Ente Ospedaliero Cantonale

Università della Svizzera italiana

# Difficoltà e gestione della cefalea acuta e cronica


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# Laura
# 27 anni

## Anamnesi

Emicrania senz'aura episodica
Esordio in età adolescenziale (attorno agli 11 anni, in concomitanza con il menarca).
Familiarità per cefalea (madre, sorella).

Ha assunto in passato EP (sospeso per peggioramento della cefalea).

Sovrappeso (BMI 26).
Ex tabagista.

# Anamnesi della cefalea

**Profilassi**

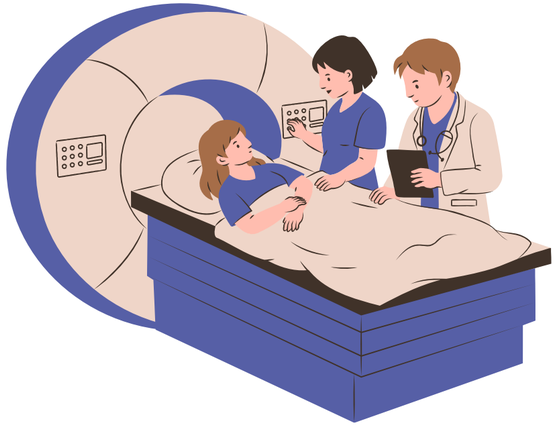
- amitriptilina fino a 25 mg (sospesa per incremento ponderale)
- propranololo (fino a 80 mg/die) con beneficio (da 6-7 a 1-2 episodi/mese).

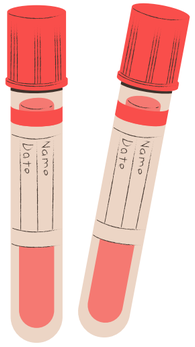
Terapia d'attacco:

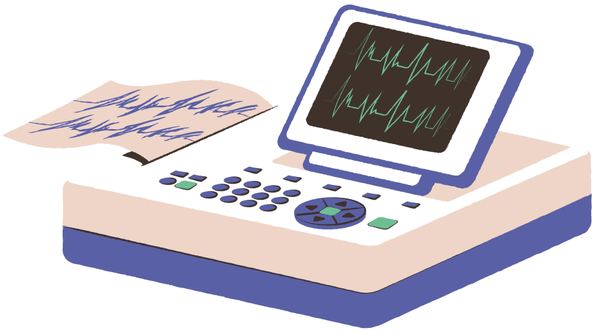
- Rizatriptan 10 mg con beneficio
- Almotriptan e zolmitriptan inefficaci
- Paracetamolo  e FANS (ibuprofene, ketoprofene, naprossene ecc.) inefficaci

Accertamenti diagnostici:

- RM encefalo con AngioRM (nella norma),
- Esami ematochimici (con assetto tiroideo, vitaminico e marziale, nella norma)
- ECG prima di introdurre il propranololo (ritmo sinusale FC 86 bpm).





# Anamnesi ostetrica-ginecologica

Ad aprile 2024 la paziente torna in visita al Centro Cefalee e ci comunica di essere al primo trimestre di gravidanza.
Frequenza cefalea: 6-7 episodi al mese, dalle caratteristiche usuali.
Gravidanza normodecorsa. Pressione arteriosa nella norma ed esami di laboratorio nei limiti.
Esame obiettivo neurologico nella norma.

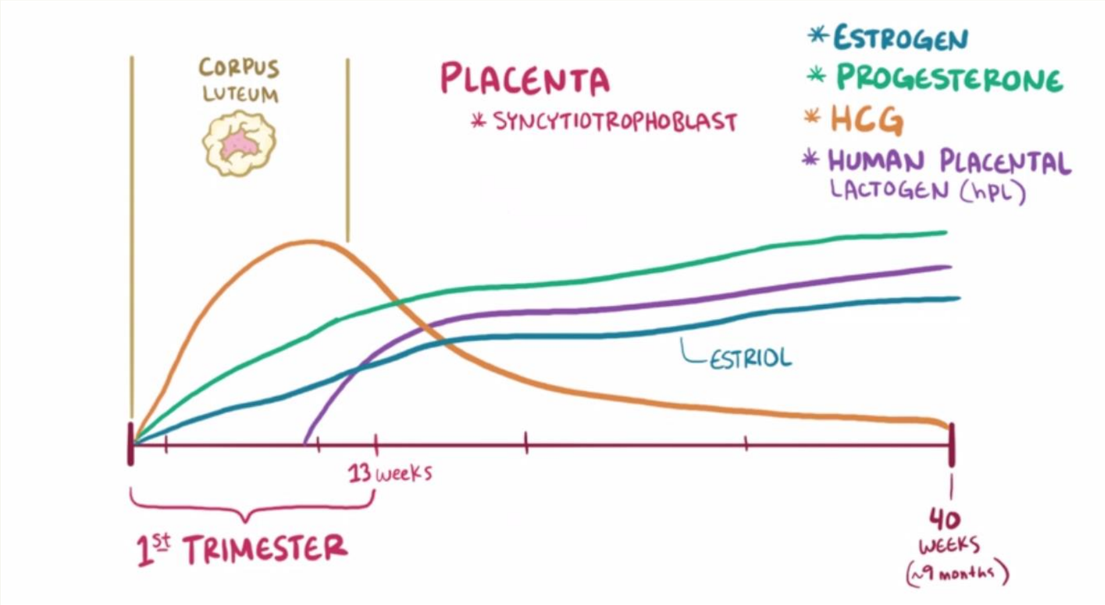
Assume già integrazione con magnesio.

# Come gestiamo la paziente?

1. Ripetiamo un esame di neuroimaging per l’aumento degli attacchi
2. Prescriviamo propranololo dal momento che in passato era stato efficace
3. Lasciamo solo magnesio aspettando che superi il primo trimestre e migliori spontaneamente

# Emicrania in gravidanza

- Dal 50 al 75% delle pazienti emicraniche migliora in gravidanza
- Solitamente miglioramento nel II e III trimestre
- Fino al 25% continua a soffrire di emicrania in gravidanza (e fino al 50% delle pazienti con aura)
- Fino al 10% esordisce in gravidanza



# Cefalea primaria o secondaria?

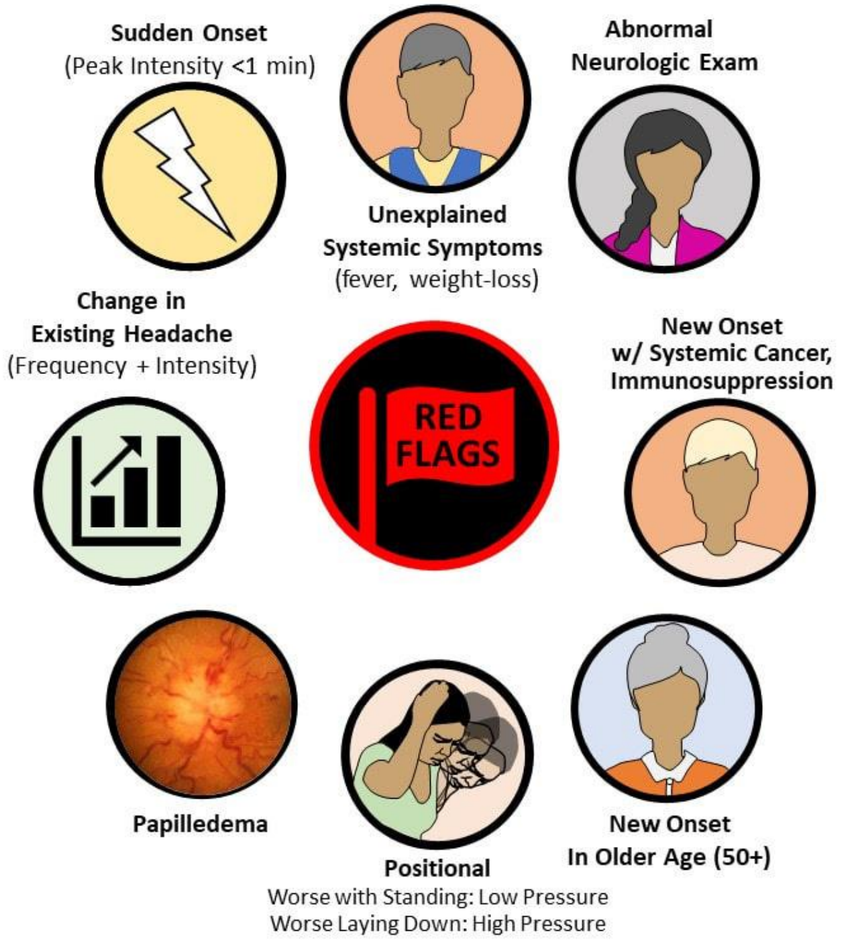



**TABLE. THE SNOOP MNEMONIC FOR SECONDARY HEADACHE DISORDER RED FLAGS**

| Mnemonic | History features | Physical examination features |
|---|---|---|
| **S**ystemic | History of malignancy, immunosuppression, or HIV or complaints of fever, chills, night sweats, myalgias, weight loss, or jaw claudication | Abnormal systemic examination, including blood pressure and temperature |
| **N**eurologic | Focal or global neurologic symptoms, including change in behavior or personality, diplopia, transient visual obscurations, pulsatile tinnitus, motor weakness, sensory loss, or ataxia | Abnormal neurologic examination |
| **O**nset, sudden | Headache reaches peak intensity in less than 1 minute (thunderclap) | |
| **O**nset age <5 or >65 | New-onset headache before age 5 years<br>New-onset headache after age 65 | |
| **P**attern change | Progressive headache (evolution to daily headache) or change in headache characteristics | |
| | Precipitated by Valsalva maneuver | |
| | Postural aggravation | |
| **P**apilledema | n/a | Papilledema |
| **P**regnancy | New-onset headache during pregnancy<br>Change in headache during pregnancy | |
| **P**henotype of rare headache | Trigeminal autonomic cephalalgia; hypnic; exercise-, cough-, or sex-induced | |

# Cefalea primaria o secondaria?

**Figure** Final headache diagnoses in pregnant women

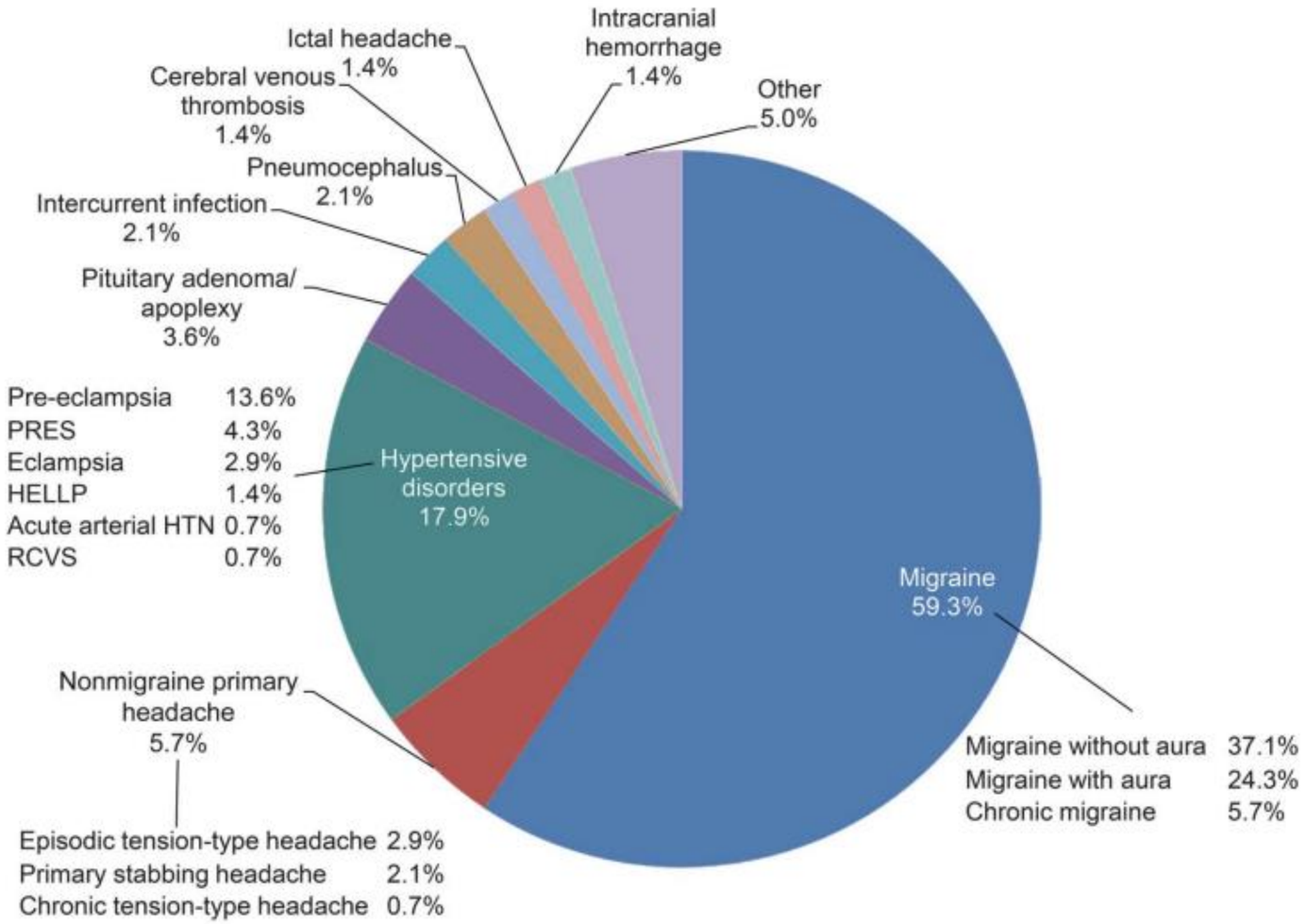



**Table 2** Among women with a history of headache, reported differences in the acute attack during pregnancy relative to the headache history

| Changed feature | All headache | Primary headache | Secondary headache | *p* Value |
|---|---|---|---|---|
| No. | 110 | 79 | 31 | — |
| Any change | 93 (84.5) | 66 (83.5) | 27 (87.1) | 0.77 |
| Longer attack duration | 49 (44.5) | 30 (38.0) | 19 (61.3) | 0.027[a] |
| Increased attack severity | 33 (30) | 24 (30.4) | 9 (29.0) | 0.89 |
| Change in attack location | 9 (8.2) | 8 (10.1) | 1 (3.2) | 0.44 |
| Change in attack frequency culminating in acute attack | 10 (9.1) | 8 (10.1) | 2 (6.5) | 0.72 |
| Associated symptoms | 44 (40.0) | 30 (38.0) | 14 (45.2) | 0.49 |

Data are n (%) unless otherwise indicated.
[a] Indicates statistical significance.

**Table 4** Relative odds of secondary headache in pregnant women: Logistic regression model

| Variable | OR (95% CI) | *p* Value |
|---|---|---|
| Lack of headache history | 4.9 (1.7-14.5) | 0.004[a] |
| Elevated blood pressure | 17.0 (5.2-56.0) | <0.001[a] |
| Gestational age | 0.99 (0.93-1.0) | 0.59 |
| Asthma | 0.32 (0.09-1.2) | 0.088 |
| Psychiatric comorbidity | 0.13 (0.021-0.78) | 0.026[a] |
| Side predominance of headache | 1.1 (0.37-3.0) | 0.93 |
| Photophobia | 1.8 (0.54-6.0) | 0.34 |
| Phonophobia | 0.29 (0.09-0.91) | 0.033[a] |
| Referable neurologic examination abnormality | 2.7 (0.85-8.8) | 0.091 |

Abbreviations: CI = confidence interval; OR = odds ratio.
[a] Indicates statistical significance.

# Neuroimaging: cosa si può fare in gravidanza

**American College of Radiology summary of the International Commission on Radiological Protection suspected in-utero induced deterministic radiation effects**

| Menstrual or gestational age | Conception age | Radiation dose | | |
|---|---|---|---|---|
| | | <50 mGy (<5 rad) | 50 to 100 mGy (5 to 10 rad) | >100 mGy (>10 rad) |
| 0 to 2 weeks (0 to 14 days) | Before conception | None | None | None |
| 3rd to 4th week (15 to 28 days) | 1st to 2nd week (1 to 14 days) | None | Probably none | Possible spontaneous abortion |
| 5th to 10th week (29 to 70 days) | 3rd to 8th week (15 to 56 days) | None | Potential effects are scientifically uncertain and probably too subtle to be clinically detectable | Possible malformations increasing in likelihood as dose increases |
| 11th to 17th week (71 to 119 days) | 9th to 15th week (57 to 105) | None | Potential effects are scientifically uncertain and probably too subtle to be clinically detectable | Increased risk of deficits in intelligence quotient or mental retardation that increase in frequency and severity with increasing dose |
| 18th to 27th week (120 to 189 days) | 16th to 25th week (106 to 175 days) | None | None | Intelligence quotient deficits not detectable at diagnostic doses |
| >27 weeks (>189 days) | >25 weeks (>175 days) | None | None | None applicable to diagnostic medicine |

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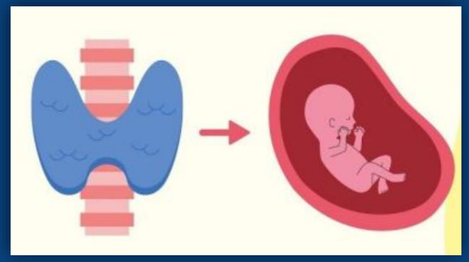
**TC encefalo**

- sicura in tutti i trimestri (da 1 a 10 mGy)
- mdc iodato: passa la barriera placentare → circolazione fetale → tiroide (no teratogeno, ipotiroidismo fetale soprattutto se nel II trimestre)



## RM encefalo

- I trimestre: sicura, ma periodo dell'organogenesi, se possibile evitare (possibili effetti sul SNC)
- II - III trimestre: sicura, AngioRM da preferire ad AngioTC per lo studio dei vasi
- mdc gadolinio: controindicato (soprattutto I trimestre), passa la barriera placentare (accumulo nei tessuti fetali, fibrosi sistemica nefrogenica )

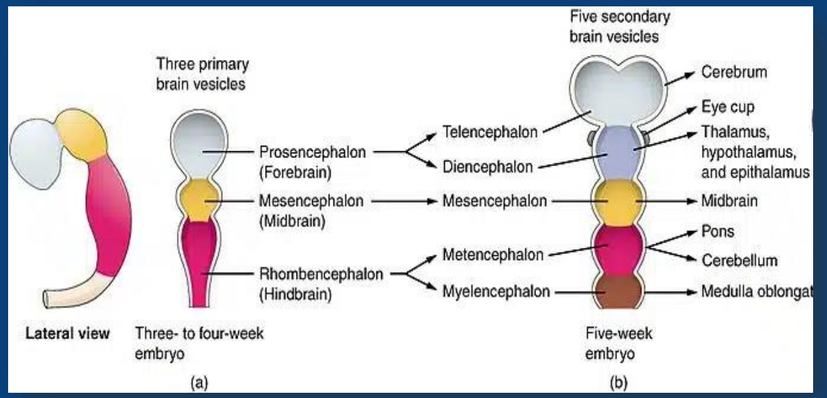



**Table 2. Risk of Adverse Outcomes at Birth and Up to a Maximum Age of 4 Years in the Offspring of Women Exposed to Magnetic Resonance Imaging in the First Trimester of Pregnancy vs Women Not Exposed**

| | Magnetic Resonance Imaging Exposure | | |
|---|---|---|---|
| | Cohort 1: Any During the First Trimester (n = 1737) | | None During Pregnancy (n = 1 418 451) |
| Outcome[a] | No. (%) | Incidence (95% CI) per 1000 Person-Years | No. (%) |
| Stillbirth or neonatal death[c] | 19 (1) | 10.9 (6.6 to 17.0) | 9844 (1) |
| Congenital anomaly | 165 (10) | 33.8 (29.0 to 39.4) | 109 053 (8) |
| Vision loss[d] | 21 (1) | 4.0 (2.6 to 6.1) | 10 124 (1) |
| Hearing loss | 50 (3) | 9.6 (7.2 to 12.6) | 38 978 (3) |
| Any neoplasm[e] | ≤5 (<1) | 0.2 (0.0 to 1.3) | 4831 (<1) |

[a] For all outcomes, we excluded pregnancies exposed to MRI after 14 weeks' gestation, or p
first-trimester exposure to MRI, in which a congenital anomaly was diagnosed prior to the
of congenital anomaly, vision loss, hearing loss, and any neoplasm, we further excluded 75
resulted in a stillbirth.

[b] Stabilized inverse probability weights were used to adjust for differences between exposu

**Table 3. Risk of Adverse Outcomes From Birth to a Maximum Age of 4 Years in the Offspring of Women Exposed to Gadolinium-Enhanced Magnetic Resonance Imaging During Pregnancy vs Women Not Exposed to Any Magnetic Resonance Imaging During Pregnancy[a]**

| | Magnetic Resonance Imaging Exposure | | | | | | |
|---|---|---|---|---|---|---|---|
| | Cohort 2: Gadolinium-Enhanced at Any Time During Pregnancy (n = 397) | | None During Pregnancy (n = 1 418 451) | | Hazard Ratio (95% CI) | | |
| Outcome | No. (%) | Incidence per 1000 Person-Years (95% CI) | No. (%) | Incidence per 1000 Person-Years (95% CI) | Crude | Inverse Probability Weight-Adjusted[c] | Inverse Probability Weight-Adjusted Risk Difference (95% CI)[c] |
| Stillbirth or neonatal death[b] | 7 (2) | 17.6 (7.1 to 36.0) | 9844 (1) | 6.9 (6.8 to 7.1) | 2.60 (1.26 to 5.37) | 3.70 (1.55 to 8.85) | 47.5 (9.7 to 138.2) |
| Connective tissue or skin disease resembling nephrogenic systemic fibrosis | ≤5 (<1)[d] | 3.3 (1.3 to 8.9) | 8705 (1) | 1.8 (1.8 to 1.8) | 1.76 (0.66 to 4.68) | 1.00 (0.33 to 3.02) | 0.0 (−2.2 to 6.7) |
| Broad rheumatological or inflammatory or infiltrative skin condition | 123 (31) | 125.8 (105.3 to 149.9) | 384 180 (27) | 93.7 (93.4 to 94.0) | 1.33 (1.11 to 1.58) | 1.36 (1.09 to 1.69) | 45.3 (11.3 to 86.8) |
| Congenital anomaly | 39 (10) | 34.8 (25.4 to 47.6) | 109 053 (8) | 24.0 (23.9 to 24.2) | 1.33 (0.98 to 1.82) | 1.25 (0.84 to 1.86) | 8.7 (−5.6 to 29.9) |

Abbreviation: MRI, magnetic resonance imaging.

[a] For all outcomes, we excluded pregnancies with first-trimester exposure to MRI, in which a congenital anomaly was diagnosed prior to the MRI. For the outcomes of connective tissue or skin disease resembling nephrogenic systemic fibrosis, broad rheumatological or inflammatory or infiltrative skin condition, and congenital anomaly, we further excluded 7542 pregnancies resulting in a stillbirth.

[b] For stillbirth or neonatal death the incidence rate is per 1000 pregnancies, the hazard ratio is a relative risk, and the adjusted risk difference is per 1000 pregnancies.

[c] Stabilized inverse probability weights were used to adjust for differences between exposure groups.

[d] Data are suppressed for counts of 5 or less.

# Come gestiamo la paziente?

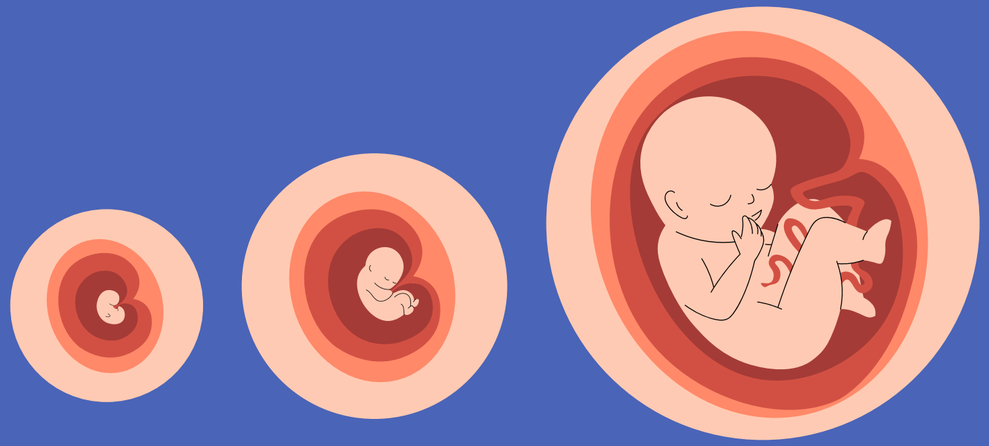
1. Ripe[illegible] un esame di [illegible] imaging per l'[illegible] degli [illegible]
2. Prescriviamo propranololo dal momento che in passato era stato efficace
3. Lasciamo solo magnesio aspettando che superi il primo trimestre e migliori spontaneamente

# Decision making challenges

No categorized guidance: "Provide prescribers with clinically relevant data that they can use in their decision making processes"

- Package inserts state use in pregnancy not recommended unless "benefit outweighs risk". How do we know?
- Drugs not tested on pregnant people
- Population based studies don't account for
  - Unusual circumstances
  - Contributions from individual risk factors
  - Frequency of use
  - Combinations of medications
  - Often: confounding by indication
- There are risks associated with undertreatment or lack of treatment
  - Disability
  - Maternal mental health

# Profilassi in gravidanza



**Integratori: magnesio (400-800 mg/die), riboflavina (400 mg/die) sicuri**

## Betabloccanti

- moderatamente sicuri (**labetalolo e metoprololo**);
- possibili effetti sul feto: bradicardia, ipotensione, ipoglicemia, ridotta crescita fetale (soprattutto propranololo e atenololo)

## CCB, ACE-I e ARB

- ACE-I, ARB controindicati; **CCB** uso possible (ipotens., bardic., etc)

## Antidepressivi

- **amitriptilina** basse dosi moderatamente sicura nel II trimestre
- possibili effetti: sedazione, astinenza neonatale
- Venlafaxina: pochi dati, non indicata

## Antiepilettici

- Topiramato e Ac. valproico: controindicati (teratogeni)

## **Onabotulinum toxinA** (Botox)

- dati in crescita, probabilmente sicuro (non passa la placenta)

## Anti-CGRP (R)

- Anticorpi monoclonali: controindicati (pochi dati; per ora non EC)
- Gepanti: controindicati (dati insufficienti)

**+ Periferal nerve blocks**

**Table 1** | Safety of commonly used antimigraine medications over the course of pregnancy and during lactation

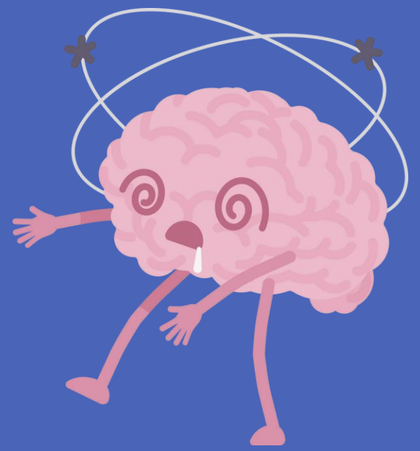
| Medication | Close to conception | First trimester | Second trimester and early third trimester | Late third trimester | During lactation |
|---|---|---|---|---|---|
| *Preventive treatment* | | | | | |
| β-blockers: metoprolol, propranolol | No evidence of increased fetal or maternal risk | Occasional reports of increased risk of some malformations, but causality not established<br>In general, no notable teratogenic effects demonstrated | Risk of adverse effects in the fetus, for example bradycardia | Risk of adverse effects in the newborn infant, for example bradycardia, hypotension and hypoglycaemia | Adverse effects in the infant are unlikely |
| Tricyclic antidepressants: amitriptyline | No evidence of increased fetal or maternal risk | Few data exist; no evidence for teratogenic effects for tricyclic antidepressants in general | Very few data exist; increased risk of pre-eclampsia in one study | Adverse effects and withdrawal symptoms in the newborn infant cannot be excluded | Low excretion in milk, but few data available<br>Impaired elimination in premature and newborn infants might cause accumulation |
| Antiepileptics: valproate | Increased risk of neural tube defects in the fetus | Increased risk of a variety of malformations | Risk of unfavourable long-term neurodevelopmental effects | Risk of unfavourable long-term neurodevelopmental effects | No risk for the breastfed infant, but an obvious risk of teratogenic effects if the mother should become pregnant again |
| Antiepileptics: topiramate | No data exist, but experience with other antiepileptic drugs suggests it is wise to avoid use | Increased risk of orofacial clefts | Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded | Few data exist, but unfavourable mental and neuromotor effects in the child cannot be excluded | Generally considered compatible with breastfeeding, but in premature and newborn infants, drug levels might accumulate to cause adverse effects |

# Prepregnancy treatment planning


+ cefaly

- **No evidence to suggest need for long withdrawal periods from oral medications prior to pregnancy**
  - Onabotulinum toxin A and CGRP mAbs should be stopped 3-5 months in advance
- **Make an acute treatment plan**
  - Most OBs don't see patients until ~8-10 weeks
- **Lifestyle optimization, start behavioral treatments**
  - Sleep, hydration, diet, biofeedback or relaxation practice
  - Acupuncture, physical treatments (craniosacral, massage)
- **Reassure patient of ongoing treatment relationship**

# Terapia d'attacco in gravidanza



**Paracetamolo (600-1000 mg) sicuro**

## Metoclopramide

- uso accessuale, considerata sicura

## Aspirina e FANS (ibuprofene, etc)

- I trimestre: aumento del rischio di aborto
- **II trimestre prima della 20a settimana**: considerati una seconda linea sicura
- > 20a settimana: rischio problemi renali feto

## Triptani

- **Sumatriptan, rizatriptan e naratriptan** generalmente considerati sicuri
- possibili effetti di vasocostrizione a livello uteroplancentare (I trimestre)

## Gepanti e ditani

- Controindicati: dati insufficienti

## Combinati

- Paracetamolo + oppioidi: controindicati (depressione respiratoria, astinenza)
- + Caffeina: non raccomandati, uso limitato

**Table 1** | Safety of commonly used antimigraine medications over the course of pregnancy and during lactation

| Medication | Close to conception | First trimester | Second trimester and early third trimester | Late third trimester | During lactation |
|---|---|---|---|---|---|
| *Acute treatment** | | | | | |
| Paracetamol | Considered safe | Considered safe | Considered safe | Considered safe | Considered safe |
| Sumatriptan | No evidence of increased fetal or maternal risk | No evidence of increased risk of malformations | No evidence of increased fetal or maternal risk | No evidence of increased fetal or maternal risk | Considered safe |
| Other triptans | No evidence of increased fetal or maternal risk, but data are limited | No clear evidence of malformations, but data are limited | No evidence of increased fetal or maternal risk | No evidence of increased fetal or maternal risk | Most triptans are probably compatible with breastfeeding |
| NSAIDs: ibuprofen, diclofenac, naproxen | Possibly increased risk of miscarriage | Possibly increased risk of malformations | Single doses considered safe in second trimester; occasional use of single doses up to week 32 in the third trimester should not pose any risk to the fetus | Risk of harmful fetal and maternal effects if used after week 32 | Generally compatible with breastfeeding, with ibuprofen being the drug of choice |

# Come gestiamo la paziente?

**Wait and see...**
Massaggio cervicale
Magnesio*B2
Neuromodulazione.
Paracetamolo + metoclopramide.

Nel secondo e terzo trimestre la paziente migliora e non presenta attacchi di cefalea.

# Controllo dopo il parto

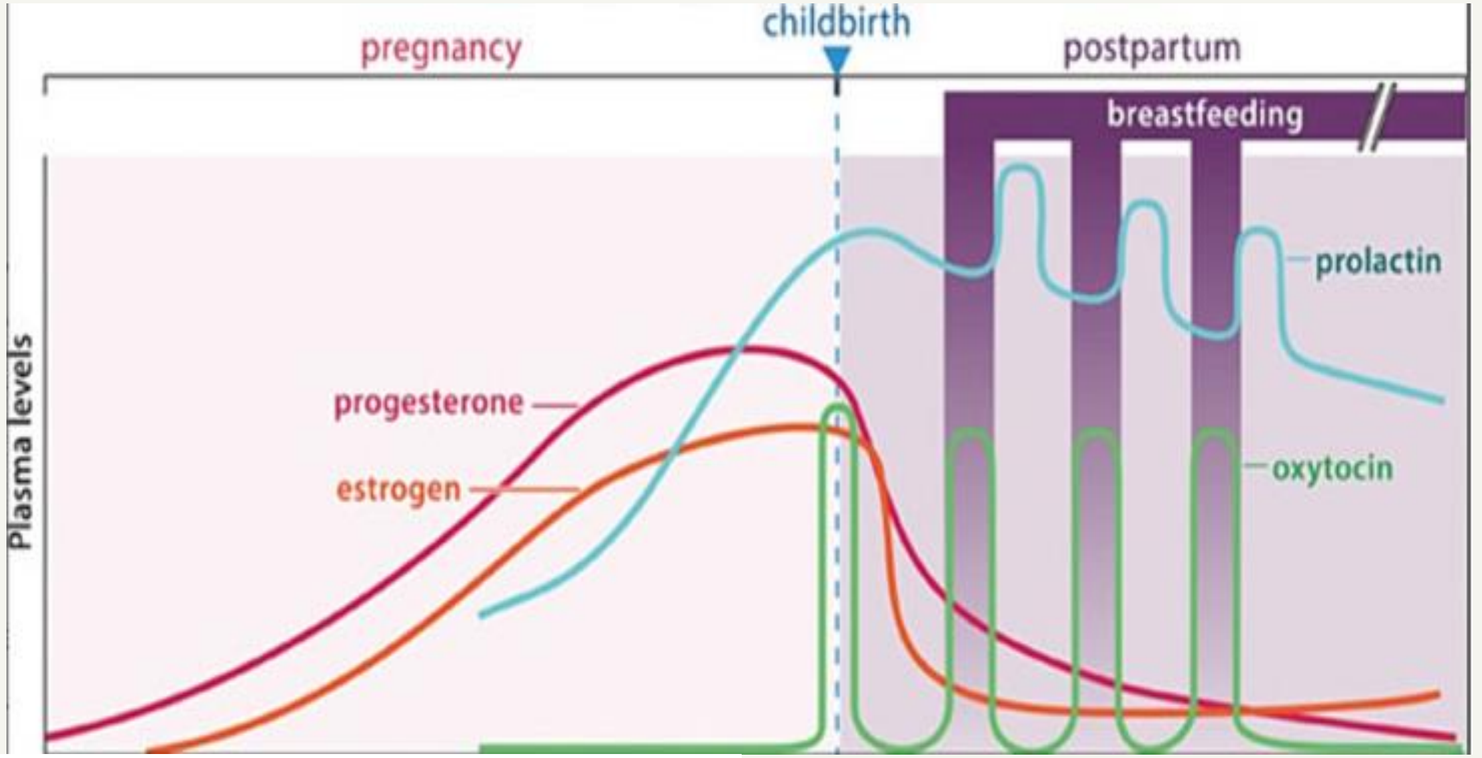
**Laura torna in visita 2 mesi dopo il parto (sta allattando):**

- Parto naturale in assenza di complicanze, PA nella norma
- Nuovo aumento della cefalea a 7-8 giorni al mese, caratteristiche abituali
- Scarsa risposta dal paracetamolo

# Come gestiamo la paziente?

1. Ripetiamo un esame di neuroimaging per il monitoraggio degli aneurismi
2. Prescriviamo propranololo dal momento che in passato era stato efficace
3. Lasciamo semplicemente maturare aspettando che regrediscano spontaneamente

# Emicrania dopo il parto




- 1/3 of women with migraine have headache in 1st week; 1/2 in 1st month
- Migraine recurrence ↑ by:
  - Falling estrogen levels
  - Sleep deprivation/interruption
  - Emotional stress
  - Dehydration/changes in eating patterns

# Terapia durante l'allattamento

**Profilassi**

- **Betabloccanti** (metoprololo, propranololo): basse dosi nel latte materno, prima linea
- **Antidepressivi:** amitriptilina escreta in minima parte nel latte materno, pochi dati su EC; seconda linea. In alternativa venlafaxina e duloxetina (bassi livelli nel latte materno)
- **Onabotulinum toxin A** considerata sicura
- **Anti-CGRP(R)**: pochi dati → mAbs e gepanti (atogepant, Rimegepant) possibilmente sicuri (escreti in minima parte nel latte materno; poco assorbiti dal neonato.

**Terapia d'attacco**

- **Paracetamolo**: sicuro, prima linea
- **FANS**: ibuprofene, naprossene, indometacina (bassissime dosi nel latte materno, seconda linea)
- combinazioni di paracetamolo + ibuprofene
- **Triptani**: sumatriptan e eletriptan considerati sicuri (seconda linea, < 0.5% nel latte materno); evitare l'allattamento nelle 12 h successive (tirare prima il latte)

# Come gestiamo la paziente?

Prescriviamo **propranololo** e terapia d’attacco con **ibuprofene** (anche associato a paracetamolo).

Laura torna al controllo dopo 4 mesi e la cefalea è migliorata (3-4 attacchi al mese).

| | Preconception | 1st trimester | 2nd trimester and early 3rd trimester | Late 3rd trimester | Breastfeeding |
|---|---|---|---|---|---|
| Propranolol | | | | bradycardia+ hypothermia, hypotension | |
| Amitriptyline | | No certain adverse effects | | | Little data |
| Candesartan Lisinopril | | Fetal renin angiotensin system blocker syndrome | | | Low levels in milk renal function? |
| Topiramate Valproate | | Growht restriction (18 %), malformations (4-9 %), autism spectrum disorder (3-4 %), intellectual disability (2-3 %) | | | TPX: Diarrhea, sedation, irritability |
| CGRP (R) antibodies | | Little human data. Theoretical adverse effects on placentation and pregnancy hypertension | | | Little data |
| Rimegepant | | No human data. Preclinical studies: no certain adverse effects | | | <1% in b.milk |
| Atogepant | | The human data available is reassuring | | | |
| Bot toxin A | | The human data available is reassuring | | | |

| | |
|---|---|
| Green | Considered safe |
| Light green | Probably safe, limited data |
| Yellow | Increased risk of harmful effects cannot be excluded |
| Red | Contraindicated |

**Spiteri JA** et al. *Expert Rev Clin Pharmacol*. 2023. **Bjork MH** et al. *Eur J Neurol*. 2021. **Bjork et al. JAMA Neurology 2022. Borthen** et al.. *Eur J Obstet Gynecol Reprod Biol* 2009 **Bullo** et al.. *Hypertension* 2012. **SPC** Aimovig, Ajovy, Emgality, Vyepti, Vydura.
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NorHead

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