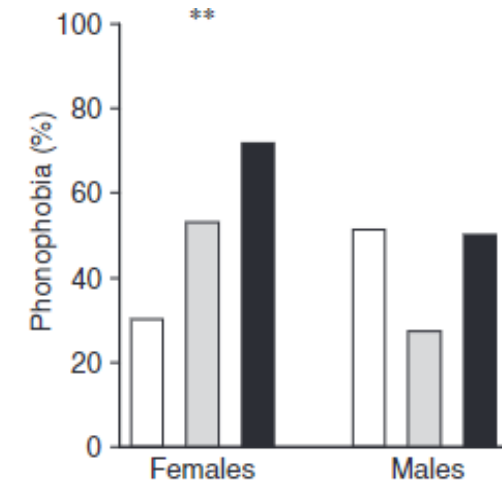
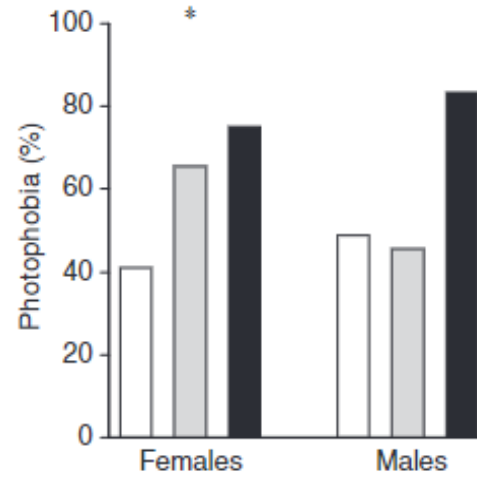
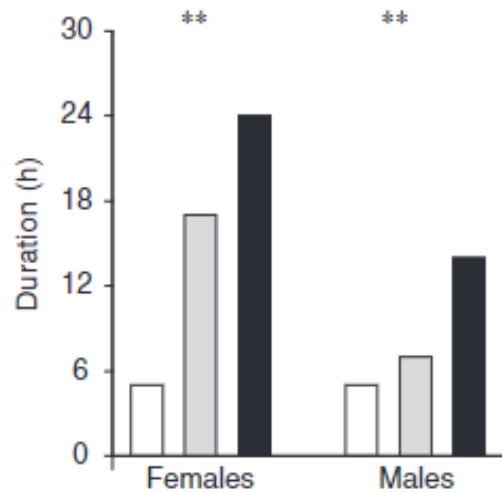
# Conflicts of interest

<b>AbbVie/Allergan</b>	Personal fees for lecturing and/or consulting
<b>Eli Lilly</b>	Personal fees for lecturing and/or consulting
<b>Lundbeck</b>	Personal fees for lecturing and/or consulting
<b>Novartis Pharma</b>	Personal fees for lecturing and/or consulting Research support
<b>Teva Pharmaceutical Industries</b>	Personal fees for lecturing and/or consulting
<b>German Research Foundation (DFG)</b>	Research support
<b>German Migraine and Headache Society (DMKG)</b>	Research support

## Migraine prevalence in women is two- to three-times higher than in men.



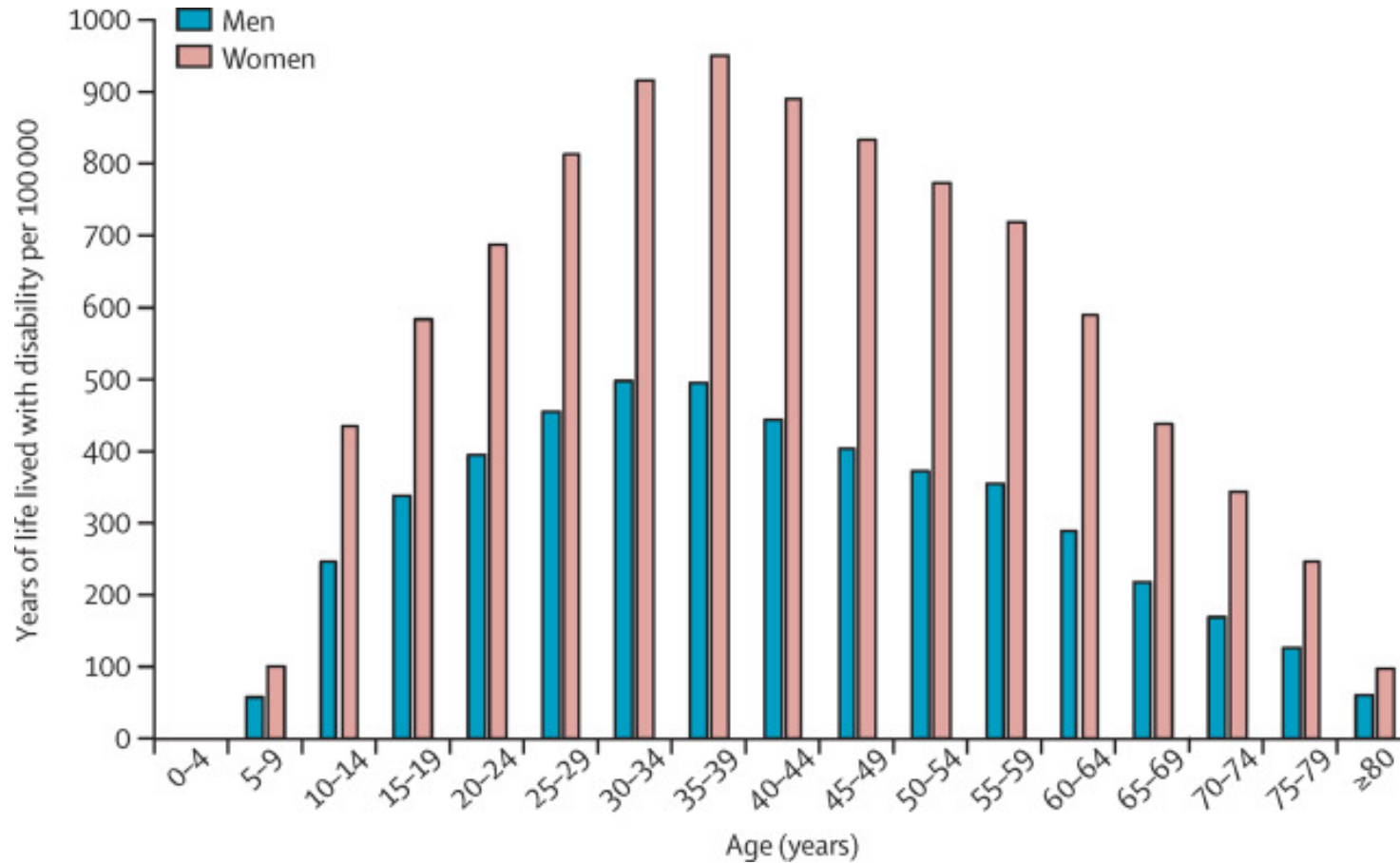
# Migraine attacks in women are longer (and more severe?) than in men.



Headache characteristics separated by age in 169 females and 91 males with migraine.

- <14 years (n= 147, 73 F)
- ▒ 15-40 years (n= 75, 64 F)
- >40 years (n= 38, 32 F). \*\*P= 0.001; \*P= 0.01.

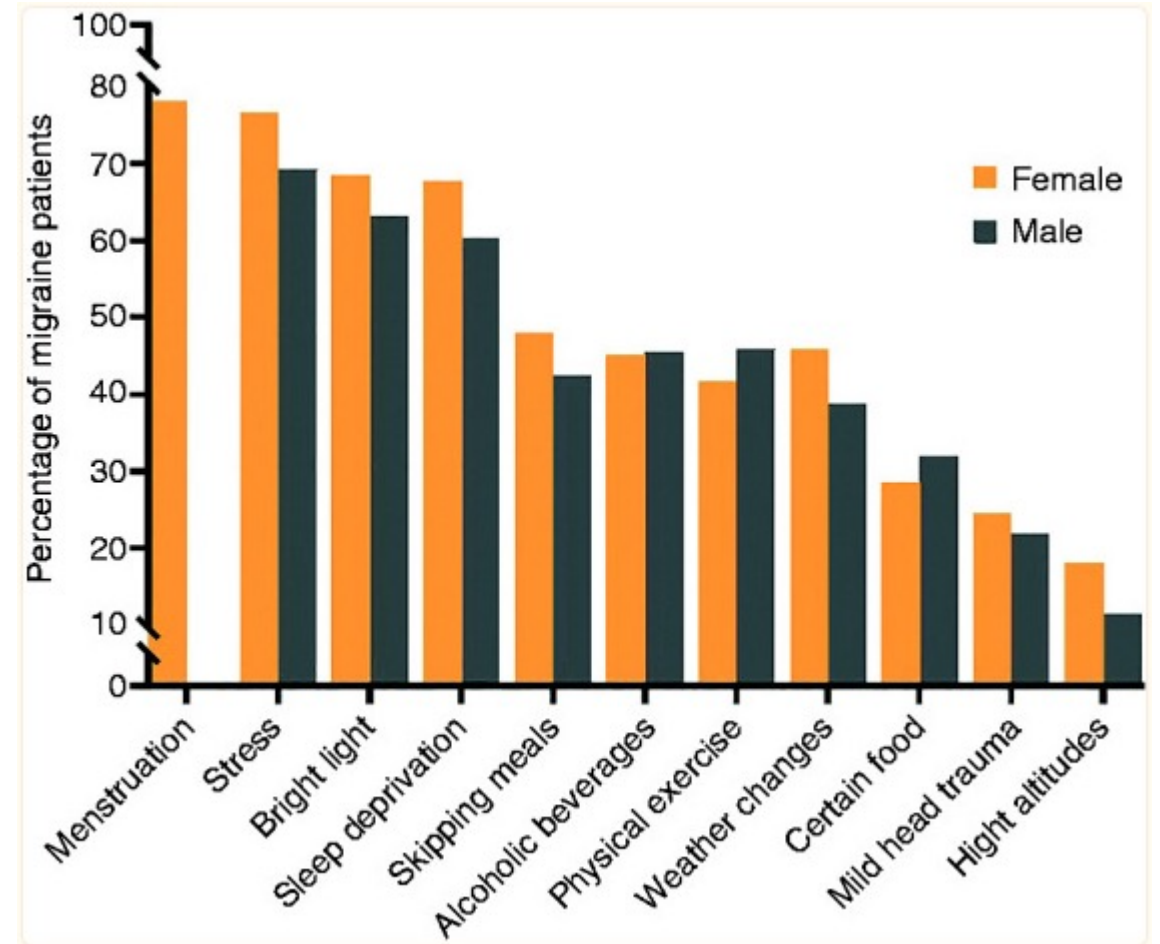
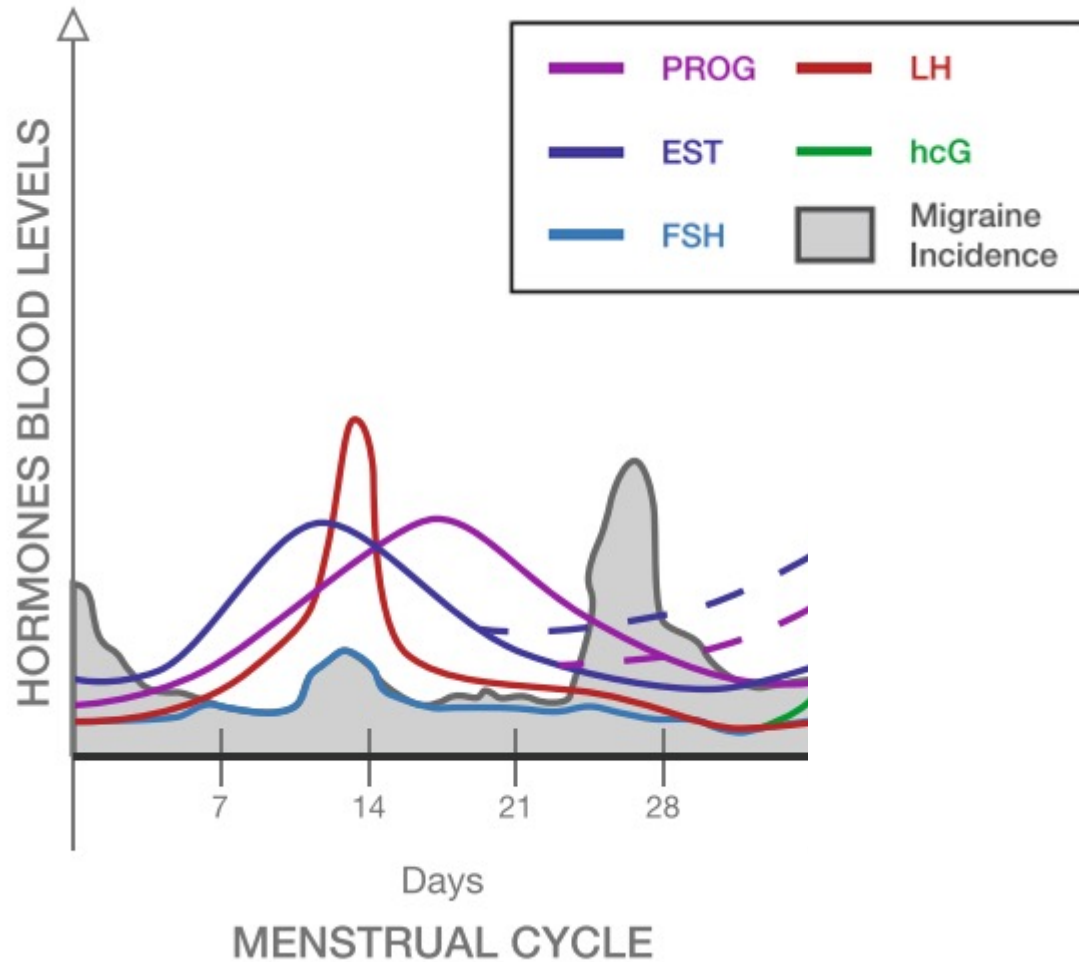
## Migraine causes a higher burden in women than in men.



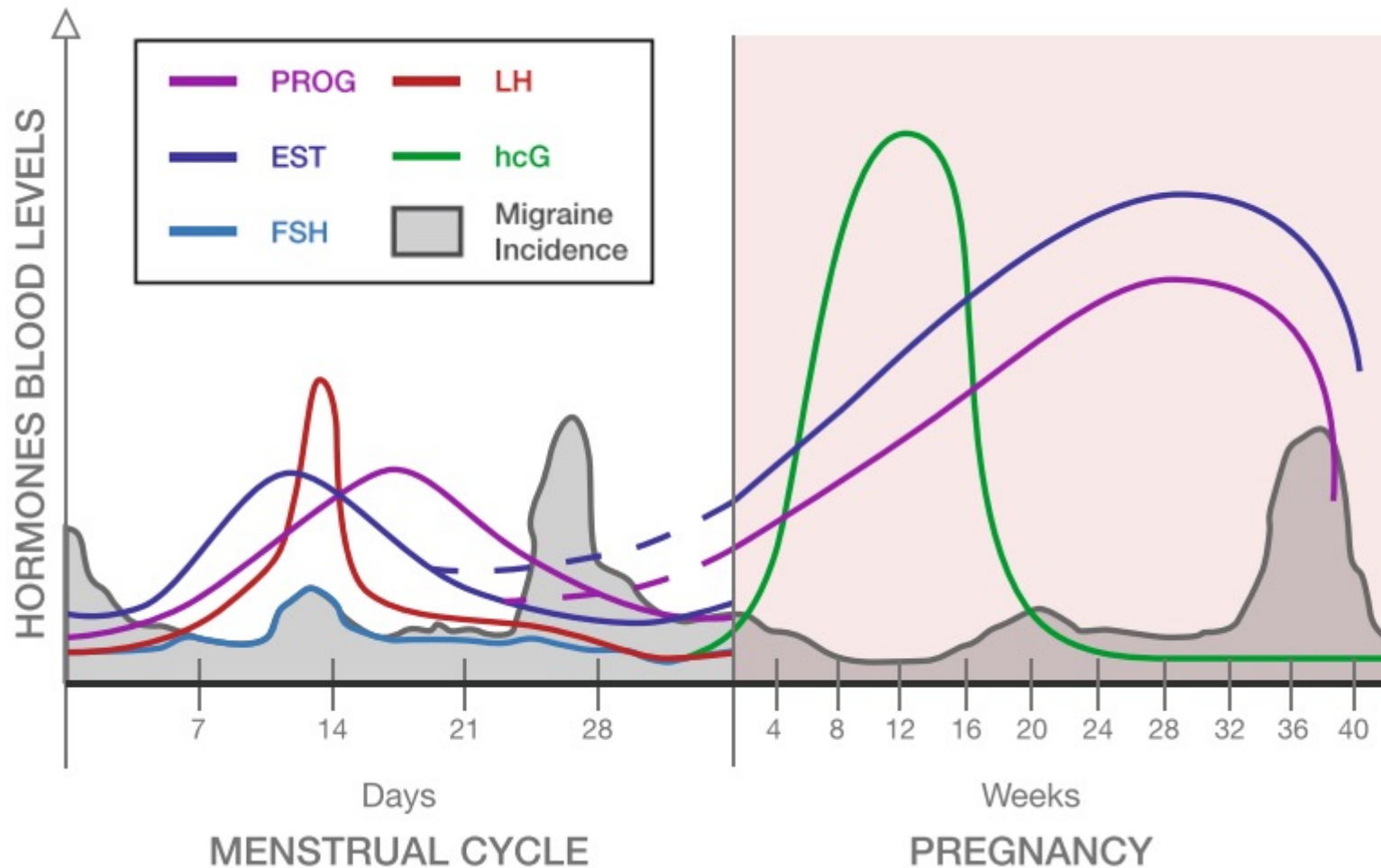


Are sex hormones the cause of sex differences?

# Sex hormone fluctuations can influence the migraine course.



## Sex hormone fluctuations can influence the migraine course.



### Migraine without aura:

- 38-90% improvement
- 8-37% no change
- 0-34% worsening
- 1-10% new onset

### Migraine with aura:

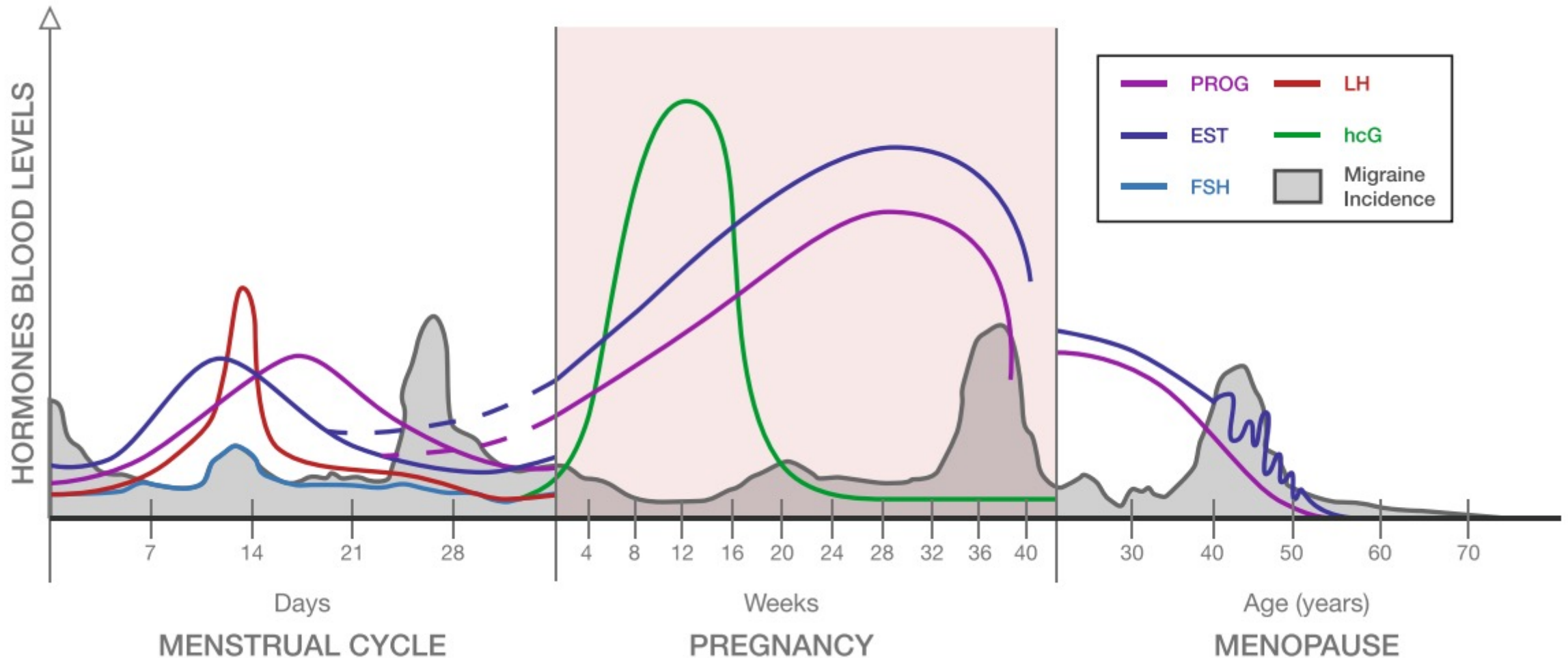
- 44-84% improvement
- 4-49% no change
- 0-17% worsening
- 11-14% new onset

### Return of attacks post partum:

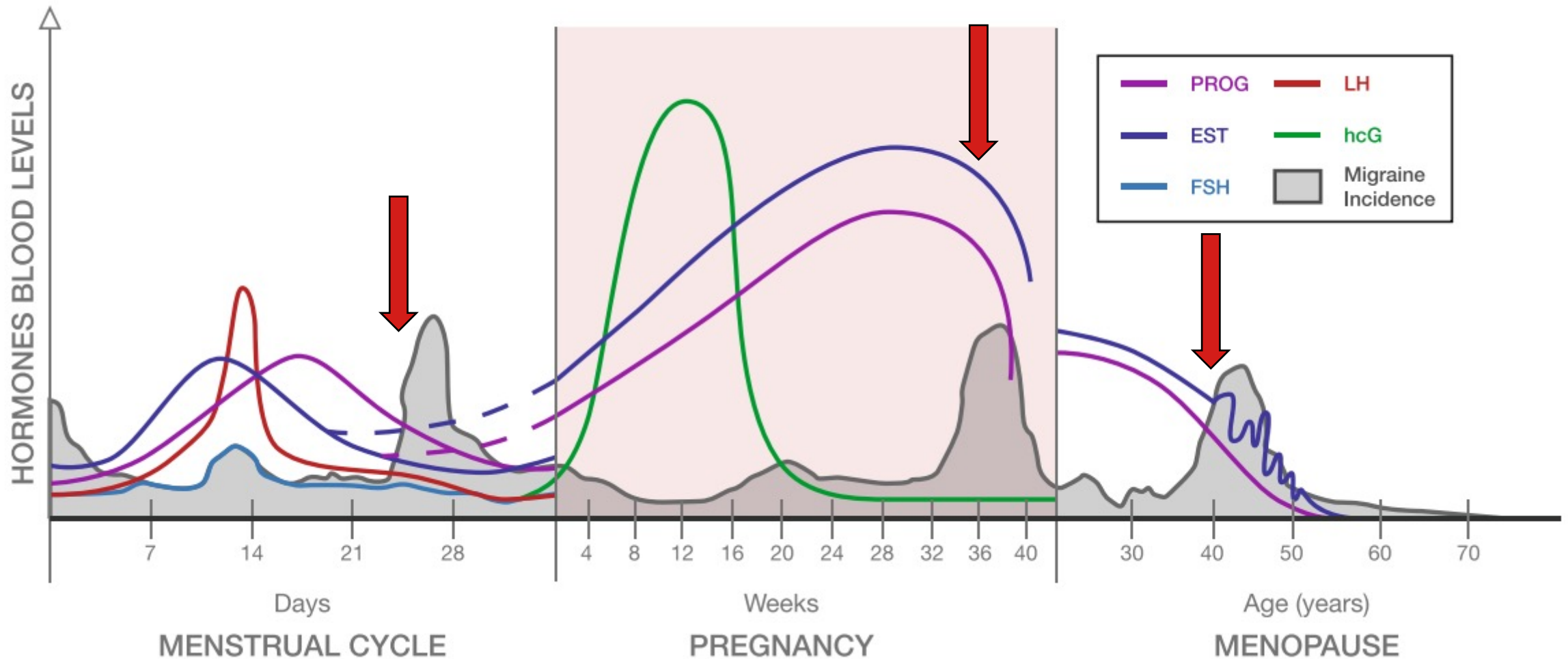
- 55% after one month



## Sex hormone fluctuations can influence the migraine course.



## Sex hormone fluctuations can influence the migraine course.



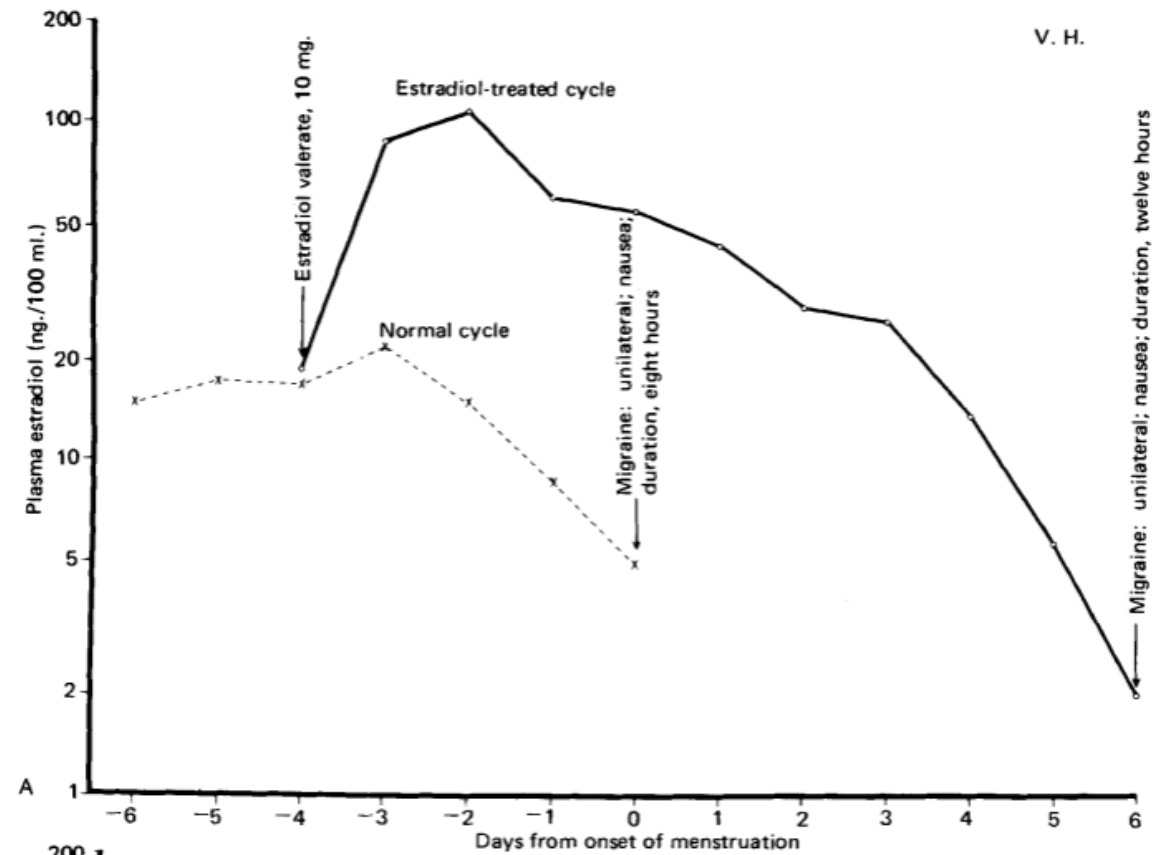
# Possible explanation: The estrogen withdrawal hypothesis (1972)

## The role of estradiol withdrawal in the etiology of menstrual migraine

Brian W. Somerville, M.R.A.C.P., M.R.C.P.

*Neurology* / Volume 22 / April 1972

Plasma estradiol determinations performed daily in both groups of women during the estradiol-treated period showed that migraine was closely related to the phase of estradiol withdrawal. It is concluded that falling levels of estradiol rather than of progesterone play a significant role in the precipitation of menstrual migraine.





## How does estrogen (withdrawal) influence pain/migraine?



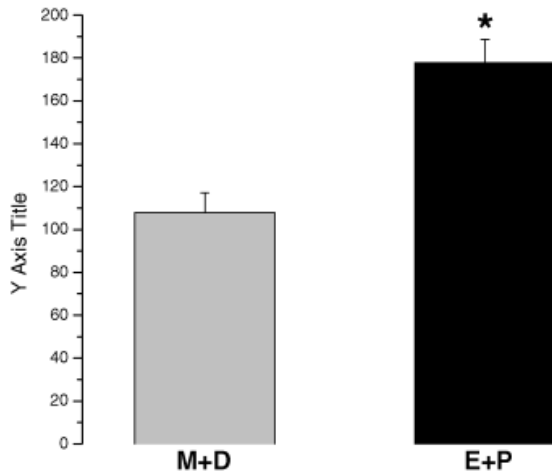
Raffaelli B et al. Menstrual migraine is caused by estrogen withdrawal: revisiting the evidence. *J Headache Pain* 2023 Sep 21;24(1):131. doi: 10.1186/s10194-023-01664-4.

# The estrogen withdrawal hypothesis: insights from animal experiments



- Different pain stimuli
- Different stimulated areas (cephalic vs. extracephalic)
- Different hormonal profiles rodents vs. humans

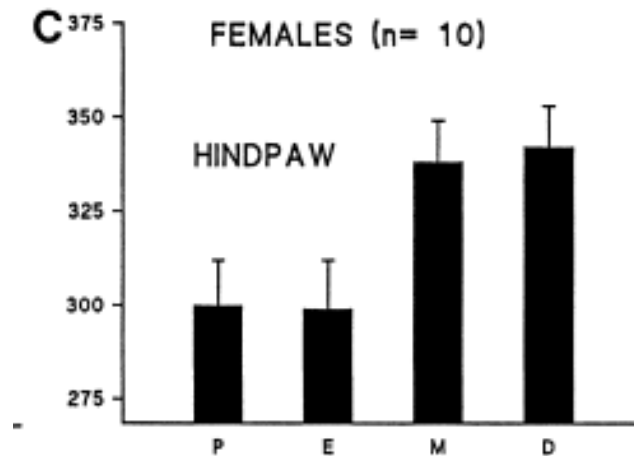
## Increased pain sensitivity during low-estrogen phases



Percent increase in cutaneous receptive field size (RFS) after application of capsaicin. M + D = metestrus/diestrus, P + E = proestrus/estrus.

VS.

## Increased pain sensitivity during high-estrogen phases

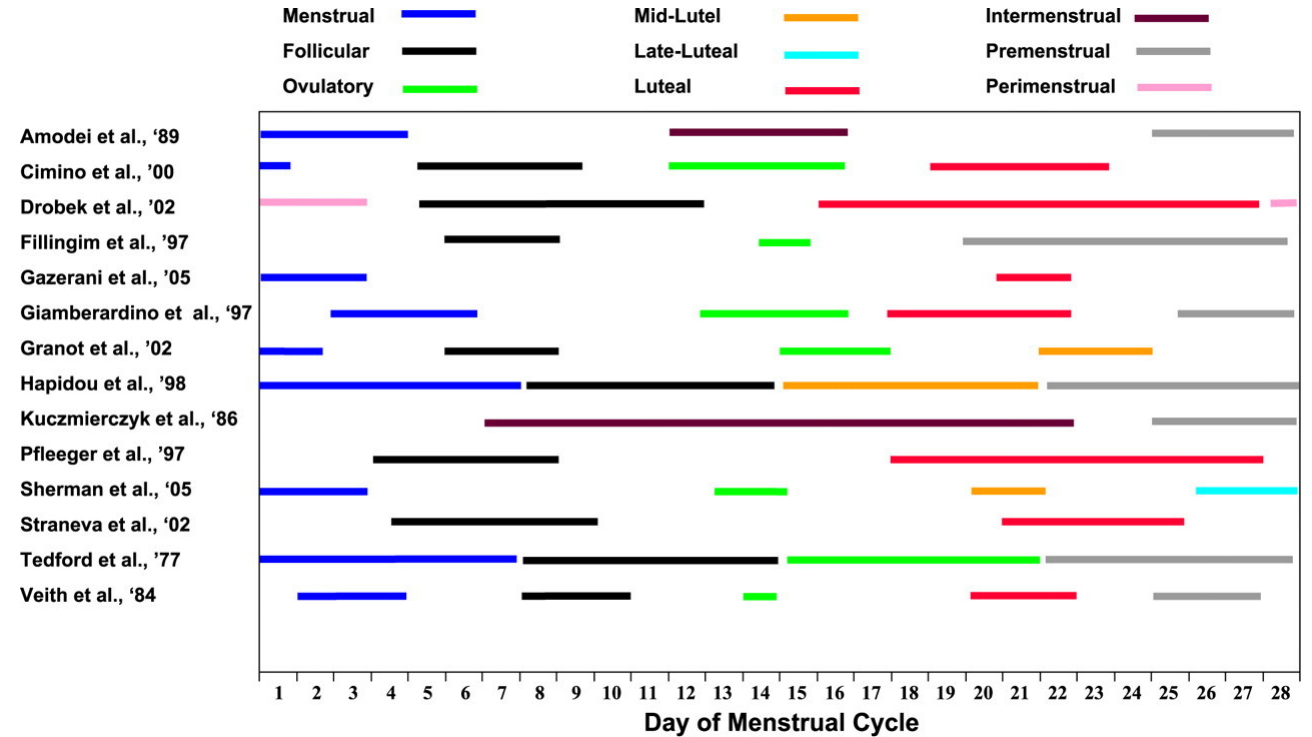


Mean vocalization thresholds to paw and tail pressure during estrous stage in female rats. P = proestrus, E = estrus, M = metestrus, D = diestrus.

# The estrogen withdrawal hypothesis: insights from human experiments (healthy controls)



- Different pain stimuli
- Different timing
- Different nomenclature



Timing of experimental sessions and terminology used to describe that timing in 14 studies assessing experimental pain response across the menstrual cycle.

# The estrogen withdrawal hypothesis: insights from human experiments (migraine)

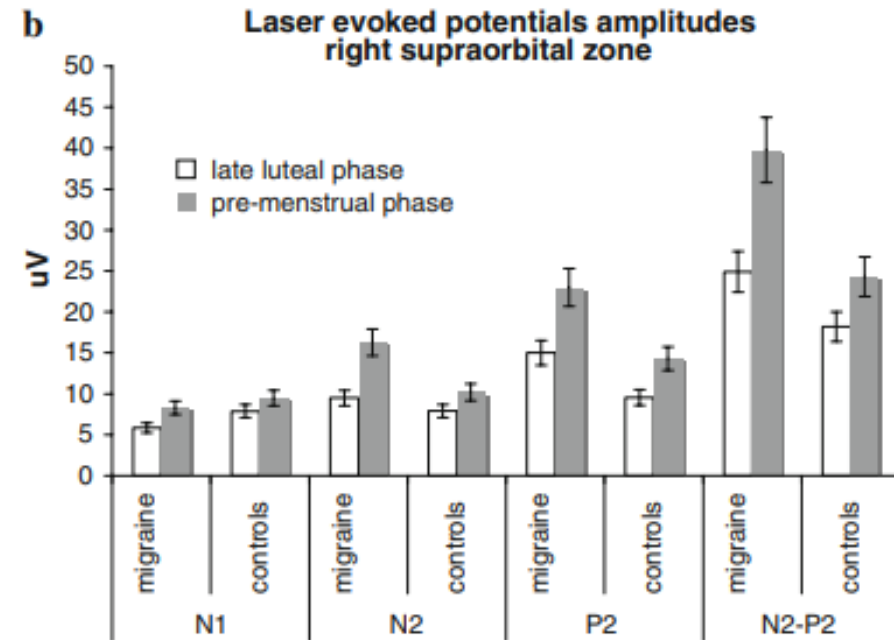
J Headache Pain (2009) 10:423–429  
DOI 10.1007/s10194-009-0150-2

ORIGINAL

## Pain perception and laser evoked potentials during menstrual cycle in migraine

Marina de Tommaso · Massimiliano Valeriani · Michele Sardaro ·  
Claudia Serpino · Olimpia Di Fruscolo · Eleonora Vecchio ·  
Rosanna Cerbo · Paolo Livrea

- Increased amplitude and decreased habituation in the premenstrual phase  
→ increased likelihood of migraine attacks?



**Fig. 1** Mean values and standard errors of laser evoked potentials amplitude in migraine patients (no. 9) and controls (no. 10)

# The estrogen withdrawal hypothesis: insights from human experiments (menstrual migraine)

De Icco et al. *The Journal of Headache and Pain* (2016) 17:70  
DOI 10.1186/s10194-016-0661-6

The Journal of Headache  
and Pain

SHORT REPORT

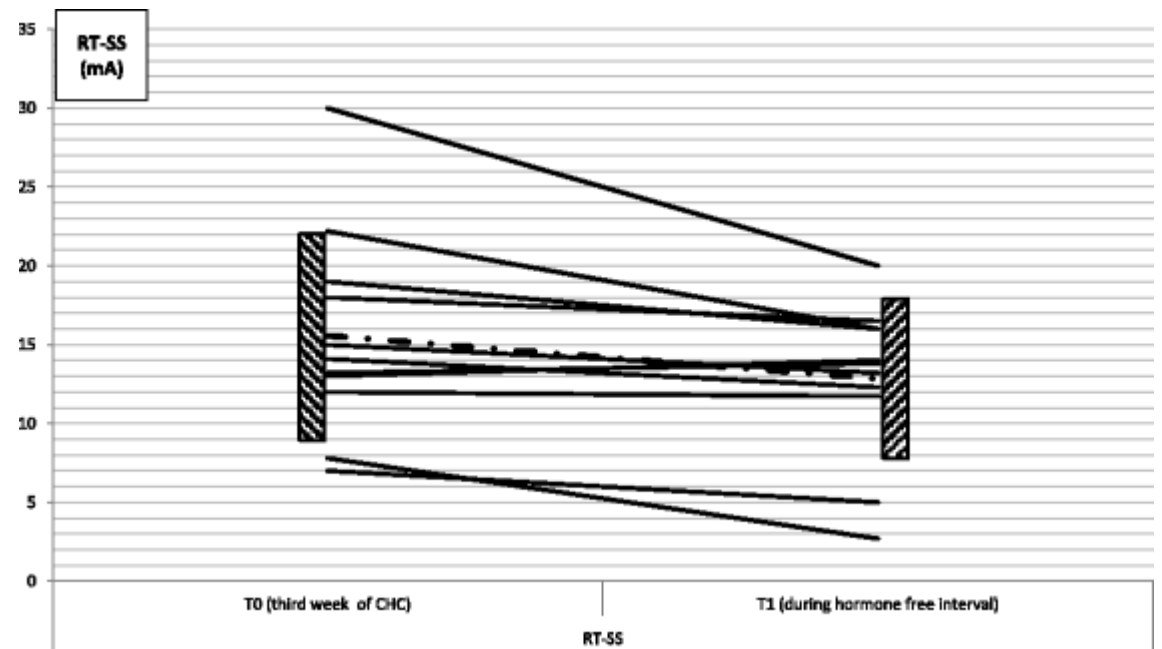
Open Access



## Modulation of nociceptive threshold by combined hormonal contraceptives in women with oestrogen-withdrawal migraine attacks: a pilot study

Roberto De Icco<sup>1,2\*</sup>, Laura Cucinella<sup>3,4</sup>, Irene De Paoli<sup>1,2</sup>, Silvia Martella<sup>3,4</sup>, Grazia Sances<sup>1</sup>, Vito Bitetto<sup>1</sup>, Giorgio Sandrini<sup>1,2</sup>, Giuseppe Nappi<sup>1</sup>, Cristina Tassorelli<sup>1,2</sup> and Rossella E. Nappi<sup>3,4</sup>

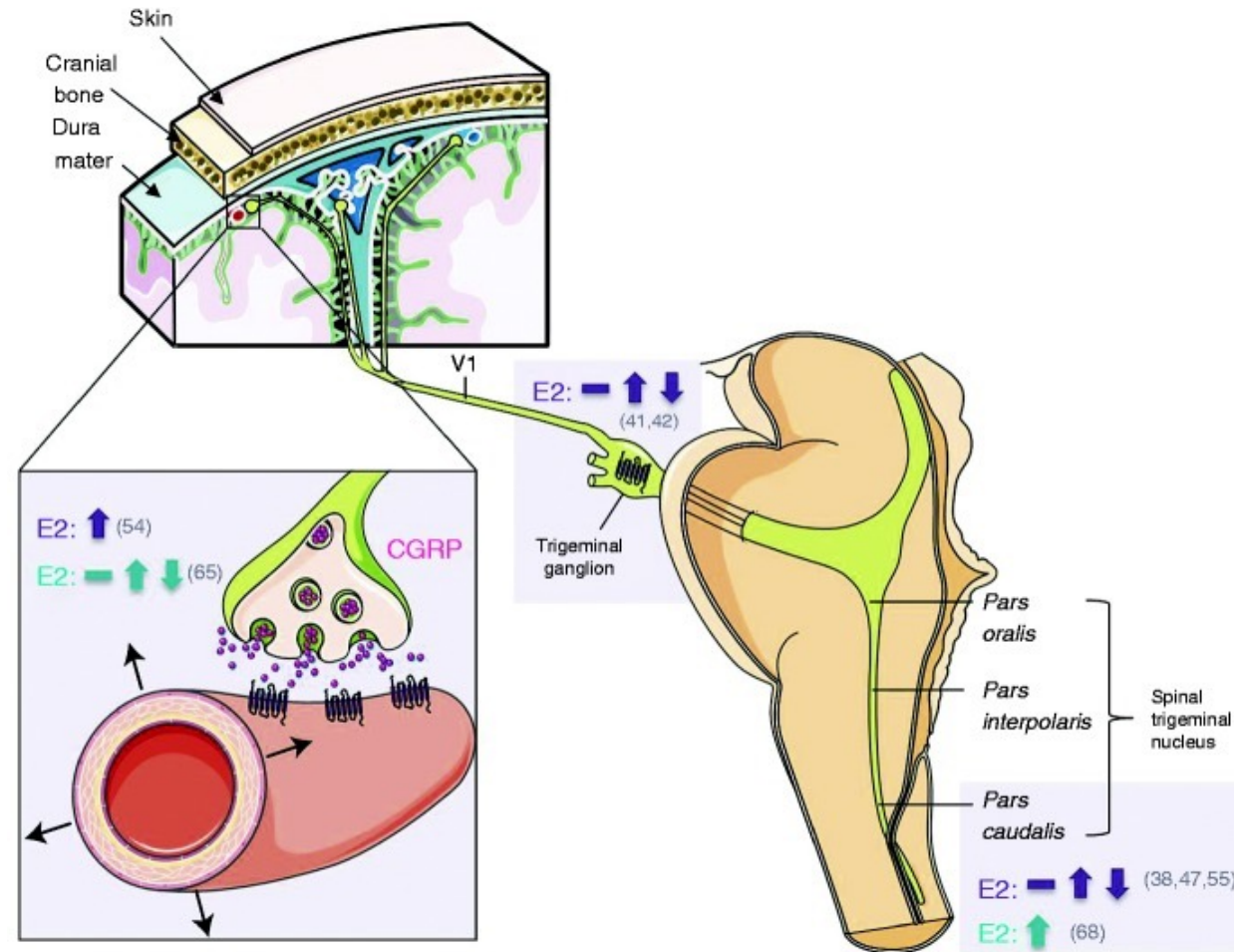
- Third week of hormone intake vs. hormone free interval
- Decreased reflex threshold during the hormone free interval  
→ estrogen withdrawal leads to pro-nociceptive response?



Changes in the threshold of the nociceptive flexion reflex following a single stimulus (RT-SS) at T0 and T1.



# Estrogen influences the CGRP pathway in a complex manner.



Trigeminovascular system. Sites where estrogens, mainly estradiol (E2), modify CGRP receptor expression/function in rodents (blue) and humans (green).

# Menstrual migraine: Dysfunction in the modulation of CGRP pathway?

RESEARCH ARTICLE OPEN ACCESS

## Sex Hormones and Calcitonin Gene-Related Peptide in Women With Migraine

A Cross-sectional, Matched Cohort Study

Bianca Raffaelli, MD, Elisabeth Storch, Lucas Hendrik Overeem, MSc, Maria Terhart, Mira Pauline Fitzek, MD, Kristin Sophie Lange, MD, and Uwe Reuter, MD

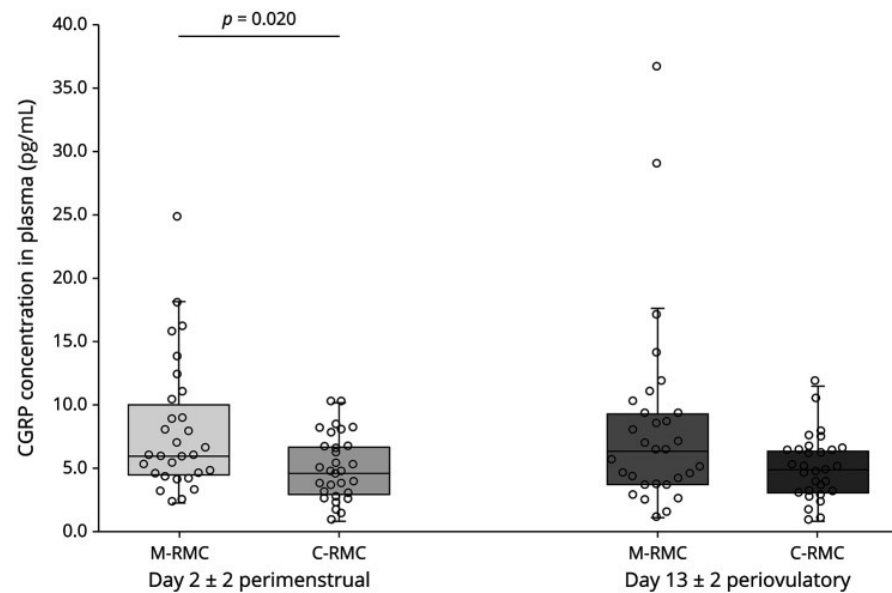
*Neurology*® 2023;100:e1825-e1835. doi:10.1212/WNL.000000000207114

Correspondence

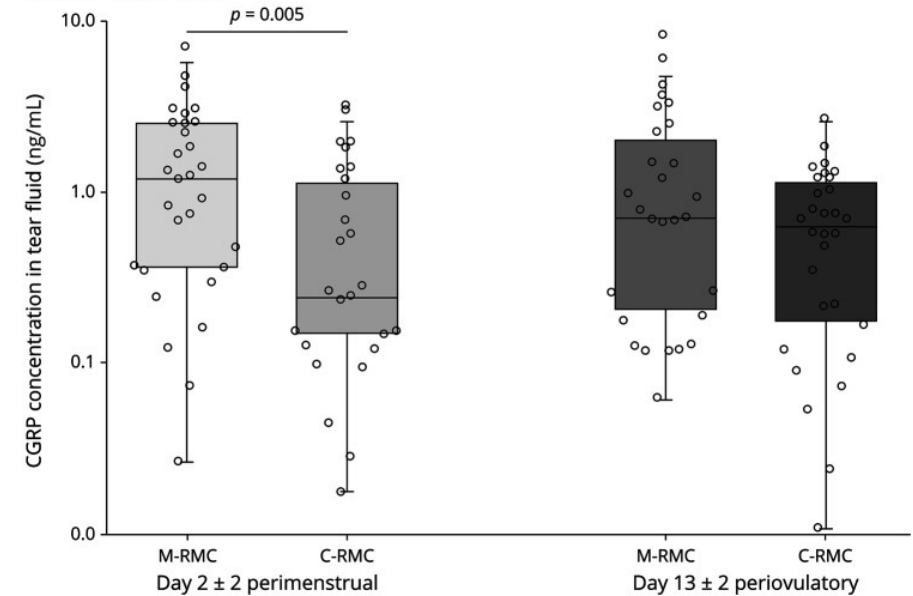
Dr. Raffaelli

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A. CGRP in blood plasma



B. CGRP in tear fluid





What about exogenous hormones?

## Variable effects of exogenous sex hormones on migraine



# Hormonal contraceptives and risk of ischemic stroke in women with migraine

Absolute risk of ischemic stroke in women aged 20 to 44 years in relation to the use of hormonal contraception and migraine status

	No migraine	Migraine with aura	Migraine without aura
Without hormonal contraception	2.5/100,000	5.9/100,000	4.0/100,000
With hormonal contraception	6.3/100,000	36.9/100,000	25.4/100,000

## Efficacy recommendations

- Patients with MRM or PMM
- Extended or continuous regimen of CHC
- Estrogen supplementation as short-term prevention during hormonal-free interval of 21/7 CHC or perimenstrual period



## Safety recommendations

- Patients without vascular risks (smoking, arterial hypertension, diabetes)
- Migraine without aura
- Low dose EE (<35 mcg)



# Gender-affirming hormonal therapy can cause headache.

August 10, 2004; 63 (3) CLINICAL/SCIENTIFIC NOTES

## Migraine prevalence in male to female transsexuals on hormone therapy

Tamara Pringsheim, Louis Gooren

First published August 9, 2004, DOI: <https://doi.org/10.1212/01.WNL.0000130338.62037.CC>

*"Compared with The Netherlands population data, the migraine prevalence of 26% in MFTs is similar to the prevalence of 25% in genetic females and significantly greater than the prevalence of 7.5% in men."*

**TABLE 2** Association between gender-affirming hormone therapy and headache status among 273 transfeminine adolescents and 490 transmasculine adolescents.

Group	With headache	Without headache	Overall sample	Odds ratio
Transfeminine, n (%)				
Treated with estrogen	9 (7)	114 (93)	123 (45)	5.8 (1.24-27.6)*
Untreated	2 (1)	148 (99)	150 (55)	
Total	11 (4)	262 (96)	273 (100)	
Transmasculine n (%)				
Treated with testosterone	28 (12)	199 (88)	227 (46)	2.71 (1.37-5.4)**
Untreated	13 (5)	250 (95)	263 (54)	
Total	41 (8)	449 (92)	490 (100)	

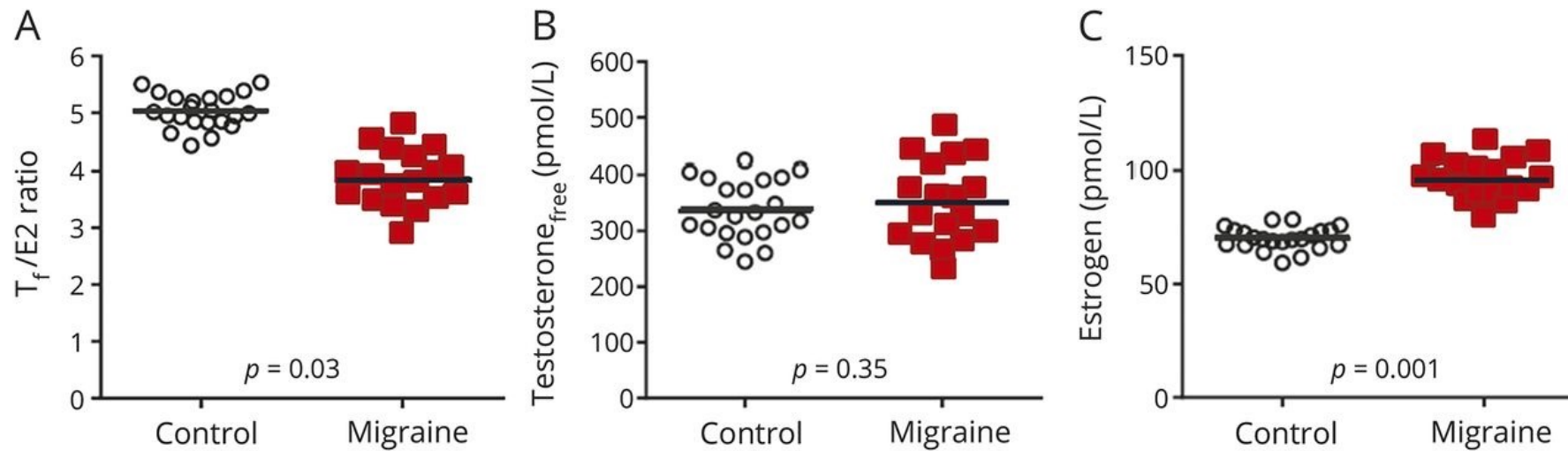
Note: 95% confidence interval Woolf exact method, significance two-sided Fisher's exact test.

\*p-value is 0.026; \*\*p-value is 0.005.



What about men?

# Estrogen dominance / relative androgen deficiency in men with migraine?



van Oosterhout.WPJ et al. Female sex hormones in men with migraine. *Neurology* 2018 Jul 24;91(4):e374-e381.

Neurology International 2019; volume 11

## Testosterone levels in men with chronic migraine

Lisa B.E. Shields,<sup>1</sup> Tad Seifert,<sup>1</sup>  
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Kobus et al. *The Journal of Headache and Pain* (2021) 22:119  
<https://doi.org/10.1186/s10194-021-01326-3>

The Journal of Headache  
and Pain

RESEARCH ARTICLE

Open Access

## Prenatal oestrogen-testosterone balance as a risk factor of migraine in adults

Magdalena Kobus<sup>1\*</sup>, Aneta Sitek<sup>1</sup>, Bogusław Antoszewski<sup>2</sup>, Jacek Roźniecki<sup>3</sup>, Jacek Pełka<sup>4</sup> and Elżbieta Żądzińska<sup>1,5</sup>





# Conclusion

- Migraine is more prevalent in women than in men.
- Endogeneous and exogeneous sex hormones can influence the migraine course.
- The estrogen withdrawal hypothesis (1972) is widely accepted but the current body of evidence is limited and conflicted.
- Estrogen can exert a modulatory effect on pain, also within the trigeminovascular system, but the exact mechanisms are still largely unknown.
- Effects of sex hormones in men and in gender minorities are underexplored.
- Future research should aim to elucidate the role of sex hormones in migraine in larger and well-defined cohorts using consistent methodological procedures.

Thank you!

