Headache in Pregnancy

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I have no conflicts of interest to disclose.

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Objectives

1. Understand frequency of headache in pregnancy
2. Differentiate conditions presenting with headache
3. Identify red flags for serious conditions
4. Briefly review treatments of primary headache in pregnancy

How common is headache?

"An almost universal human experience"

- Lifetime prevalence = 96%
- Female > Male
- $14 billion US direct/indirect economic burden
- Most common reason outpatient Neurology consultation
- Globally 7th leading cause of years lived with disability

Rizzoli et al 2018
Hu et al 1999

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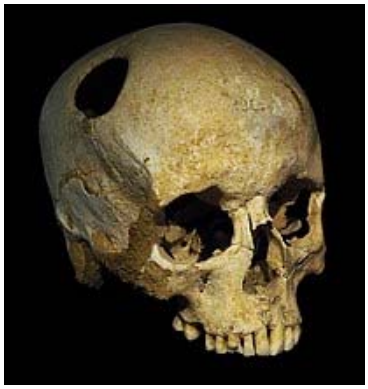
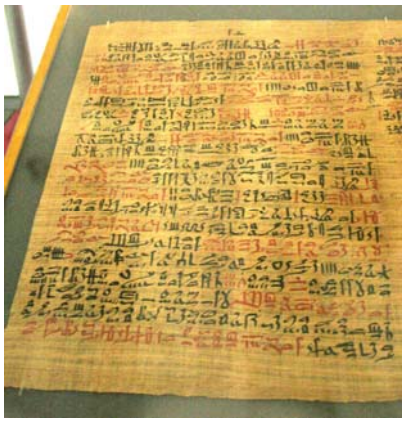
How common is headache?



Neolithic trepanation
c. 6,000 BCE

Oldest surgical procedure with archaeological evidence



Ebers Papyrus
c. 1,500 BCE

Egyptian medical text documented neuralgia, headache symptoms

Aretaeus of Cappadocia
c. 150 CE

Greek physician codified the earliest known classification of headache

How common is headache *in pregnancy*?

- HeadHUNT cross-sectional study, Norway
- N=9,760 women
- Age<40

- Headache prevalence:
- Nonpreg: 58%
- Preg, Nullip (G1): 40%
- Preg, Multip (G2+): 54%

N	Headache			
9281	n	%	OR	95% CI
Not pregnant (8731)	5054	57.9	1 (ref.)	
Nulliparous (143)	56	39.2	0.5 (0.5)	0.4-0.7 (0.3-0.7)
Primi- and multiparous (407)	222	54.5	0.8 (0.9)	0.7-1.0 (0.7-1.0)
First trimester (205)	106	51.7	0.8 (0.8)	0.6-1.0 (0.6-1.1)
Second trimester (152)	90	59.2	1.0 (1.1)	0.7-1.4 (0.8-1.5)
Third trimester (122)	45	36.9	0.4 (0.4)	0.3-0.6 (0.3-0.6)

Aegidius et al 2009

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How common is headache *in pregnancy*?

- HeadHUNT cross-sectional study, Norway
- N=9,760 women
- Age<40

- Headache prevalence:
- T1: 52%
- T2: 59%
- **T3: 37%**

N	Headache			
9281	n	%	OR	95% CI
Not pregnant (8731)	5054	57.9	1 (ref.)	
Nulliparous (143)	56	39.2	0.5 (0.5)	0.4-0.7 (0.3-0.7)
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Aegidius et al 2009

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Author	Study design	Sample size	Improvement or remission (%)	Unchanged (%)	Worsening (%)
Migraine without aura					
Granella et al. [8]	R	571	67.3	29.2	3.5
Scharff et al. [9]	P	19	56.7	36.6	6.7
Maggioni et al. [5]	R	81	89.5	7.7	2.5
Marcus et al. [10]	P	49	40.8	51	8.2
Granella et al. [11]	R	200	76.8	22.2	1
Mattsson [12]	R	728	81.4	17.6	1
Sances et al. [13]	P	47	87.2	12.8	0
Kelman [14]	R	504	38.2	27.8	34
Ertresvåg et al. [15]	P	410	65.9	19.8	14.4
Melhado et al. [16]	P	737	65	26.1	8.9
Summary		3346	66.9	25.8	8
Migraine with aura					
Maggioni et al. [5]	R	12	83.4	16.6	0
Granella et al. [11]	R	100	43.6	48.7	7.7
Mattsson [12]	R	728	78.3	4.3	17.4
Summary		840	68.4	23.2	8.4
Tension-type Headache					
Maggioni et al. [5]	R	33	82,1	17,9	0
Melhado et al. [16]	P	112	N/A (≈ 60)	N/A (≈ 35)	N/A (≈ 5)
Summary		145	–	–	–
Cluster Headache					
Van Vliet et al. [31]	R	53	69,9	20,7	9,4

Pregnancy effects on headache

Migraine, no aura
Better 67%
Same 26%
Worse 8%

Improvement for 1/2 to 2/3 in pregnancy

Migraine + aura
Better 68%
Same 23%
Worse 8%

Tension-type
Better most
Worse few

Cluster
Better most
Worse few

Negro et al 2017

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Headache course in pregnancy

- MIGRA: Prospective cohort study in Norway
- N=1,273
- Headache frequency in pregnancy, postpartum

- No headache pre-pregnancy → 1st headache in pregnancy: **6%**
- Headaches pre-pregnancy → No headache in pregnancy: **15%**

Volden Kvisvik et al 2011

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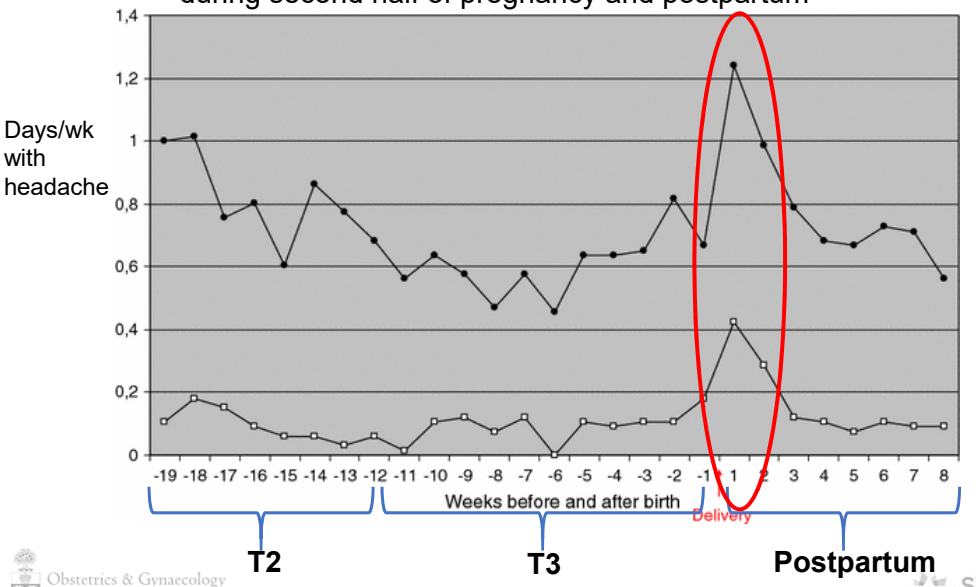
Frequency of headache (**black** line) and migraine (**grey**) during second half of pregnancy and postpartum



- **Lower during T3**
- **Higher immediately postpartum**
- **Gradual return to prepreg baseline**

Volden Kvisvik et al 2011

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Confounding…

The Myth

The Reality

Take home points

1. Headache is very common (during pregnancy and in general)
2. Many experience overall reduction of headache frequency in pregnancy
3. Lowest headache frequency in 3rd trimester
4. Highest headache frequency 1st trimester / immediately postpartum

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Headache differential diagnosis

I. Primary headache disorders
   1. Migraine
   2. Tension-type headache
   3. Trigeminal autonomic cephalalgias
   4. Others

II. Secondary headache
   5. Trauma
   6. Vascular disorder
   7. Non-vascular intracranial disorder
   8. Substance use / withdrawal
   9. Infection
   10. Homeostasis disorder
   11. Pain attributed to head/neck disorder
   12. Psychiatric disorder

III. Neuropathies and facial pain

Underlying problem is a **headache disorder**
"Your headache is 'just' a headache"

Underlying problem is **something else**, and headache is a ***symptom***
"Your headache is not just a headache"

Other causes of head/neck/face pain
"Your headache is not a headache"

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ICHD 3rd ed. Cephalalgia 2018.

Detailed Differential Dx!

For example, under "**migraine**"…

Hierarchical diagnostic classification system

Goal is not to diagnose every headache disorder

Goal is to identify **risk factors**, and **serious life-threatening conditions**

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ICHD-3 code	Diagnosis
1.	**Migraine**
1.1	Migraine without aura
1.2	Migraine with aura
1.2.1	Migraine with typical aura
1.2.1.1	Typical aura with headache
1.2.1.2	Typical aura without headache
1.2.2	Migraine with brainstem aura
1.2.3	Hemiplegic migraine
1.2.3.1	Familial hemiplegic migraine (FHM)
1.2.3.1.1	Familial hemiplegic migraine type 1 (FHM1)
1.2.3.1.2	Familial hemiplegic migraine type 2 (FHM2)
1.2.3.1.3	Familial hemiplegic migraine type 3 (FHM3)
1.2.3.1.4	Familial hemiplegic migraine, other loci
1.2.3.2	Sporadic hemiplegic migraine (SHM)
1.2.4	Retinal migraine
1.3	Chronic migraine
1.4	Complications of migraine
1.4.1	Status migrainosus
1.4.2	Persistent aura without infarction
1.4.3	Migrainous infarction
1.4.4	Migraine aura-triggered seizure
1.5	Probable migraine
1.5.1	Probable migraine without aura
1.5.2	Probable migraine with aura
1.6	Episodic syndromes that may be associated with migraine
1.6.1	Recurrent gastrointestinal disturbance
1.6.1.1	Cyclical vomiting syndrome
1.6.1.2	Abdominal migraine
1.6.2	Benign paroxysmal vertigo
1.6.3	Benign paroxysmal torticollis

Headache differential diagnosis—*what not to miss*

I. Primary headache disorders
   1. Migraine
   2. Tension-type headache
   3. Trigeminal autonomic cephalalgias
   4. Others

II. Secondary headache
   5. Trauma
   6. Vascular disorder
   7. Non-vascular intracranial disorder
   8. Substance use / withdrawal
   9. Infection
   10. Homeostasis disorder
   11. Pain attributed to head/neck disorder
   12. Psychiatric disorder

Migraine is a **risk factor**:
- Preeclampsia / hypertensive disorders
- Ischaemic stroke
- Hemorrhagic stroke
- Preterm birth?

Serious / potentially life-threatening conditions

ICHD 3rd ed. 2018
Negro et al 2017
Wabnitz & Bushnell 2015

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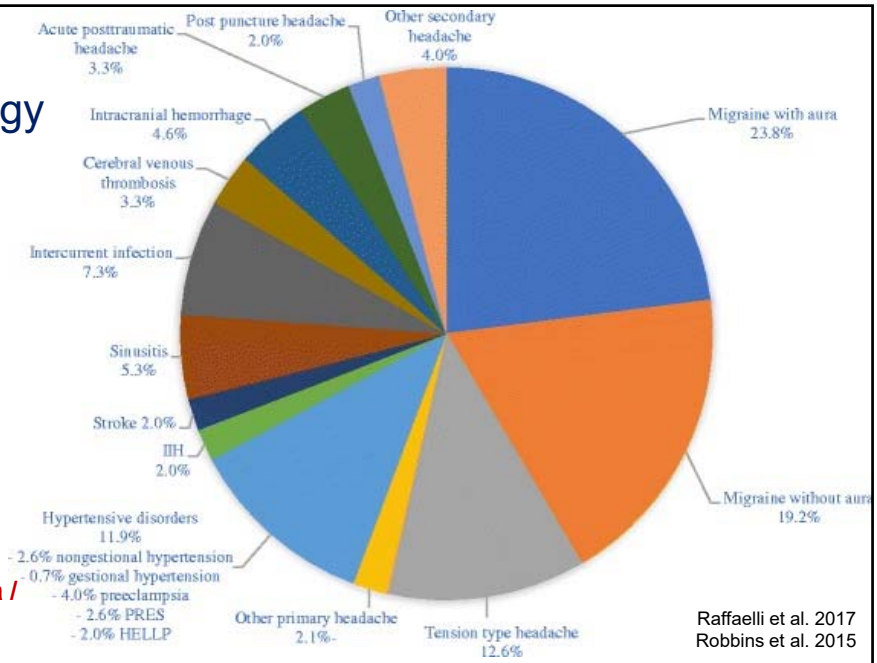
Headache etiology

Of all acute headaches in pregnancy:
Primary headache: 60%
Secondary headache: 40%
- **Hypertensive 12%**
- Infection 7%
- Hemorrhage 5%
- CVT, trauma 3%
- Stroke, IIH, post-dural 2%

Up to **half** of secondary headaches are **preeclampsia / hypertensive disorders**



Raffaelli et al. 2017
Robbins et al. 2015

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Central venous thrombosis (CVT)

- Headache 80-90%, most frequent first symptom
- Non-specific, diffuse, progressive, severe
- Other signs 90% of cases:
  - Focal neurological signs, seizure
  - Intracranial hypertension: papilledema, nausea
  - Subacute encephalopathy
  - Cavernous sinus syndrome

    ophthalmoplegia (CN III, IV, VI), autonomic dysfunction (Horner syndrome), trigeminal sensory loss (CN V1-V2)

ICHD 3rd ed. 2018
Negro et al 2017

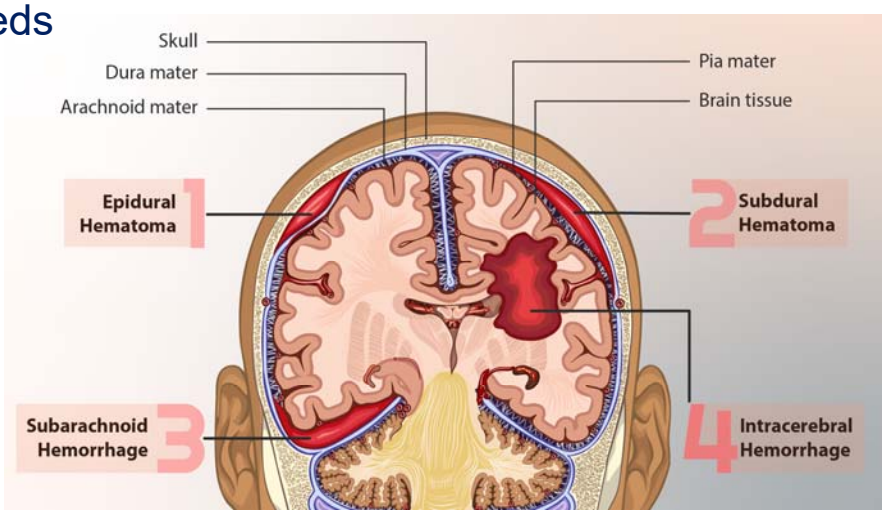
Intracranial bleeds

Hemorrhagic stroke:

- SAH: rapid onset, severe, thunderclap
- Intracerebral: location-specific neuro deficits

Trauma:

- Subdural: usually traumatic
- Epidural: awareness → progressive loss of consciousness



ICHD 3rd ed. 2018
Negro et al 2017

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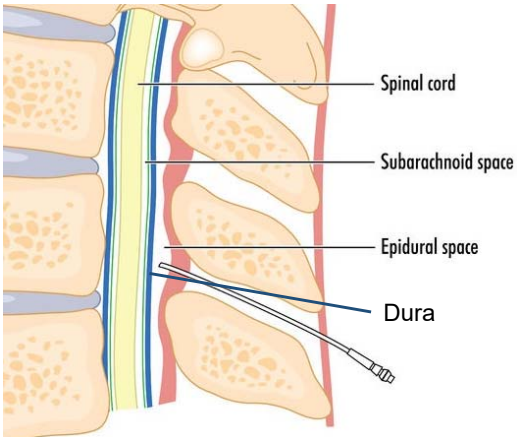
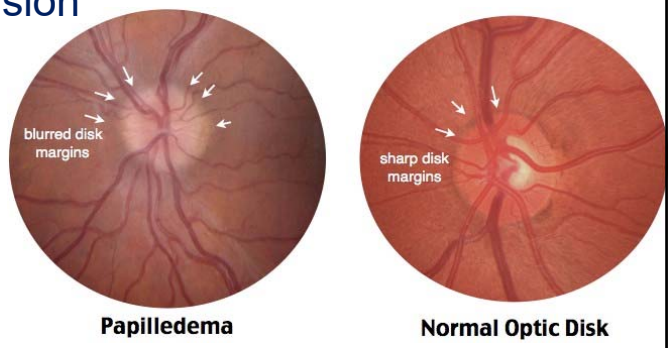
Intracranial hypo / hypertension



Postdural puncture headache

- Postural: worse with sit/stand, improves lying-down



Idiopathic intracranial hypertension

- Obesity
- Worse with Valsalva
- Tinnitus, visual deficits, CN VI palsy, papilledema

#1 Red Flag Headache in Pregnancy?

PREECLAMPSIA

ECLAMPSIA

HELLP

Preeclampsia / Eclampsia / HELLP

- **Most common prodromal symptom** preceding eclampsia, >75%
- Headache temporally associated with Dx
- Worsens as conditions worsens, improves with resolution
- Features:
  - Bilateral
  - Pulsating
  - Aggravated by physical activity

- Sign of cortical dysfunction / CNS injury?

Gudu 2017
ICHD 3rd ed. 2018

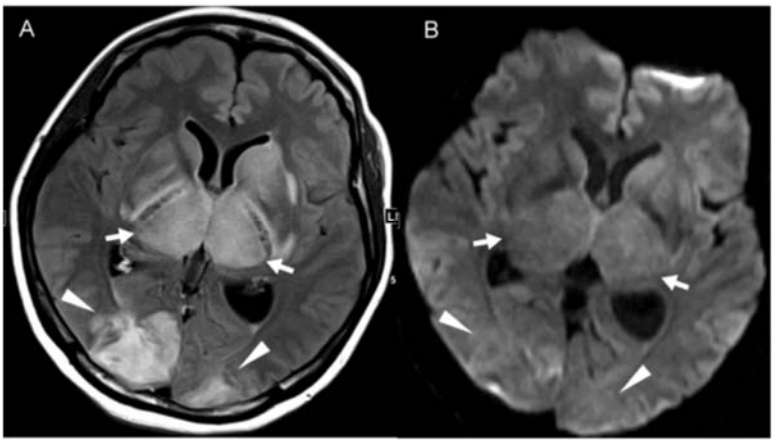
Posterior **R**eversible **E**ncephalopathy **S**yndrome

- Neuro-radiological syndrome
- Headache: occipital, bilateral, dull or severe
- Vision loss, nausea/vomiting, seizure
- White matter vasogenic edema, occipital / parietal lobes
- Associated conditions: **preeclampsia**, infection, hypertension, autoimmune disease

Chao et al 2020
Negro et al 2017

PRES—more common than we think?

- Brain MRI, severe preeclampsia patients: 15/18 (83%) PRES
- White matter changes in occipital, parietal lobes



35 y/o at 37 wk, HELLP syndrome. Hyperintensities over basal ganglia (arrows) and occipital lobe (arrowheads) with FLAIR (A), minimal hyperintensities with DWI (B)

Chao et al. BMC Preg Childbirth 2020

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Red Flags *PREGNANT HA*

+

- First/Worst
- Change in pattern
- **Longer duration***

***most common red flag** for those with pre-existing headache disorder

	Red flag	Associated conditions
P	Proteinuria	Preeclampsia/eclampsia
R	Rapid onset (thunderclap)	SAH, ICH, RCVS, pituitary apoplexy, intracranial hypotension
E	Elevated BP or temperature	Preeclampsia/eclampsia, PRES, RCVS, infection
G	Gestational age 3rd trimester	Preeclampsia/eclampsia, PRES, CVST, ICH
N	Neurological signs/symptoms	Preeclampsia/eclampsia (seizures), PRES (seizures, visual disturbance), RCVS, SAH, CVST, pituitary apoplexy (visual or focal neurological), space-occupying lesion, IIH
A	Altered level of consciousness	Preeclampsia/eclampsia, PRES, CVST, ICH, pituitary apoplexy, space-occupying lesion
N	No headache history, or history of a secondary headache disorder	Any
T	Thrombocytopenia/thrombocytosis	Preeclampsia/eclampsia, CVST
H	High liver function tests or CRP	Preeclampsia/eclampsia, CVST (CRP)
A	Agonizingly severe	Any

Sandoe & Lay. Curr Neurol Neurosci Rep. 2019;19:27

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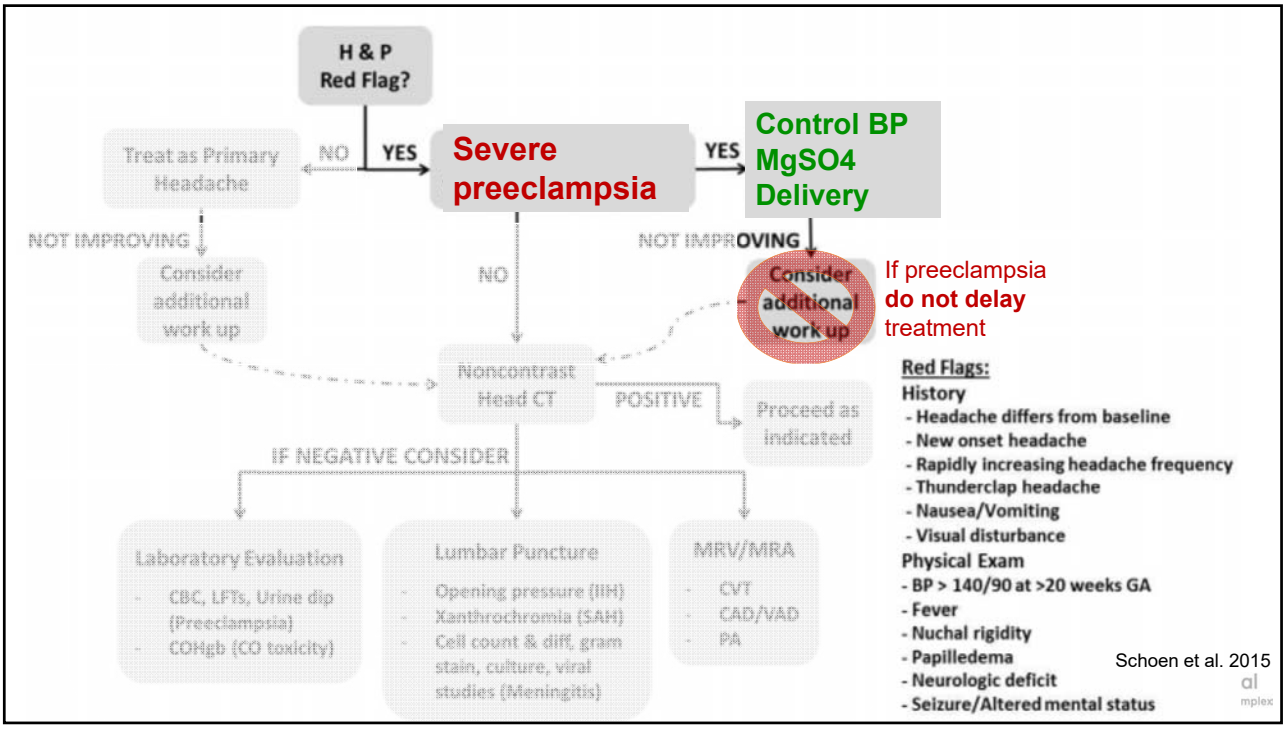
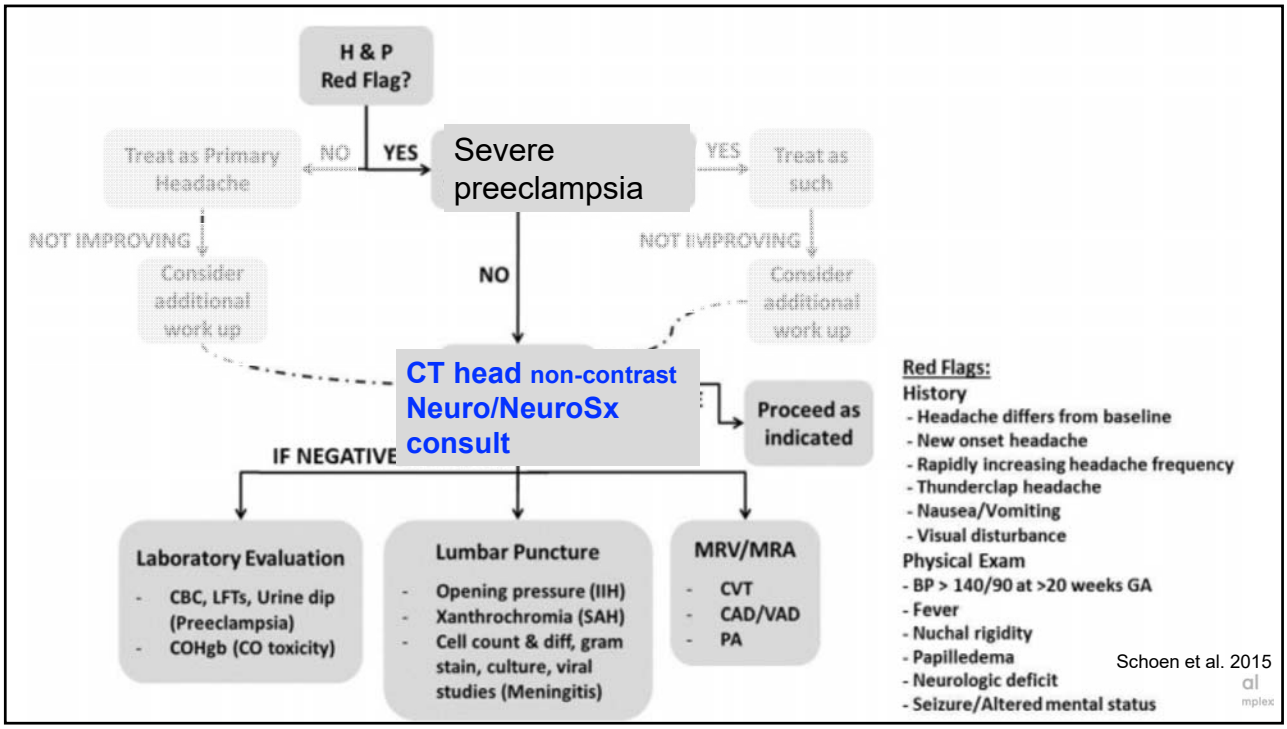
Severe headache: Initial management

- Targeted history
  - Red flags
  - Associated symptoms
- BP, vitals, temperature, bloodwork
  - Severe preeclampsia → Antihypertensives + MgSO4 + ***Delivery***
- Monitored setting
- Fetal assessment
  - NST, BPP
- Neurological workup
  - Imaging
  - Lumbar puncture?
  - *Phone a friend:* Neurology / Neurosurgery consult



Schoen et al. 2015



Take home points

1. Acute headache in pregnancy is more often a serious condition than in same-aged non-pregnant people
2. Preeclampsia is a common cause of acute headache
3. Severe headache not attributable to preeclampsia should prompt neuroimaging (CT head, non contrast)
4. Neurology / Neurosurgery consult should be considered: severe, unclear diagnosis, for treatment

Primary headache disorders: Treatment in pregnancy

1. Non-pharmacological
   - Environmental
   - Hydration
   - RMT/physio
   - Acupuncture
   - Neuromodulation
2. Medication: acute treatment
3. Medication: prophylaxis

springTMS	Single-pulse transcranial magnetic stimulation		Lipton et al. 2010 (53)	*n* = 164 Episodic migraine	Acute
gammaCore	Transcutaneous vagus nerve stimulator		Silberstein et al. 2014 (49)	*n* = 59 Chronic migraine	Preventive
Cefaly	Transcutaneous supraorbital stimulation		Schoenen et al. 2013 (40)	*n* = 67 Chronic migraine	Preventive/ Acute
tDCS	Anodal transcranial direct current stimulation		Auvichayapat et al. 2012 (58)	*n* = 37 Episodic migraine	Preventive

Puledda & Shields Neurotherapeutics 2018.

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Pharmacological options

Medication	Safety	Notes
Acetaminophen (Tylenol)	Safe in pregnancy	1st line, careful with prolonged use
NSAIDS	T1? T2: safe T3: premature closure of DA	
Caffeine	Safe in lower doses	
Triptans (eg. sumatriptan)	Safe in pregnancy	Serotonin (5HT) agonists Sumatriptan: most preg data
β-blockers (eg. propranolol, metoprolol)	Safe in pregnancy. FGR (some, e.g. atenolol)	1st line prophylaxis
Metoclopramide	Safe in pregnancy	Centrally-acting (D2 antagonist), treats nausea/Vx
TCA (eg. amytriptiline)	Safe, neonatal withdrawal	2nd line prophylaxis
Antiepileptic drugs (some)	Safe (levetiracetam, lamotrigine) Teratogenic: valproic acid	Not first line agents

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Ephross & Sinclair 2014
Negro 2017

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Pharmacological contraindications

Medication	Safety	Notes
ACE inhibitors, ARBs	Fetal growth restriction, oligohydramnios, teratogenicity	Don't use!
Ergots / Ergot alkaloids	Uterotonic effects, fetal distress	Don't use!
Antiepileptic drugs (some)	Valproic acid	Don't use!

Ephross & Sinclair 2014
Negro 2017

What about Botox?

Medication	Safety	Notes
Botulinum toxin A injections (Botox)	Minimal data Probably safe	No systemic exposure with correct injection technique

Wong et al 2020

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Metoclopramide: MAD Headache Study

- Migraine in pregnancy, failed acetaminophen
- RCT, N=70
  - Codeine 30mg PO
  - Metoclopramide 10mg IV + Diphenhydramine 25mg IV (MAD)
- MAD: Better pain scores at 30min, 1h, 12h
- MAD: Faster relief, 20 mins vs 35 mins

Childress et al. 2018

Triptans

Variable	Sumatriptan	Naratriptan	Sumatriptan/ Naproxen Sodium	Total Exposures
Total pregnancies enrolled, *n*†	810	92	9	911‡
Closed with known outcomes†	617 (76.2%)	57 (62.0%)	6 (67.7%)	680 (74.6%)
Loss to follow up	193 (23.8%)	35 (38.0%)	3 (33.3%)	231 (25.4%)‡
Reasons loss to follow up, %	193	35	3	231
No response from reporting HCP	111 (57.5%)	22 (62.9%)	2 (67.7%)	135 (58.4%)
Patient did not remain under the reporting HCP's care	39 (20.2%)	8 (22.9%)	0 (0.0%)	47 (20.3%)
Reporter unable to identify patient at follow up	21 (10.9%)	4 (11.4%)	1 (33.3%)	26 (11.3%)
Reporting HCP left practice and was not contactable	13 (6.7%)	1 (2.9%)	0 (0.0%)	14 (6.1%)
Other	9 (4.7%)	0 (0.0%)	0 (0.0%)	9 (3.9%)

- Serotonin (5HT) agonists
- Longest safety data for sumatriptan: 16 year registry study
  - N=680 pregnancies; exposure to sumatriptan: 626
- No pattern of fetal congenital anomalies
- Teratogenicity rate ≈ population baseline

Ephross & Sinclair. *Headache* 2014;54:1158-1172

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Take home points

1. Non-pharmacologic treatments can be effective in reducing headache symptoms
2. Safe medication options exist for headache treatment, prophylaxis in pregnancy

Thank you!

1. Headache is very common
2. Many experience overall reduction of headache frequency
3. Lowest headache frequency in 3rd trimester; highest in 1st / immediately postpartum
4. Acute headache in pregnancy often represents a serious condition
5. Preeclampsia: most common cause of severe acute headache
6. Severe headache (non-preeclampsia) → neuroimaging
7. Get a Neurology / Neurosurgery consult: severe / Dx? / Tx
8. Non-pharmacologic treatments can be effective for primary headache
9. Safe medication options exist for headache treatment, prophylaxis

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