Migraine in Women

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Essen
Germany
Migraine in Women - Overview

• History / Epidemiology
• Definition of menstrual and menstrually related migraine
• Pathophysiology
• Treatment options for menstrual migraine
• Migraine in pregnancy and lactation
• Migraine and oral contraception
• Migraine in menopause /HRT
Hormones and Headaches History

- **1962**: Ad-hoc-Committee „premenstrual/menstrual migraine“
- **1988**: IHS excludes menstrual migraine as an entity, provides a definition (90% of all attacks within 2 days of onset of menstruation)
- **2004**: IHS defines criteria for studies: „pure menstrual migraine“ und „menstrually related migraine“
History of menstrual migraine

500

1660

1780

Auguste Tissot

1846 Moritz Romberg

1873 Edward Liveing
Appendix

A1.1 Migraine without aura

A1.1.1 Pure menstrual migraine without aura

A: Attacks, in a menstruating woman, fulfilling IHS criteria for migraine without aura

B: Attacks occur exclusively on day 1+2 (i.e. day -2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle.

Menstrual Migraine – Definition
ICHD-3 BETA
Menstrual Migraine – Definition
ICHD-3BETA

A1.1 2 Menstrually-related migraine without aura
A: Attacks, in a menstruating woman, fulfilling IHS criteria for migraine without aura
B: Attacks occur 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

A1.1 3 Non menstrual migraine without aura
Migraine Epidemiology

- **Before puberty**: ♀:♂ = 1:1
- **After puberty**: ♀:♂ = 2-3:1

![Bar chart showing prevalence of migraine by gender and region.](chart.png)

*Scher et al. In: Combie I, ed. Epidemiology of Pain, 1999*


Background
Fifty-three percent of adolescent girls report headaches at the onset of menses, suggesting fluctuations of ovarian hormones trigger migraine during puberty.

Aims: To determine if urinary metabolites of estrogen and progesterone are associated with days of headache onset (HO) or severity in girls with migraine.

Methods: This was a pilot study and included 34 girls with migraine balanced across three age strata (pre-pubertal (8-11), pubertal (12-15), and post-pubertal (16-17) years of age).

They collected daily urine samples and recorded the occurrence and severity of headache in a daily diary. Urine samples were assayed for estrone glucuronide (E1G) and pregnandiol glucuronide (PdG) and the daily change was calculated (ΔE1G, ΔPdG). Pubertal development was assessed by age, pubertal development score (PDS), and menstrual cycle variance.

The primary outcome measures were HO days and headache severity.

Results:
Models of HO days demonstrate a significant age*PdG interaction (OR 0.85 [95% CI 0.75, 0.97]) for a 1 standard deviation increase in PdG and three-year increase in age. A separate model showed a significant PDS*PdG interaction (OR -0.85 [95% CI; 0.76, 0.95]). ΔPdG was associated with headache severity in unadjusted models (p < 0.017).

Conclusion: Age and pubertal development could moderate the effect of ovarian hormones on days of headache onset in girls with migraine.
Investigation of polymorphisms in genes involved in estrogen metabolism in menstrual migraine.


• It has been hypothesized that the drop in estrogen during menses is an important trigger for menstrual migraine.

• Catechol-O-methyltransferase (COMT) and Cytochrome P450 (CYP) enzymes are involved in estrogen synthesis and metabolism.

• Functional polymorphisms in these genes can influence estrogen levels and therefore may be associated with risk of menstrual migraine.

• In this study four single nucleotide polymorphisms were investigated in three genes involved in estrogen metabolism that have been reported to impact enzyme levels or function, in a specific menstrual migraine cohort.

• 268 menstrual migraine cases and 142 controls were genotyped for rs4680 in COMT (Val158Met), rs4646903 and rs1048943 in CYP1A1 (T3801C and Ile462Val) and rs700519 in CYP19A1 (Cys264Arg).

• Neither genotype nor allele frequencies for the COMT and CYP SNPs genotyped were found to be significantly different between menstrual migraineurs and controls by chi-square analysis (P>0.05).

• Further studies are required to assess whether menstrual migraine is genetically distinct from the common migraine subtypes and identify genes that influence risk.
Menarchy with 12.8 years (9.1-17.7 years) [Östradiol] serum level: 10-156 pg/ml
Manifestation of migraine with menarchy in 1/3

- **With Aura** 12-13 years (shortly before or with menarchy)
- **Without Aura** 14-17 years (stable cycle)

Migraine in Women

- 3 : 1 ♀:♂
- 20. – 40.Year
Menstrual Cycle

**Follikelphase**
- Dauer variabel
- Follikelreifung
- Ovulation
- Gelbkörperreifung

**Lutealphase**
- Dauer 12–16 Tage
- in °C
- Körper-temperatur

**Hormone**
- Estradiol
- Progesteron
- luteinisierendes Hormon (LH)
- follicelstimulierendes Hormon (FSH)

**Menses**
- Zyklusbeginn
- Eisprung
- Zyklusende

**Uterusschleimhaut**
- Uterusschleimhaut

**Menstrual Cycle**
- Estradiol
- Progesteron
- FSH
- LH
Menstrual migraine: Influence of estrogens

Somerville 1972
Fall of estrogens and migraines

MacGregor et al. Cephalagia 2003;23:684
Ovarian hormones and migraine

• N = 38, diagnosed with pure or menstrually related migraine, age: 29-49
• Urine was collected daily for assay over 3 months
• Migraine was *inversely associated* with urinary estrogen levels throughout the cycle
• Attacks were more likely to occur with falling estrogens in the late luteal/early follicular phase

Mac Gregor et al, Neurology 2006
Effect of estrogen in trigeminal pain model in humans

A human experimental capsaicin model for trigeminal sensitization.

Gender-specific differences

Parisa Gazerani, Ole Kaeseler Andersen, Lars Arendt-Nielsen*

Pain 118 (2005) 155–163
Influence of Estrogen on trigeminal inflammation
Migraine & Menstruation

Waters W, O’Connor JNNP 1971;34:148
117♀: highest incidence of migraine during menstruation, 42 Pat.,
2 Cycles: during menstruation double increase of attacks

Dalton K Headache 1973;13:151
52♀, 512 attacks: 36% day –4 to –1, 30% day1 to + 3

MacGregor Cephalalgia 1990;10:305
55♀, 3 cycles: Increase of attacks during menstruation (day 1±2),
MwA, no association to ovulation

Stewart Neurology 2000;55:1076
81♀, 3 months: MwA mostly probable day- 1+-1

MacGregor Neurology 2004;63:351
155♀, 693 cycles: attack frequency increased 1,7x day –2, 2,5x on
day -1+-2
Migraine & Menstruation

• Attacks mostly probable during the first 3 days of menstruation (day 1±2)
• Menstrual migraine is migraine without aura
• Menstrual migraine attacks are longer, more intense
• No association between migraine and ovulation
# Migraine & Menstruation

<table>
<thead>
<tr>
<th>Study</th>
<th>Onset of attacks</th>
<th>Pure menstrual migraine</th>
<th>Menstrually related migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacGregor et al, 1990 (n=55)</td>
<td>-2 to +2</td>
<td>7.2%</td>
<td>34.5%</td>
</tr>
<tr>
<td>Granella et al, 1993 (n=1277)</td>
<td>-3 to +3</td>
<td>9.1%</td>
<td>50.8%</td>
</tr>
<tr>
<td>Granella et al, 2000 (n=300)</td>
<td>-2 to +2</td>
<td>3.5%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Dzoljic et al, 2002 (n=1298)</td>
<td>-2 to +2</td>
<td>12.0%</td>
<td>49.0%</td>
</tr>
<tr>
<td>Mattsson, 2003 (n=728)</td>
<td>-2 to +3</td>
<td>21.2%</td>
<td>Not known</td>
</tr>
</tbody>
</table>
Specific prophylaxis

Perimenstrual estrogen supplements:
- 100μg patches or 1.5 mg transcutaneous gel
  (serum levels of 75 pg/ml
2 days before expected headache, change the pad after 3.5 days

# Therapy of menstrual migraine

## Trancutaneus Estrogen replacement

<table>
<thead>
<tr>
<th></th>
<th>N of patients</th>
<th>Cycle/pat</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dennerstein, 1988</td>
<td>18</td>
<td>7</td>
<td>Significant reduction of migraine days perimenstruell, 14 Pat. preferred Estrogen</td>
</tr>
<tr>
<td>MacGregor, 2003</td>
<td>27</td>
<td>6</td>
<td>Significant reduction of migraine days and attack frequency, intensity</td>
</tr>
<tr>
<td>MacGregor, 2006</td>
<td>35</td>
<td>6</td>
<td>Estrogen: 22% - reduction of migraine days, less intense, nausea reduced</td>
</tr>
</tbody>
</table>
Therapy of menstrual migraine

Non steroidal/ anti inflammatory drugs

• Naproxen 550 mg once or twice daily (1)
• Mefenamic acid 500 mg 3-4/ daily (2)

→ Both given 2-3 days before the expected onset of menstruation

1) Sances Headache 2007
2) Owens Am J Obstet Gyn 1984
Therapy of menstrual migraine

Perimenstrual Triptans

Trials for frovatriptan(1), naratriptan (2), sumatriptan(3) and zolmitriptan(4) for perimenstrual prophylaxis show efficacy

1) Silberstein Headache 2002
2) Mannix Headache 2007
3) Newmann Neurology 1998
4) Tuchmann CNS Drugs 2008
Spotlight on frovatriptan: a review of its efficacy in the treatment of migraine.

Allais G¹, Benedetto C¹.

- Frovatriptan is a second-generation triptan with a longer terminal elimination half-life in blood than other triptans (~26 hours).
- Three double-blind, randomized crossover preference studies have been recently conducted, assessing efficacy and safety of frovatriptan versus rizatriptan, zolmitriptan, and almotriptan, respectively.
- Frovatriptan showed favorable tolerability and sustained effect, with a significantly lower rate of relapse over 48 hours versus the other triptans.
- These findings were confirmed in a series of analyses of patient subsets from the three studies, including patients with menstrually related and oral contraceptive-induced migraine, hypertension, obesity, weekend migraine, as well as patients with migraine with aura.
- In all patient subsets analyzed, lower headache recurrence rates were observed versus the comparator triptans, indicating a more sustained pain-relieving effect on migraine symptoms.
A further randomized, double-blind study demonstrated that frovatriptan given in combination with the fast-acting cyclooxygenase inhibitor dexketoprofen provided improved migraine pain-free activity at 2 hours, and gave more sustained pain-free activity at 24 hours, versus frovatriptan alone.

These benefits were observed both when the combination was administered early (<1 hour after symptom onset) or late (>1 hour after onset). Different pharmacokinetic, but synergistic, properties between frovatriptan and dexketoprofen may make the combination of these agents particularly effective in migraine treatment, with rapid onset of action and sustained effect over 48 hours.

- Randomized (2:1), placebo controlled, double blind trial to investigate the efficacy of Rizatriptan 10 mg in MM (ICHD 2, 2004)
- Primary endpoint: 2 hour pain freedom
- N = 94
- Rizatriptan 63.5%
- Placebo 29.0%
- Effective both in MM and non menstrual migraine (63.5% vs 57.5%)
A randomized double blind study comparing Rizatriptan, Dexametasone and the combination of both in the acute treatment of menstrually related migraine (Bigal et al 2008)
Migraine and oral contraception

• N= 13.944, cross sectional study, Norway
• Significant association between the use of COC and migraine
  (30 mcg estradiol OR 1.4, 95% CI 1.2-1.7, p<0.001)
• Low dose COC / levornogestrel – greater improvement frequency/ intensity
  (OR 34.9, 95% CI 1.64-707.97)
• Progesteron only pills - no association
  (OR 1.3, 95% CI 0.9-1.8)

Aegidus Neurology 2006
Migraine and oral contraception

**Prospective studies**

*Ryan 1988*
Open, cross over, n= 40, 2 months oral contraception (50 mcg Ethinylöstradiol, 0,5 mg Norgestrel) vs no therapy
Worsening: 70% Improvement: 30%

*Calhoun 2004*
Open label study, n=11, 28 days cycle 0.02mg ethynylestradiol for 21 days, followed 0.9 mg conjugated equine estrogen for 7 days
All woman achieved 50% reduction of headache

Retrospective studies:

**No change:** 44-67%
**Worsening:** 24-35% (bei MA 56%)
**Improvement:** 50-80%
Modification of contraception

Open, monocentre study
102 Pat.
1. 2 months contraception usual 21/7 days
2. 168 days continuous contraception

Primary endpoint: incidence of headache, Intensity of headache, weekly MIDAS

Results:
Pat. with severe headache (n=50):
Significant reduction of headache from day 28 over the whole time

## Effect of ethinylestradiol dose on risk of ischemic stroke


<table>
<thead>
<tr>
<th>Design</th>
<th>Sample size</th>
<th>Setting</th>
<th>Dose of ethinylestradiol (mcg)</th>
<th>Risk of ischemic stroke OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Group for the Study of Stroke in Young Women (1975) [77]</td>
<td>Case-control 430 cases 151 controls</td>
<td>91 hospitals in 12 US cities</td>
<td>≥50</td>
<td>4.9 (2.9–8.3)</td>
</tr>
<tr>
<td>Lidegaard (1993 &amp; 1995) [78,79]</td>
<td>Case-control 320 cases 1197 controls</td>
<td>Denmark</td>
<td>50</td>
<td>2.9 (1.6–5.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30–40</td>
<td>1.8 (1.1–2.9)</td>
</tr>
<tr>
<td>Lidegaard (2002) [57]</td>
<td>Case-control 626 cases 4054 controls</td>
<td>Denmark</td>
<td>50</td>
<td>4.5 (2.6–7.7)</td>
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<td></td>
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<td></td>
<td>30–40</td>
<td>1.6 (1.3–2.0)</td>
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<td></td>
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<td></td>
<td>20</td>
<td>1.7 (1.0–3.1)</td>
</tr>
<tr>
<td>Tzourio et al. (1995) [53]</td>
<td>Case-control 72 cases 173 controls</td>
<td>France</td>
<td>All doses</td>
<td>3.1 (1.2–8.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>4.8</td>
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<td>30–40</td>
<td>2.7</td>
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<td></td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td>Carolei et al. (1996) [60]</td>
<td>Case-control 308 cases 591 controls</td>
<td>Italy</td>
<td>All doses</td>
<td>1.3 (0.6–2.6)</td>
</tr>
<tr>
<td>Petitti et al. (1996) [80]</td>
<td>Case-control 295 cases 774 controls</td>
<td>USA</td>
<td>&lt;50</td>
<td>1.18 (0.54–2.59)</td>
</tr>
<tr>
<td>WHO Collaborative study (1996) [81]</td>
<td>Case-control 697 cases 1962 controls</td>
<td>International</td>
<td>All doses (Europe)</td>
<td>2.24 (1.31–3.82)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>≥50</td>
<td>5.3 (2.56–11.0)</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;50</td>
<td>1.53 (0.71–3.31)</td>
</tr>
<tr>
<td>Schwarz et al. (1998) [82]</td>
<td>Case-control 175 cases 191 controls</td>
<td>USA</td>
<td>&lt;50</td>
<td>0.88 (0.44–1.76)</td>
</tr>
<tr>
<td>Chang et al. (1999) [101]</td>
<td>Case-control 291 cases 736 controls</td>
<td>5 European centres</td>
<td>All doses</td>
<td>2.76 (1.01–7.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥50</td>
<td>7.95 (1.94–32.6)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;50</td>
<td>1.19 (0.33–4.29)</td>
</tr>
<tr>
<td>Kemmeren et al. (2002) [84]</td>
<td>Case-control 203 cases 925 controls</td>
<td>9 Dutch centers population all types based</td>
<td>&lt;50</td>
<td>2.3 (1.6–3.3)</td>
</tr>
<tr>
<td>Siritho et al. (2003) [85]</td>
<td>Case-control 234 cases 234 controls</td>
<td>4 Australian Hospitals</td>
<td>≤50</td>
<td>1.76 (0.86–3.61)</td>
</tr>
<tr>
<td>Nightingale and Farmer (2004) [56]</td>
<td>Case-control 190 cases 1129 controls</td>
<td>UK General Practice Research Database</td>
<td>&lt;50</td>
<td>2.30 (1.15–4.59)</td>
</tr>
</tbody>
</table>
Effectiveness of the progestin-only pill for migraine treatment in women: A systematic review and meta-analysis.


- **Background:**

Migraine is highly prevalent in women (18%). Peak morbidity affects their most productive years, coinciding with peak fertility. Hormonal contraception is often tailored for migraine prevention. Estrogen-containing contraceptives may be contraindicated in women experiencing migraine with aura due to the risk of vascular events.

While Improvements in migraine with a progestin-only pill (POP), which inhibits ovulation are documented, the strength and quality of evidence has not been formally evaluated.
Effectiveness of the progestin-only pill for migraine treatment in women: A systematic review and meta-analysis.

Warhurst S¹, Rofe CJ², Brew BJ²,³, Bateson D⁴,⁵, McGeechan K⁵, Merki-Feld GS⁶, Garrick R², Tomlinson SE 2017

Objectives:

→ To determine the effectiveness of progestin-only contraceptives for migraine treatment by systematic review and meta-analysis.

Data sources and selection MEDLINE, EMBASE and Cochrane Libraries were searched (1980 to September 2016) for studies on progestin-only treatments for migraine. Studies in English on >4 non-menopausal women aged 18-50 with migraine diagnosed by formal criteria were included.
Effectiveness of the progestin-only pill for migraine treatment in women: A systematic review and meta-analysis.

Warhurst S1, Rofe CJ2, Brew BJ2,3, Bateson D4,5, McGeechan K5, Merki-Feld GS6, Garrick R2, Tomlinson SE2017

Results
Pooled analyses of four studies demonstrated that desogestrel 75 mcg/day, POP significantly but modestly reduced the number of migraine attacks and migraine days. Reduced intensity and duration, reduced analgesic and triptan use were observed, along with improved headache-related quality of life.
Two studies compared desogestrel POP to a combined oral contraceptive, demonstrating similar migraine outcomes for both treatments.

Conclusions The desogestrel POP shows promise in improving migraine in women. Current evidence is observational and based on small samples of women using only one oral progestin-only formulation. Further randomized trials on additional progestin-only contraceptives are required to confirm their role in migraine management.
Practical conclusions – Hormonal contraceptives

• Combined hormonal contraception inhibits ovulation (21 days, 7 days hormone free interval)

• Migraine without aura is the consequence of hormone withdrawal and can be treated with extended or continuous regimen

• Preexisting Migraine with aura is likely to worsen or start de novo with COC
Practical conclusions – Hormonal contraceptives

- Migraine with aura is a risk factor for ischemic stroke
- Migraine with aura is a contraindication for the use of combined oral contraception which further increases the risk of ischemic stroke
- Progesteron-only contraceptives are not associated with an increased risk of stroke and are an alternative method
Headache in Pregnancy

Epidemiology 1

- **Migraine**
  - Rasmussen 1993: 48% no change; 48% improvement/no migraine; 4% worsening (2./3. trimenon)
  - First manifestation in pregnancy: Migraine with aura, (Massey 1977; Cupini 1995)
  - Returning to former pattern after stop breastfeeding (CAVE: sinusthrombosis, eclampsy etc.)
Headache in pregnancy
Epidemiology 2

- Tension type headache
- Rasmussen 1993: 67% no change; 28% improvement/no headache;
- 5% worsening
- Cluster headache
  
  No influence (van Vliet 2006)

- Cervikogenic headache
  
  No influence (Sjaastad 2002)
Migraine and pregnancy

5 retrospective studies (n = 1674)
**Improvement/remission** 67-86%
**Remission** 17-32%
**Worsening/no change** 3,5-23%

4 prospective studies (n= 538)
**Improvement/remission** 64-87, 2%
**Remission** 58-78,7%
**Worsening/no change** 12,8-20%
Migraine during pregnancy

- High levels of estrogens are protective
- Habituation
- Influence of other hormones
- Unknown factors/ psychosocial
Migraine during pregnancy

Effects of pregnancy on slow cortical potentials in migraine patients and healthy controls

S Darabaneanu¹, P Kropp², U Niederberger¹, H Strenge¹ & W-D Gerber¹

¹Institute of Medical Psychology and Medical Sociology, University Clinic of Kiel, Kiel, and ²Institute of Medical Psychology, University Clinic of Rostock, Rostock, Germany
Therapy of migraine during pregnancy

Acute therapy

1. Acetaminophen: strict indication
2. Acetylic acid, Ibuprofen Naproxen: containedicated in 3rd Trimenon, strict indication in 1rst and 2nd trimenon
3. Metamizol: containedicated in 3rd trimenon, strict indication in 1rst and 2nd trimenon
4. Ergotamin: contraindicated
5. Triptans: strict indication

Pregnancy registers: n>1000 show no hint for higher abortion rate
During lactation: 24 hours stop of breast feeding
Therapy of migraine during pregnancy and lactation

**Prophylactic therapy**

### Pregnancy

1. Metoprolol/Propranol: strict indication, CI 48-72 h before birth
2. Topiramate: contraindicated
3. Valproate: contraindicated
4. Flunarizine: strict indication
5. Amitripiline: strict indication
6. Riboflavin/ Vit B: no restriction
7. Mg: no restriction
8. Petasides: contraindicated
9. ASS: contraindicated 3rd trimenon, strict indication 1st and 2nd trimenon

### Lactation

1. Metoprolol/Propranol: strict indication
2. Topiramate: contraindicated
3. Valproate: strict indication
4. Flunarizine: contraindicated
5. Amitripiline: contraindicated
6. Riboflavin/ Vit B: no restriction
7. Mg: no restriction
8. Petasides: contraindicated
9. ASS: contraindicated
Effect of menopause on migraine

- **Perimenopause**
  Mattson 2003, Wang 2003
  Prevalence higher than in early menopause

- **Menopause** ([Östradiol] 10-20 pg/ml)

  - **Improvement:** 25-67%
  - **no change:** 24-48%
  - **worsening:** 9-42%

- Improvement 2 years after menopause
Effect of HRT on migraine

Muller Headache 2000
N= 120, 64.1% reported improvement or complete remission, 22.5 no change, 13.3 worsening

N= 6588 (30.2%) had never used HRT, N= 10.519 (48.3%) current users
IHS diagnosis: 8.2%

Multivariant analysis controlled for age, race, smoking, alcohol, former contraception use, age at the onset of menopause, type of menopause

Current use of HRT was associated with a 42% risk of migraine headache (OR 1.42, CI 1.24-1.62)

Compared to never users of estrogen: 39% increased risk OR 1.39 (95CI 1.14-1.69)

Users of estrogen and progesteron: 41% risk (OR 1.41, 95CI 1.22-1.63)
The effect of different regimens of HRT on migraine

<table>
<thead>
<tr>
<th>Study design</th>
<th>Duration</th>
<th>Sample size</th>
<th>HRT Regime</th>
<th>Effect on migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facchini et al. (2002)[48]</td>
<td>RCT</td>
<td>6 months</td>
<td>38</td>
<td>Oral continuous combined 1mg estradiol hemihydrate plus 0.5mg NET daily</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Oral cyclical combined 0.625mg CEE daily plus 10mg MPA days 15–28</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Oral sequential combined 2mg estradiol valerate daily for 21 plus 1mg cyproterone acetate days 12–21; no treatment on days 22–28</td>
</tr>
<tr>
<td>Nappi et al. (2006)[49]</td>
<td>RCT</td>
<td>6 months</td>
<td>40</td>
<td>Continuous combined 1mg 17-beta-estradiol plus 0.5mg NET daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous combined 2.5mg tibolone daily</td>
</tr>
</tbody>
</table>

CEE, continuous equine estrogens; MPA, medroxyprogesterone acetate; NET, norethisterone; RCT, randomized controlled trial
Effect of HRT on Aura

Retrospective studies
*Mueller 2000, Hodson 2000*

- Improvement: 22%
- no change: 57%-77%
- worsening: 21-23%

*MacGregor, 1999*

New onset of aura after HRT (conjugated equine estrogens 1.25 mg/225 estradiol) (CEE 0.625/2 mg estrogen)
Reduction to estrogen only improved aura
Practical conclusions - HRT

• HRT uses natural estrogen and provides estrogen levels equivalent to the menstrual cycle (oral, percutaneous, transvaginal)

• No contraindication to use HRT during perimenopause (the lowest possible dose is recommended)

• If aura starts de novo change the route of application HRT/reduce dose

• With intact uterus progesterons are necessary for endometrical protection
Transsexuality

Cross-sex hormone administration changes pain in transsexual women and men

Anna Maria Aloisi a,*, Valeria Bachiocco a,b, Antonietta Costantino c, Rita Stefani d, Ilaria Ceccarelli a, Alessandro Bertaccini c, Maria Cristina Meriggiola c


<table>
<thead>
<tr>
<th>Males to females: number of subjects suffering chronic pain and kind of pain</th>
</tr>
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Gender and headache

- Epidemiological data supports a relationship between sex hormones and migraine
- Tension type headache seems not to be influenced
- Changes in Estrogen levels might be the most relevant factor
- Genetics are still to be investigated
- Pathophysiology is still to be investigated
Case history 1

- PM, 32 years, history of migraine without aura since childhood
- Attack frequency 3-4 attacks during 19-30 years of age, different oral contraception, best option was progesteron based
- Pregnancy at the age of 31
- No migraine attacks during months 2-9 of pregnancy
- Onset of migraine a couple of weeks after birth of her daughter, 3-4 attacks a month lasting 2-3 days
- Wishes to continue breastfeeding her child for 6-9 months
Case history 2

- TR, age 42, Migraine with and without aura since onset of menarchy, attack frequency 3-4/ month, menstrually related, no oral contraception, acute therapy with triptans po (8-12 per month), no prophylaxis
- Triptans have an effect 1 h after intake and reduce headache sufficiently in 80% of all attacks
- Attacks occurring with menstruation seem to be less responsive to triptans lately with headache recurrence in 100% after 5-7 h
- TR asks for specific prophylaxis and change of acute treatment