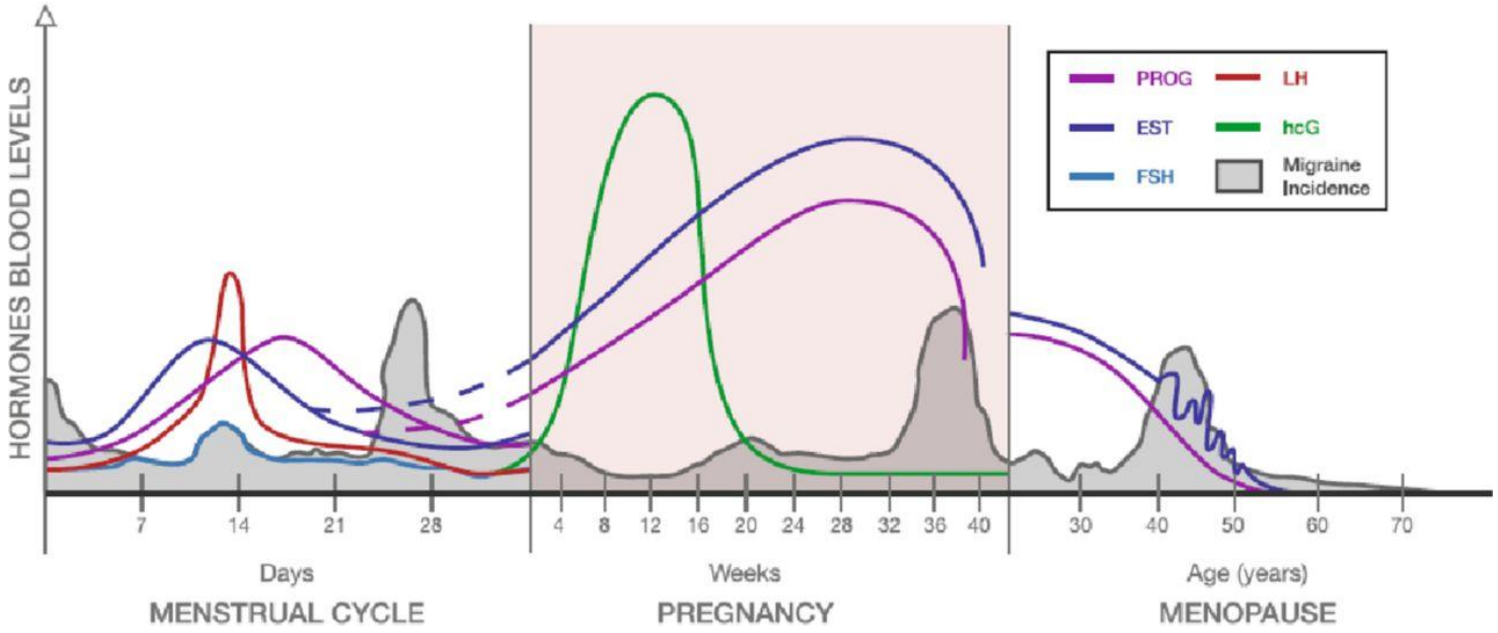

Hormonal Influences in Migraine: Contraception, Pregnancy, Lactation and Menopause

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Disclosures

- Abbvie – educational talks
- Pfizer – funding for educational sessions






Migraine is more common in women

- Before puberty, migraine prevalence is similar in boys and girls.[1,2]
- After puberty, the prevalence rises significantly in women.[1,2]
- This difference becomes greater with age, peaking early in the fifth decade of life and then declining (figure 1)[3].
- During women's reproductive years, migraine is 3 times more common than in men of a similar age.[4]

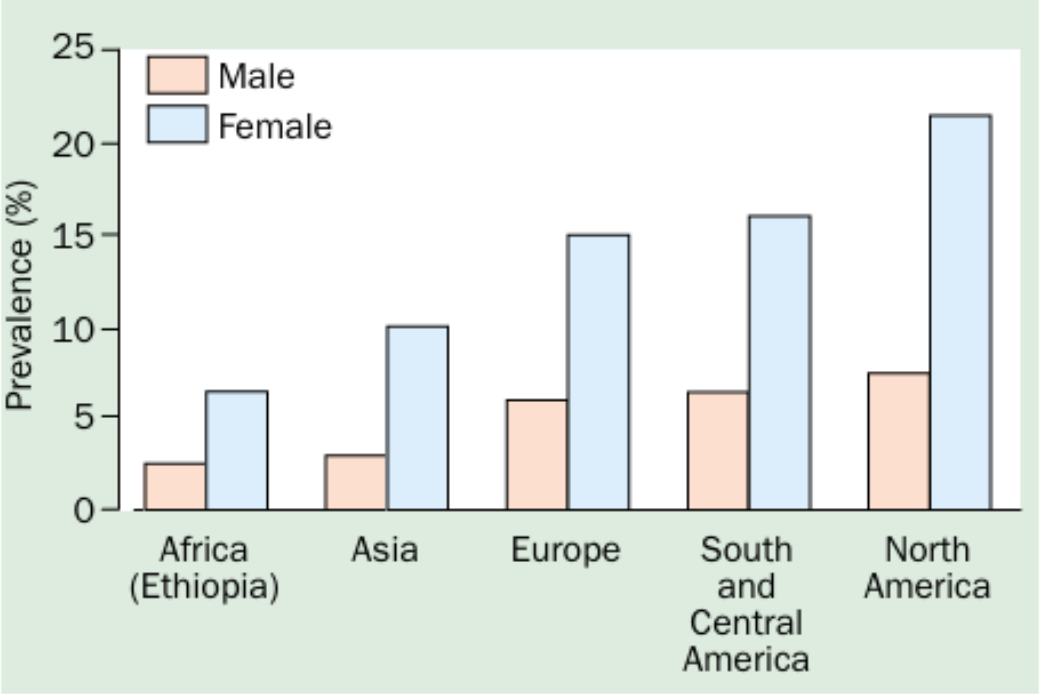
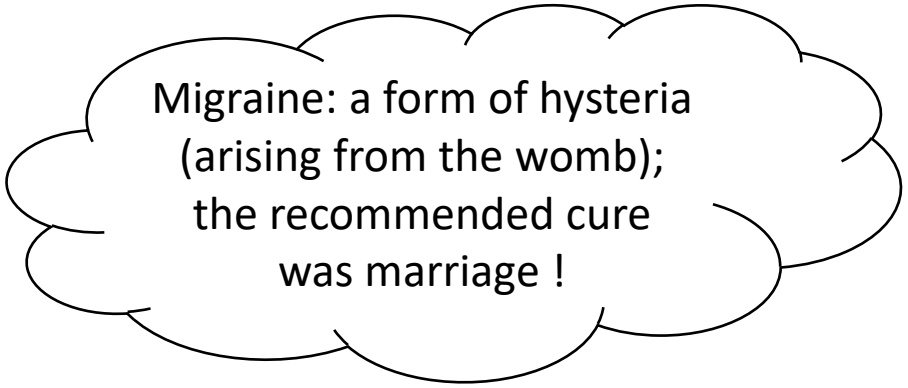


Figure 1. Migraine prevalence at age 40 years. Based on 18 population studies that used IHS criteria[2]

1. Abu-Arefeh I, Russell G. Prevalence of headache and migraine in schoolchildren. BMJ. 1994 Sep 24;309(6957):765-9.
2. Bille B. Migraine in school children. Acta Paed Scand 1962;51(suppl 136):1–151.
3. Scher A, Stewart W, Lipton R. Migraine and headache: a meta-analytic approach. In: Crombie I, ed. Epidemiology of Pain. Seattle: IASP Press, 1999.
4. Lipton RB, et al. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. Neurology, 68(5): 343–349..

The role of hormones



- This difference between men and women pointed toward the role of fluctuating hormone levels during the menstrual cycle.
- An early association was recognised between migraine and menstruation.
- This led to the term ‘menstrual migraine’.[1]

“Shivering, lassitude, and heaviness of the head denotes the onset of menstruation.”

Hippocrates

In 1666, Johannis van der Linden described a particularly severe case of one-sided headache with nausea and vomiting associated with menstruation.[2]

1. Vetvik KG, MacGregor EA (2021) Menstrual migraine: a distinct disorder needing greater recognition. Lancet Neurol 20(4):304–315.
2. Van der Linden J. De Hemicrania Menstrua. London, 1666.

Oestrogen withdrawal and menstrual migraine

- Evidence suggests menstrual attacks are associated - at least in some women - with falling concentrations, or 'withdrawal', of oestrogen.[1]
- The drop in oestrogen before menstruation increases the risk of developing a migraine attack.[2]
- A migraine attack is significantly more likely to occur in association with falling oestrogen.[3]

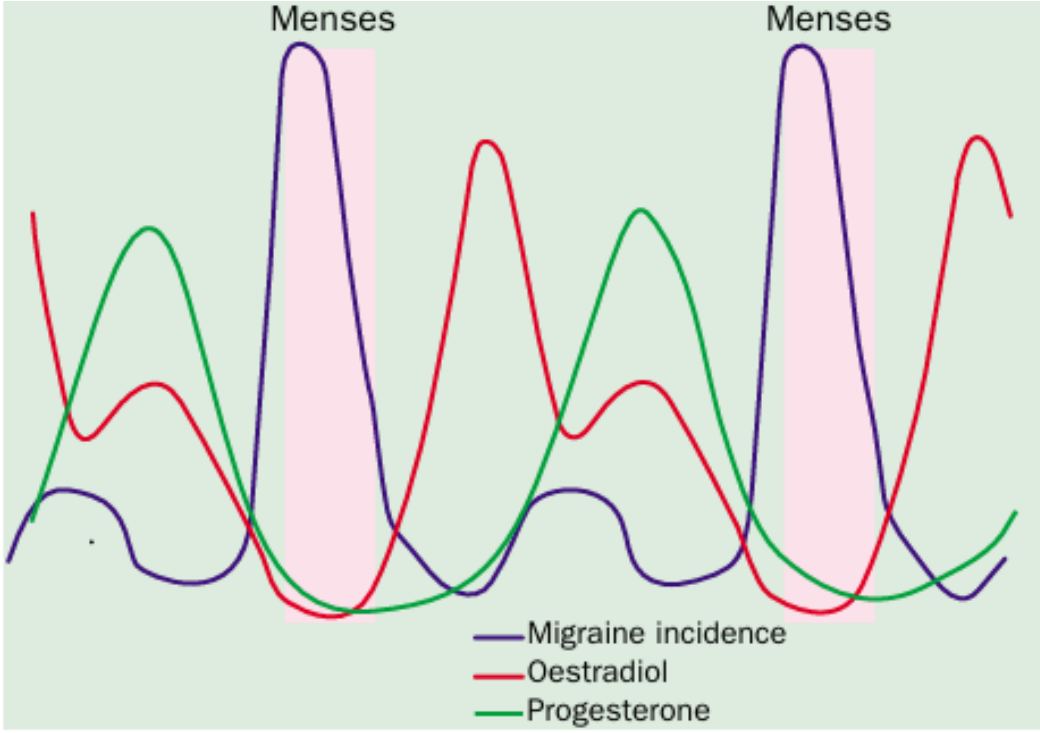


Figure 5. Graphical representation of incidence of migraine versus plasma concentrations of oestrogen and progesterone in a group of women with migraine.[3]

1. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A (2006) Incidence of migraine relative to menstrual cycle phases of rising and falling oestrogen. Neurology 67(12):2154–2158
2. Somerville BW (1972) The role of estradiol withdrawal in the etiology of menstrual migraine. Neurology 22(4):355–365.
3. Lichten EM, Lichten JB, Whitty A, Pieper D. The confirmation of a biochemical marker for women's hormonal migraine: the depo-oestradiol challenge test. Headache 1996; 36: 367–71.

Oestrogen affects several systems implicated in migraine

Trigeminovascular system

- Oestrogen modulates the excitability of the trigeminal nerve and related pain pathways.
- Low oestrogen increases release of CGRP.

Serotonin system

- Oestrogen upregulates serotonin synthesis and receptor sensitivity.
- Falling oestrogen lowers serotonin activity, which can trigger migraine onset.

Cortical excitability

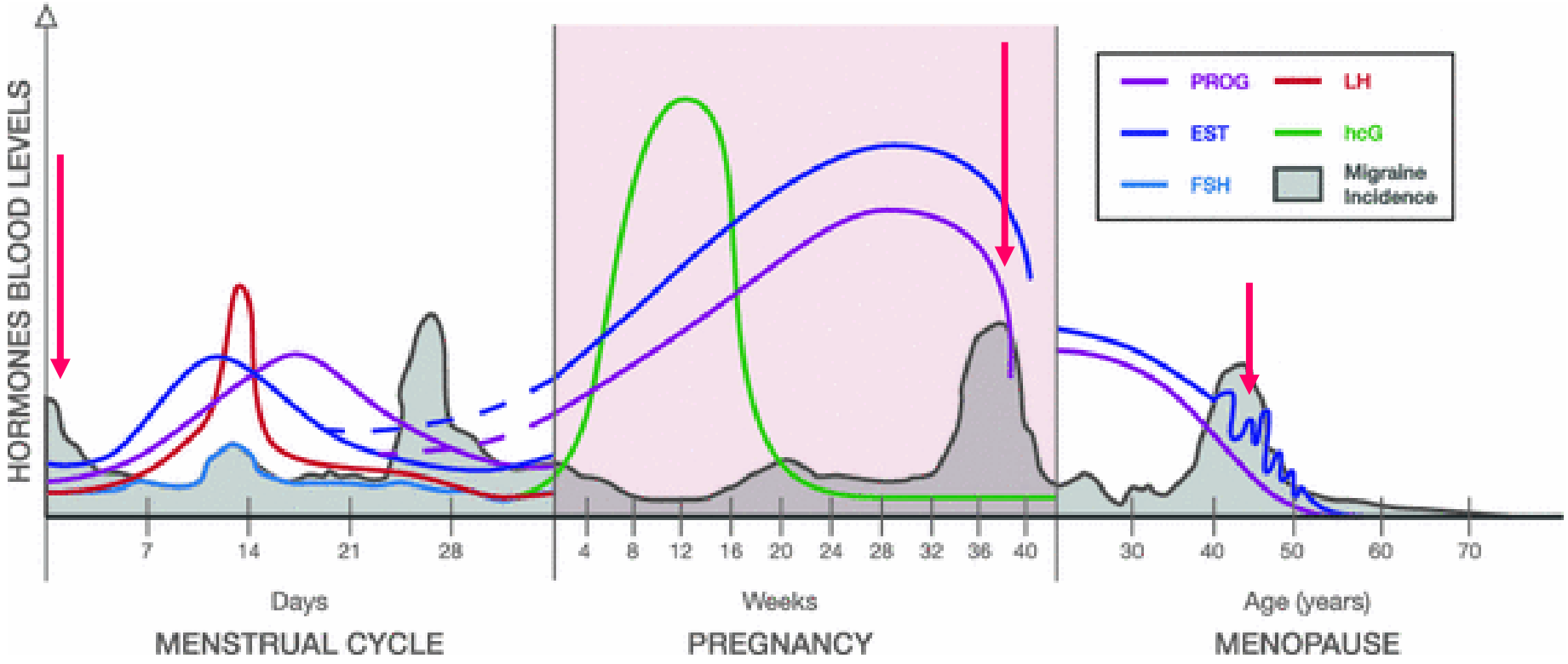
- Oestrogen influences glutamate and GABA neurotransmission. Drops in oestrogen may increase cortical hyperexcitability, a feature of migraine with aura.

Vascular reactivity

- Oestrogen modulates nitric oxide pathways, influencing cerebral blood vessel dilation.

Raffaelli, B., Do, T.P., Chaudhry, B.A. *et al.* Menstrual migraine is caused by estrogen withdrawal: revisiting the evidence. *J Headache Pain* **24**, 131 (2023).

Hormonal changes across a woman's life



Drop in oestrogen end of the luteal phase (day -2 to +3 days of menstruation)

Post partum sharp drop in oestrogen

Perimenstrual erratic fluctuations in oestrogen

Other factors making migraine more common in women

- Genetics might regulate individual-level sensitivity to oestrogen fluctuations, making some women more susceptible to develop menstrual migraine.
- Differences in brain structure and networks may contribute to different pain processing in men and women.[1,2]
- The use of hormonal contraceptives and hormone replacement therapy can impact oestrogen levels, leading to more frequent or severe migraines.
- Social roles and lifestyle (work-family balance, sleep disruption) often interacting with hormonal influences.

1. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurol Sci. 2020 Dec;41(Suppl 2):429-436.
2. Rossi MF, Tumminello A, Marconi M, Gualano MR, Santoro PE, Malorni W, Moscato U. Sex and gender differences in migraines: a narrative review. Neurol Sci. 2022 Sep;43(9):5729-5734.

Menstrual migraine - ICHD-3 Diagnostic Criteria.

- **A1.1.1 Pure menstrual migraine without aura**
- Attacks, in a menstruating woman fulfilling criteria for 1.1 *Migraine without aura.*
- Occurring exclusively on day 1 ± 2 (*i.e.* days −2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle.

- **A1.1.2 Menstrually-related migraine without aura**
- Attacks, in a menstruating woman fulfilling criteria for 1.1 *Migraine without aura.*
- Occurring on day 1 ± 2 (*i.e.* days −2 to +3) of menstruation in at least two out of three menstrual cycles, and additionally at other times of the cycle.

The International Classification of Headache Disorders

Treating menstrual migraine

Acute treatment

- Monotherapy – Paracetamol / NSAID / Triptan
- Combination therapy – Triptan + Paracetamol OR NSAID

‘Perimenstrual mini’ prophylaxis

- Starting 2 days before the period and continuing during the period:
  - Frovatriptan 2.5 mg twice daily, zolmitriptan 2.5 mg three times a day, naratriptan 1 mg BD, naproxen 500 mg twice daily or mefenamic acid 500 mg three times a day.
  - Contraceptive-induced amenorrhoea can be effective, for example, with tricyling or continuous combined contraceptive pill (no 7 day break).[1]
  - Oestrogen gel (better than the patch) can ameliorate the effect of falling serum hormone concentrations before and during the period (e.g. 1.5 mg).

1. Sinclair AJ, Sturrock A, Davies B*, et al.* Headache management: pharmacological approaches. *Practical Neurology* 2015;**15:**411-423.
2. Vetvik, K.G., MacGregor, E.A., Lundqvist, C. *et al.* Contraceptive-induced amenorrhoea leads to reduced migraine frequency in women with menstrual migraine without aura. *J Headache Pain* **15**, 30 (2014).

Contraception and migraine

- **Hormonal**
  - Combined hormonal contraceptives (pill, vaginal ring, patch)
    - Oestrogen (esthinylestradiol 10-50 micrograms) and progestin
  - Progestin-only methods (mini-pill, implant, depot injection, IUD)

- **Non hormonal**
  - Copper intrauterine device
  - Barrier contraception (condoms and diaphragms)
  - Sterilisation
  - Fertility awareness methods (tracking cycles, temperature)
  - Spermicides

Combined Hormonal Contraceptives (COC pill, patch, vaginal ring)

Migraine with aura

- ***Not recommended*** due to increased risk of stroke.
- Evidence suggests a two-fold higher risk of stroke.[1]
- Smoking and the COC further increase the stroke risk. [2]
- NICE recommends avoiding.

Migraine without aura

- Can be used with caution.
- Review individual stroke risk factors, such as smoking, age, and high blood pressure.
- Continuous or extended-cycle COC may reduce menstrual migraines by preventing oestrogen withdrawal.

1. Kurth T, Gaziano JM, Cook NR, et al. Migraine and risk of cardiovascular disease in women. JAMA 2006;296:283–91.
2. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914.

Absolute ischaemic stroke risk in women < 45 years and non-smokers (per 100,000 women per year)

Migraine status	No hormonal contraception	Combined Hormonal Contraception
No migraine	~2-4	~5-10
Migraine without aura	~4	~10-20
Migraine with aura	~6-12	~20-40 (up to 80 if additional risk factors such as smoking / HTN).

Migraine with aura + COC = Higher stroke risk.
Although the *absolute risk* is low, the relative increase is high enough that guidelines contraindicate use.

1. MacGregor, E. A. (2016). Contraception and headache. Headache: The Journal of Head and Face Pain, 56(2), 403–412.
2. Etminan, M., Takkouche, B., & Isorna, F. C. (2005). Risk of ischaemic stroke in people with migraine: Systematic review and meta-analysis of observational studies. BMJ, 330(7482), 63.
3. Curtis, K. M., Tepper, N. K., Jatlaoui, T. C., Berry-Bibee, E., Horton, L. G., Zapata, L. B., Simmons, K. B., Pagano, H. P., Jamieson, D. J., & Whiteman, M. K. (2016). U.S. Medical Eligibility Criteria for Contraceptive Use, 2016.
4. Sacco, S., Merki-Feld, G. S., Ægidius, K. L., Bitzer, J., Canonico, M., Gantenbein, A. R., Kurth, T., Lidegaard, Ø., MaassenVanDenBrink, A., Panay, N., & MacGregor, E. A. (2017). Hormonal contraceptives and risk of ischemic stroke in women with migraine: A consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). The Journal of Headache and Pain, 18(1), 108.

Progestogen-Only Methods

- Includes: progestogen-only pill (‘mini pill’), implant, depot injection, IUD
  - Safe in women with migraine **with or without aura**.
  - Do not increase stroke risk.
  - Can improve migraines (but evidence is mixed):
    - Taken continuously, it can help stabilize hormone levels, preventing the fluctuations that can trigger menstrual migraines.
    - By preventing ovulation and being taken daily without a break, leads to fewer or no periods, which can significantly reduce or eliminate migraine attacks that occur with menstruation.

1. Allais, G., Cagnacci, A., Facchinetti, F., Nappi, R. E., Sances, G., Benedetto, C., & Bussone, G. (2019). Hormonal contraception in women with migraine: Is progestogen-only contraception a better choice? Neurological Sciences, 40(Suppl 1), 47–53.
2. Curtis, K. M., Tepper, N. K., Jatlaoui, T. C., Berry-Bibee, E., Horton, L. G., Zapata, L. B., Simmons, K. B., Pagano, H. P., Jamieson, D. J., & Whiteman, M. K. (2016). U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. Contraception, 94(2), 133–135.

Non-hormonal methods

- Include:
  - Copper intrauterine device
  - Barrier contraception (condoms and diaphragms)
  - Sterilisation
  - Fertility awareness methods (tracking cycles, temperature)
  - Withdrawal
  - Spermicides
- Safe in women with migraine **with or without aura**.
- Do not increase stroke risk.

Which contraceptive is best?

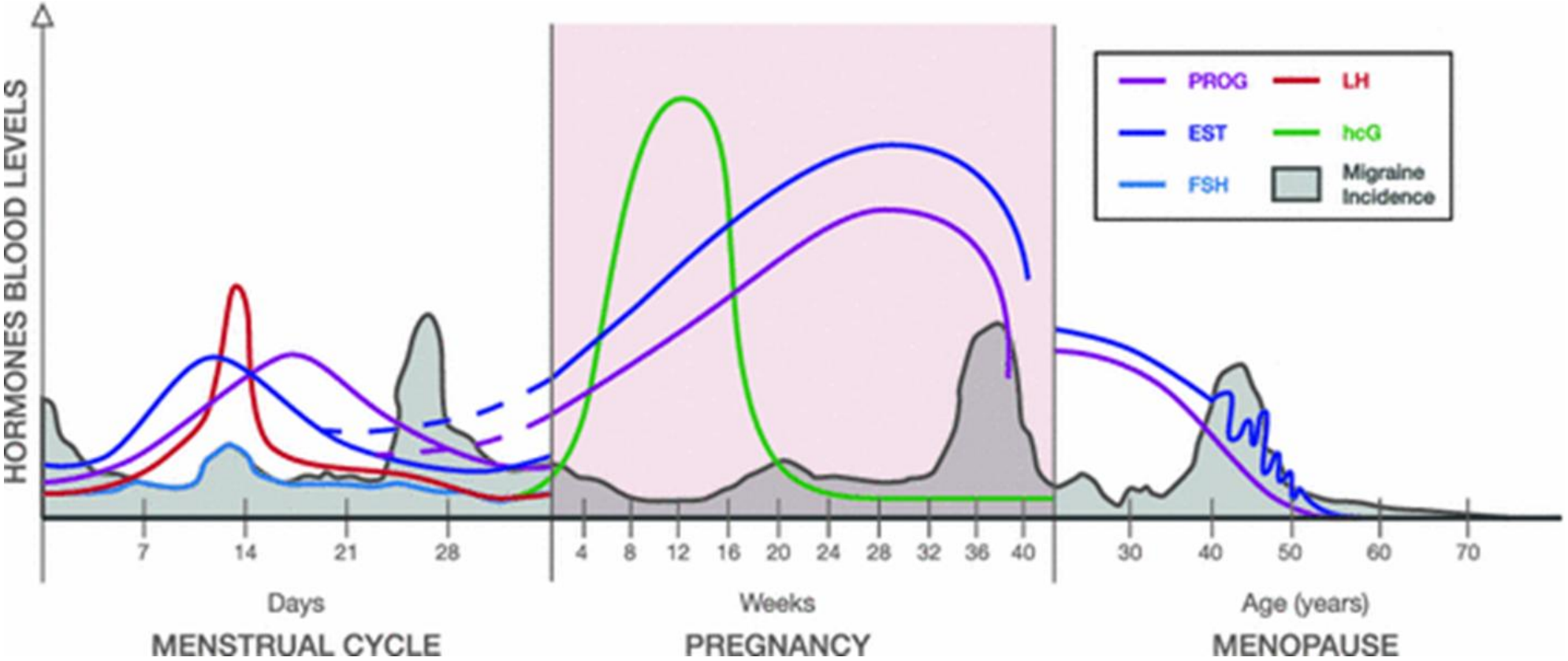
- COC can worsen of headache in patients with migraine +/- aura
- COC have a small but significant vascular risk, especially in migraine + aura.
- Continuous COC may reduce menstrual migraines by preventing oestrogen withdrawal.

- **Progestogen-only contraception is a safer option. It does not seem to be associated with increased risk of venous thromboembolism and ischaemic stroke.**
- **Can help stabilise oestrogen levels reducing the number of migraine days, reducing migraine intensity and improving symptoms.**

Nappi, R.E., Merki-Feld, G.S., Terreno, E. *et al.*Hormonal contraception in women with migraine: is progestogen-only contraception a better choice?. *J Headache Pain* 14, 66 (2013).

Migraine in pregnancy

- Commonest neurological complaint in pregnancy.
- Most migraines (in about 50-75% of women) will improve by the second and third trimester.



Migraine in pregnancy

Many women with a pre-existing history of migraine attacks will see an improvement during pregnancy (particularly those with menstrual related migraine)

Those who have migraine with aura are more likely to have an unpredictable course.

For a few women, migraine may occur for the first time during pregnancy, which causes anxiety and poses a diagnostic challenge.

Arvis S, Dassan P, Piercy C N. Managing migraine in pregnancy BMJ 2018

What to do in pregnancy

- Improve sleep hygiene
- Increase water intake
- Reduce caffeine intake
- Don’t skip meals
- Regular exercise (minimum 150mins per week)

Acute treatment of migraine in pregnancy

First Line

- Paracetamol
- Anti-emetics – metoclopramide can be used at any stage of pregnancy.

Second Line

- NSAIDs – *except* in the third trimester

Third

- Sumatriptan – considered safe. No adverse outcomes.

Greater occipital nerve blocks

- Can be helpful. Lack of evidence this does harm.

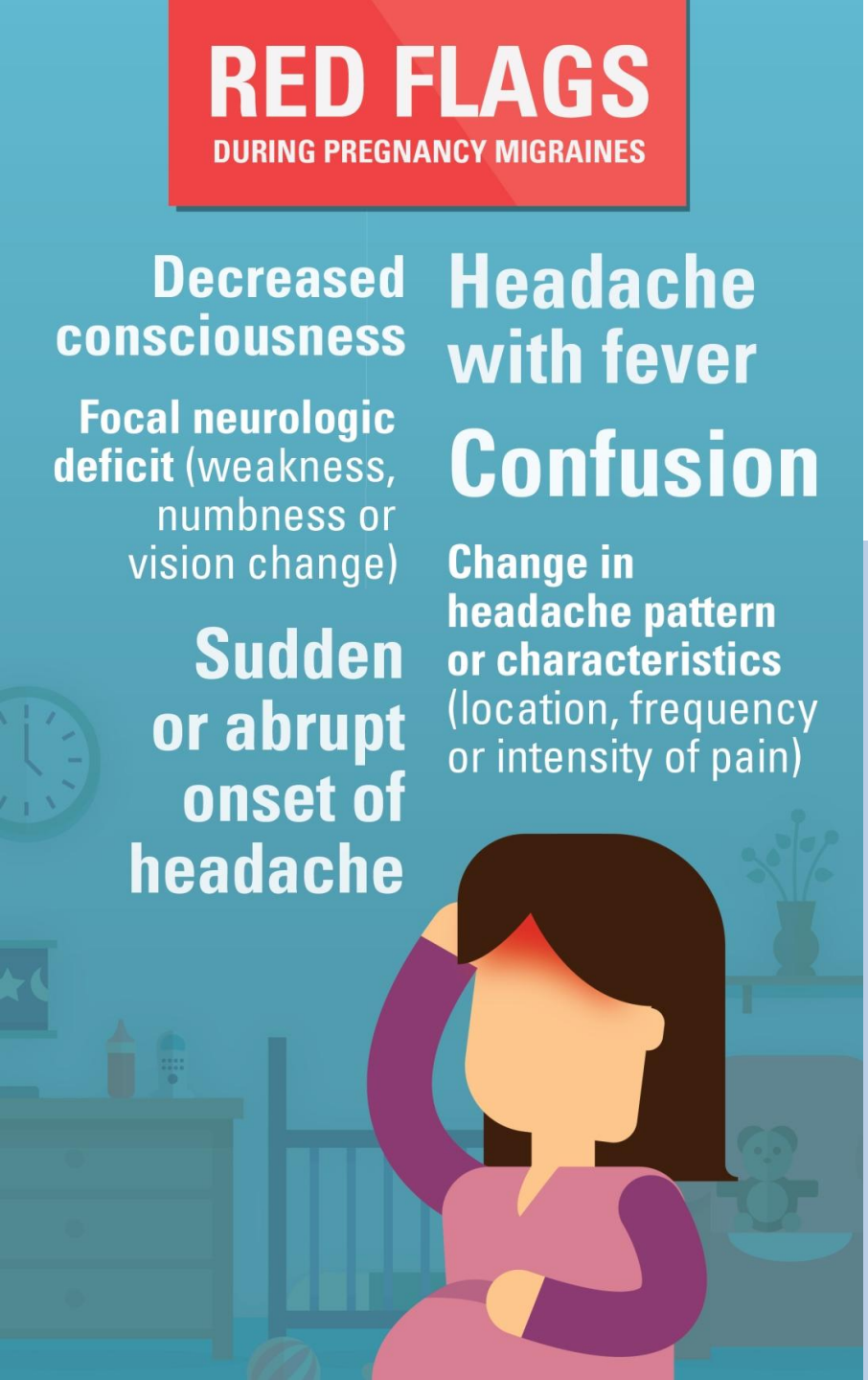
Avoid Opiates

- Codeine is safe during pregnancy. Avoid first line.

Preventative treatment in pregnancy

- Very little data on which agents are safe in pregnancy.
- Low dose Amitriptyline or low dose Propranolol can be used.
- Botox treatment (theoretically safe – not enough evidence).
- For CGRP therapy, this has to be stopped 6 months before conception.
- Gepants have to be stopped 2.5 days before conception.
- External neuromodulation using e.g. Cefaly device, Nerivio have been shown to be safe.
- Nutritional supplements such as magnesium can be trialled (avoid high dose vitamin B2).
- Low dose aspirin 75 mg used by obstetricians (not much evidence).

Bumps - Best use of medicines in pregnancy
https://www.medicinesinpregnancy.org



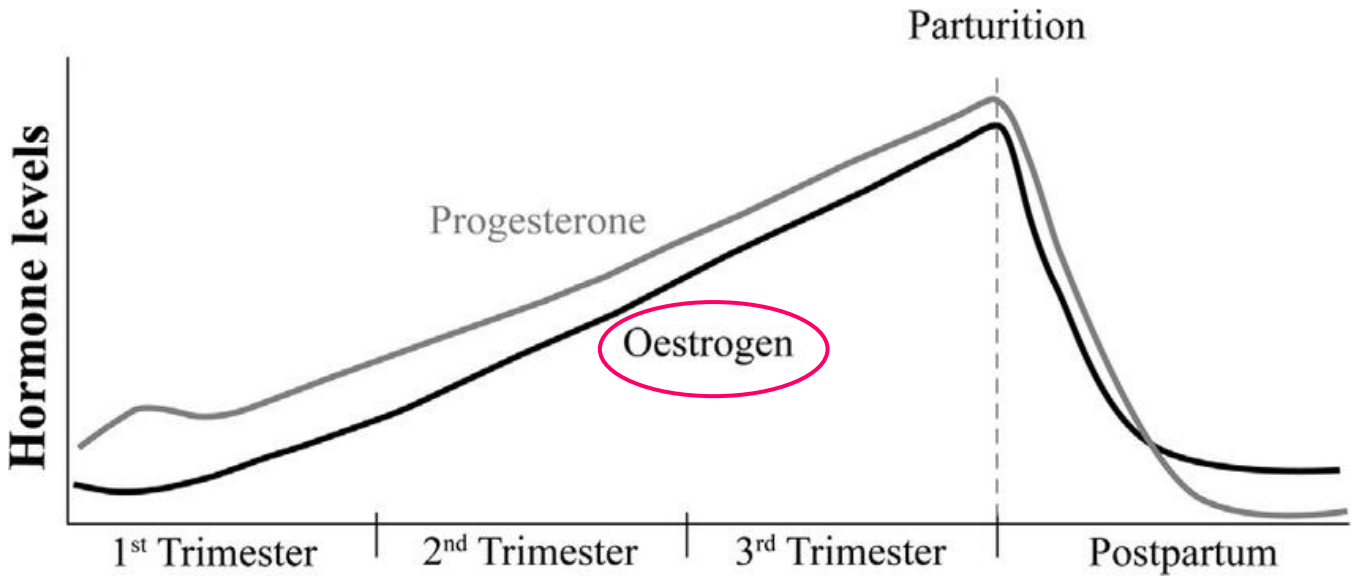
Red flags in pregnancy

Box 1 Red Flag symptoms and signs in a patient presenting with headache in pregnancy (adapted from SIGN guidelines[4])

- Thunderclap headache (intense headache with abrupt onset)
- New onset of severe headache or significant changes in headache like phenotype.
- Headache with unusual aura (duration >1 hour, or including motor weakness) Fever and meningism
- Progressive headache worsening over weeks or months
- New headache with cognitive change or personality changes
- Symptoms and signs of raised intracranial pressure (drowsiness, may be posturally-related vomiting, diplopia, papilloedema)
- New-onset seizures
- History of HIV, syphilis or cancer
- Progressive neurologic deficit (weakness, sensory loss, dysphasia, ataxia)
- Visual disturbance or visual field defect

Postpartum headache

- Common at day 3-6 post delivery.
- Occurs in 30-40% of women, and not only women with migraine.
- Secondary headaches are more likely postpartum (preeclampsia, CVST, RCVS etc).
- The sharp dip in oestrogen levels can worsen migraines.
- Exacerbated by sleep deprivation, stress and anxiety.



Migraine treatment during breastfeeding

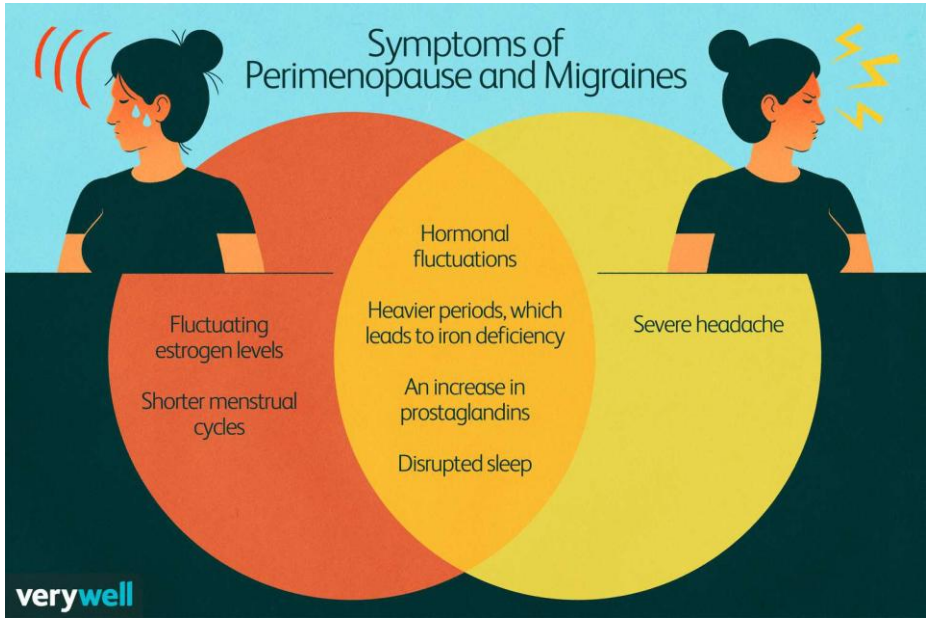
Acute treatment

- Paracetamol and NSAIDs are safest
- Caution with aspirin (risk of Reye's syndrome)
- Shorter acting triptans are safer (best data is for sumatriptan)

Preventative treatment

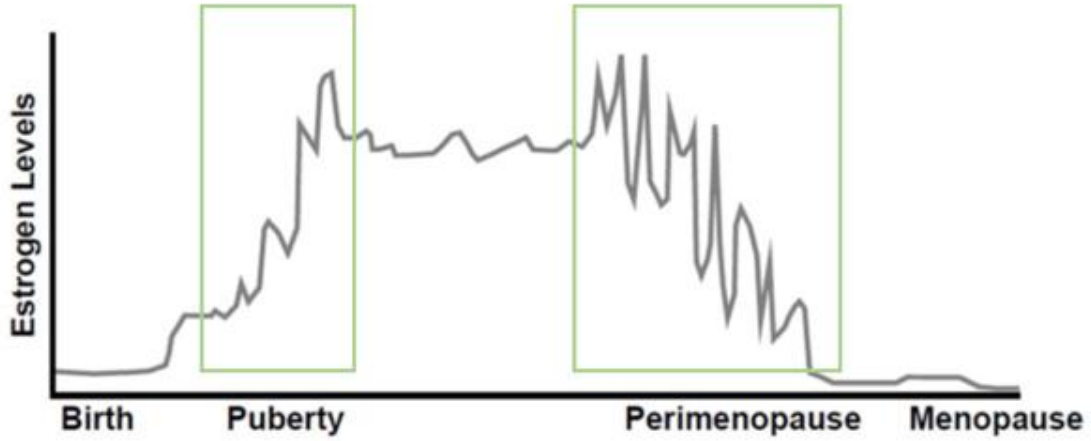
- Propranolol and amitriptyline are felt to be relatively safe at low doses

Migraine and perimenopause



"When I first started working at a specialist migraine clinic back in 1988, over 80 percent of people attending the clinic were women, typically women in their 40s. Most of them had had migraine since their teens or early 20s but attacks were becoming much more troublesome. Many also experienced typical perimenopause symptoms with more frequent periods, hot flushes, night sweats, anxiety and disturbed sleep."

Ann McGregor



Worsening of migraine

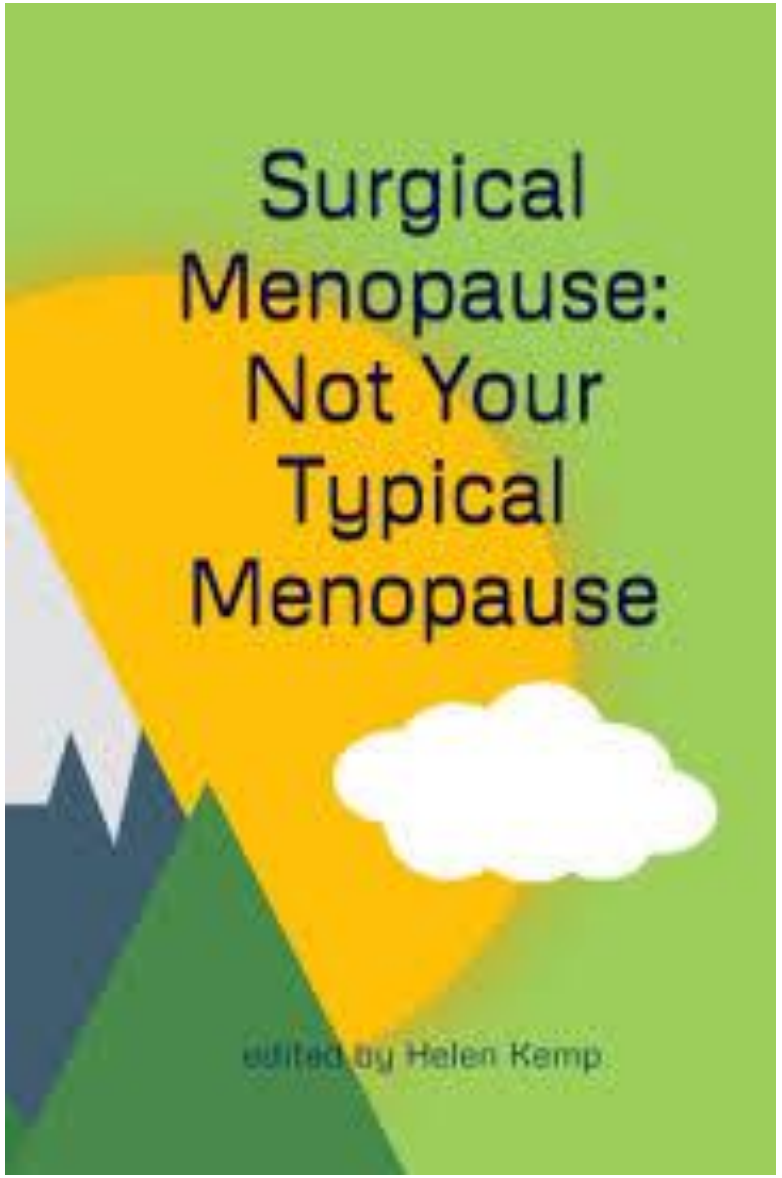
- Perimenopause begins in the early to mid-40s and can last up to 10 years.. !
- Fluctuating levels of oestrogen during perimenopause increase the likelihood of migraine, especially menstrual migraine.
- As menstrual cycles shorten during perimenopause, menstrual attacks occur more frequently.
- Menstrual attacks are longer, more severe and are more disabling than attacks at other times of the cycle.
- Hot flushes and night sweats disrupt sleep, acting as an additional migraine trigger.

Menopause

- While migraine symptoms can worsen in the years leading up to the menopause, towards the end of menopause migraines usually lessen.
- For women who have noticed a strong link between migraine and hormonal triggers, post-menopause migraine is very likely to improve.
- This may take 2 or 3 years after the last period, as it can take this long for the hormones to settle.
- Non-hormonal triggers can still persist after menopause so if these are causes for migraine, attacks will still continue.

Natural vs surgical menopause

- Migraines worsen after surgical menopause because the sudden removal of the ovaries leads to a dramatic drop in oestrogen.
- This rapid hormonal change can initially trigger more severe or frequent migraines.
- In contrast, natural menopause, with its gradual hormone decline, is more often associated with migraine improvement, though this can take a few years to occur.
- Following surgical menopause, migraine prevalence initially worsens (in 2/3) but generally settles again after a few years.



Should I take HRT?

- **HRT should not be used as a treatment for migraine.**
- HRT during perimenopause can worsen migraine.
- HRT ONLY to manage the menopause symptoms.
- Migraine aura does not contraindicate use of HRT.

- If HRT is not needed - optimisation of standard acute and prophylactic therapy.

- Women with migraine and menopause symptoms e.g. hot flushes, who do not wish to use HRT or where oestrogens are contraindicated (hx breast cancer, VTE etc) may benefit from escitalopram or venlafaxine.

NB: many women notice that migraine is more likely to occur when they have hot flushes and night sweats. Since HRT is effective at controlling these menopause symptoms, it may reduce the likelihood of migraine.

Best form of HRT in those with migraine

- Use a transdermal form e.g. oestrogen patches, gel or spray which help maintain more stable hormone levels with fewer fluctuations.
- HRT tablets worsen hormone fluctuations and *can trigger migraine*.
- The best dose of oestrogen is the lowest dose to control flushes and sweats e.g 25 mcg oestrogen patches or one pump of oestrogen gel. Start low and gradually increase.

- Where progesterone is required (no history of hysterectomy) continuous delivery is recommended, with preparations such as:

    - Mirena intrauterine system (mirena coil) – advantages are: *lightens periods / contraceptive / acts directly on the womb*
    - Transdermal (combined with oestrogen in patches)
    - Micronised progesterone (capsules)

Why do I still get migraine even though I’m through the menopause?

- Even after periods have stopped, it can take a few years for hormone fluctuations to completely settle.
- This is usually one or two years, although some women find that they still get hot flushes and migraine ten or more years after the menopause.
- More often, even when hormonal triggers have settled, non-hormonal ones persist and may even increase post menopause.
- Chronic medical conditions can make migraine more likely to occur.
- Maintaining good ‘migraine habits’, such as regular meals, regular exercise, a good sleep routine, balancing triggers are just as important after the menopause as before.

A migraine free life?