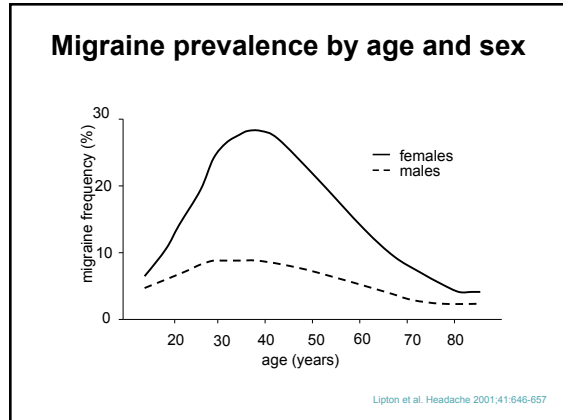


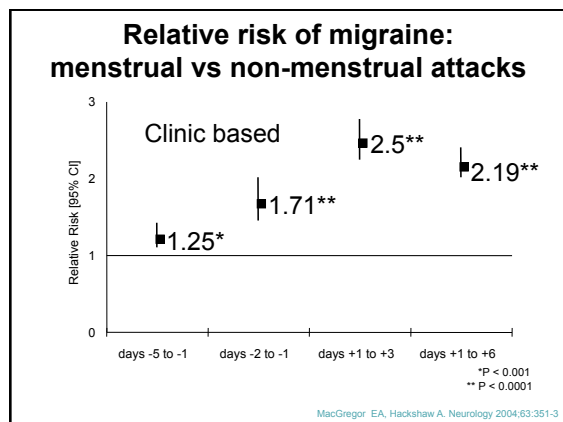
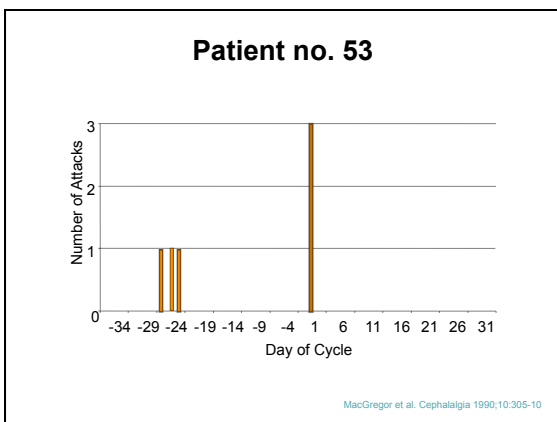
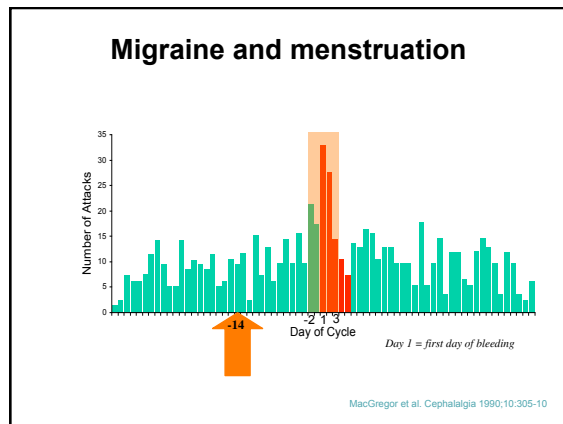
### Female hormones and headache: what's the connection?

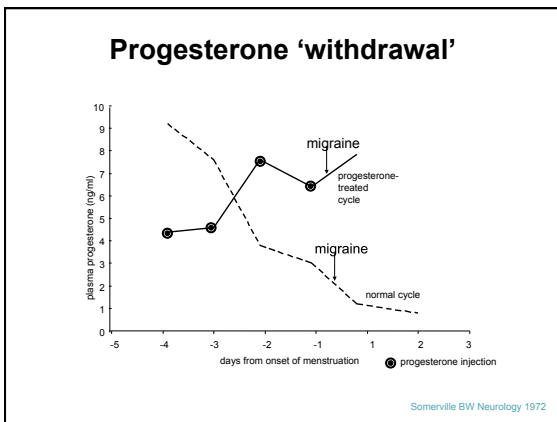
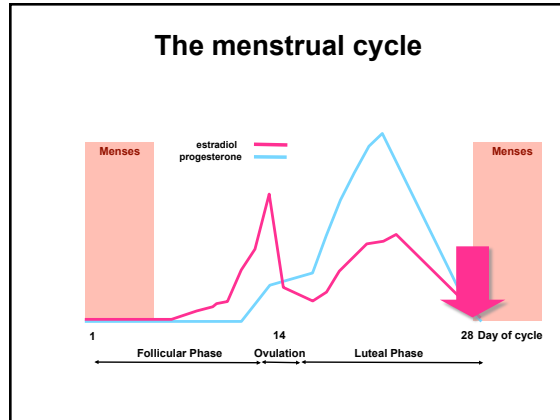
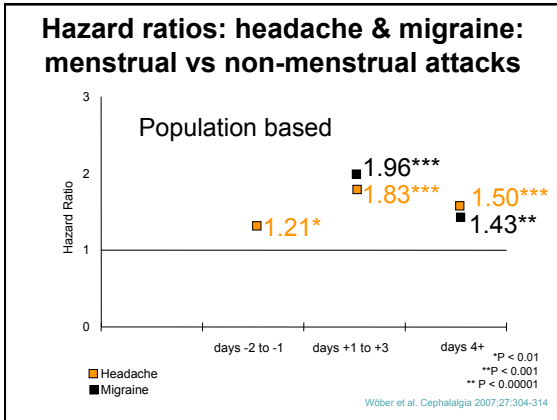
Dr Anne MacGregor  
[www.migraineclinic.org.uk](http://www.migraineclinic.org.uk)  
 anne.macgregor747@migraineclinic.org.uk



### Estrogen and Migraine

- Migraine *without* aura
  - Association with 'menstrual' migraine
- Migraine *with* aura
  - Association with high levels of estrogen

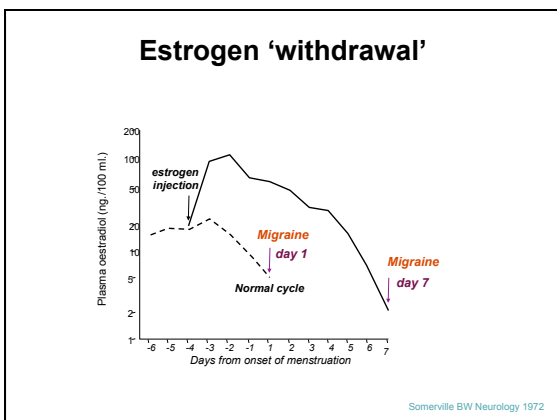




### Continuous progesterone

- Continuous progestogen at doses sufficient to suppress the endogenous menstrual cycle, have been effective in preventing menstrual migraine

Source: Bradley WG et al BMJ 1968;3:531-533; Somerville B & Carey M med J aust 1970;1:1043-1045



### Estrogen 'withdrawal'

- Migraine without aura
  - 'Menstrual' migraine
  - In the pill-free interval of COCs
  - In the estrogen-free week of HRT
  - Following estrogen challenge in post-menopausal women

Source: Somerville BW, Neurology 1972; Epstein MT et al. Lancet 1975; Whitty CWM et al. Lancet 1966; Kudrow L. Headache 1975; Lichten E. Headache 1996

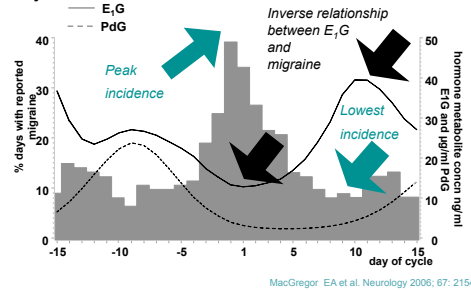
### Estrogen 'withdrawal' migraine

- Independent of progesterone
- Independent of ovulation

Somerville BW Headache 1972;12:93-102  
Lichten E et al (1996) Headache 36:367-371

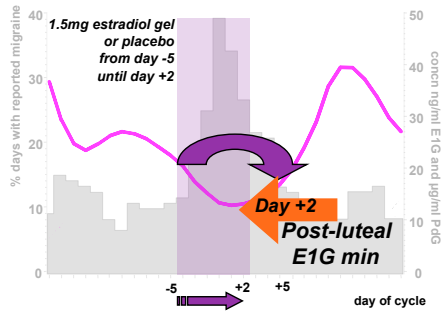
### Estrogen and menstrual migraine

38 women  
120 cycles



MacGregor EA et al. Neurology 2006; 67: 2154-8

### Double-blind crossover study: perimenstrual estradiol vs placebo



MacGregor et al. Neurology 2006;67:2159-63

### Evidence-based treatment of menstrual migraine: perimenstrual

- Transcutaneous estrogen 1.5mg daily
  - de Lignieres et al, 1986 (day -2 to day +5)
  - Dennerstein et al, 1988 (7 days perimenstrually)
  - MacGregor et al, 2006 (day -5 to day +2)
    - Significant reduction during treatment, followed by 40% increase in migraine post treatment

Fringsheim et al. Neurology 2008;70:1555-63

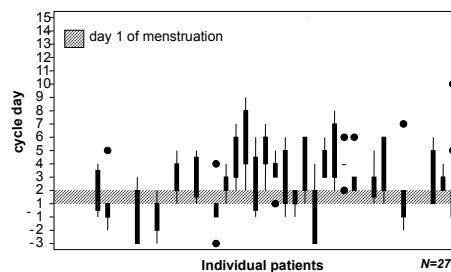
### Relative Risk of migraine: estradiol vs placebo n=35

	RR [95%CI]	p
during gel	0.78 [0.62 to 0.99]	<0.05
days 1-5 post gel*	1.40 [1.03 to 1.92]	<0.05
days 6-10 post gel	1.04 [0.67 to 1.62]	NS

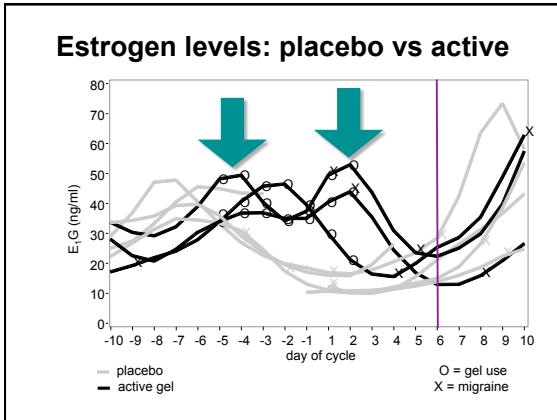
\*peak increase day 3 post gel

MacGregor et al. Neurology 2006;67:2159-63

### Cycle day of E<sub>1</sub>G minimum



MacGregor et al. Curr Head Rep 2008



- ### Estrogen 'withdrawal' migraine
- Maintain stable low estrogen levels
    - Danazol
    - Tamoxifen
    - GnRH analogue
  - Maintain stable high estrogen levels
    - Continuous combined oral contraception
    - Transdermal oestrogens 200µg + cyclical progestogens
    - GnRH analogue + addback HRT
- O'Dea & Davis, 1990; Holdaway et al., 1991; Lichten et al., 1991; Murray & Kluse, 1997; Mathew & Fung, 1999; Magos AL, Zikha KJ & Sludd JW J Neurol Neurosurg Psychiatr 1983; 46:1044-1046; Calhoun AH (2004) A novel specific prophylaxis for menstrual-associated migraine Southern Med J 2004; Martin V. Headache, 2003

**BUT NOT TOO HIGH**

Epidemiological studies confirm the clinical impression that migraine is a predominantly female disorder. Although migraine is equally common in both sexes before puberty, there is increased female prevalence following menarche. This difference between the sexes becomes more pronounced with increasing age, peaking during the 30s and declining thereafter. Some studies suggest that the lifetime prevalence of migraine in women is as great as 20 per cent, compared with only 8 per cent in men, considered to result from the additional influence of the fluctuating hormones of the menstrual cycle, an association that has long been recognised. Hippocrates noted that "Shivering, lassitude and heaviness of the head denotes the onset of

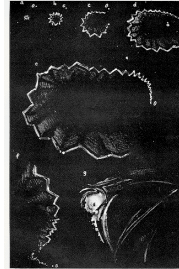
**BUT NOT TOO HIGH**

- ### Migraine and menstruation
- Migraine with aura
    - Mean estradiol 94.4 ± 28.3 pg/ml
  - Migraine without aura
    - Mean estradiol 41.6 ± 7.1 pg/ml
  - Controls
    - Mean estradiol 50.6 ± 8.6 pg/ml
- Nagele-Leiby S et al. Cephalalgia 1990

- ### 'High' estrogen and migraine
- Migraine aura
    - CHCs
    - Pregnancy
    - HRT
- 
- Granella F, et al Cephalalgia 2000;20(8):701-7  
Wright G & Patel M. BMJ 1985;293:1557-8  
Chancellor AM, et al. Headache 1990;30(4):224-227  
Cupini L, et al. Cephalalgia 1995;15:140-4  
MacGregor A. Headache 1999;39:674-678  
Kaiser HJ, & Meinenberg O. J Neurol Neurosurg Psychiatr. 1993;240(3):195-7

### 'High' estrogen and migraine

- Aura initiated by high estrogen states can revert to migraine without aura
  - CHCs discontinued
  - Post-partum
  - ERT dose reduction



### 'High' estrogen and migraine

- Independent of progesterone
- Independent of ovulation

### Estrogen and migraine

- Mechanisms?

