Prolactinomas and pregnancy

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Severe headache in pregnancy - etiologies

Chief complaint

27 yo, with PMC @ 31+3w, BCBA twins
Complaints of severe rt parietal and retrobulbar headaches
Conditions that may cause episodic headaches:

- Migraine
- Cluster headaches
- Tension headache

May be acute and severe at presentation

Usually episodic and chronic
1. **Cerebrovascular disorders**

- Subarachnoid hemorrhage
- Intracerebral hemorrhage
- Ischemic infarction
- Cerebral venous thrombosis
- Subdural hematoma

Conditions that may cause severe non-episodic headaches:

Severe headaches often lead to prompt imaging studies and diagnosis.
2. Intracranial lesions

- Brain tumors
- Pituitary adenomas
- A-V malformations

3. Hypertensive disorders

- PIH
- Preeclampsia-eclampsia
- HELLP

4. Increased intracranial pressure

- Pseudotumor cerebri
- Acute hydrocephalus
5. Head trauma

Domestic
Accidental

6. Infections

Meningitis
Encephalitis
Radiculitis
Sinusitis
Viral infections (CMV, Influenza)
Pulpitis

7. Systemic

SLE
TTP
Hypoxia
Hypoglycemia
Bell’s palsy
7. Drugs

Pressolat
Progesterone

8. Metabolic

Hypoglycemia
Hyponatremia
Hypokalemia
Thyroid storm

8. Inflammatory

CNS Lupus
MIND VT

Metabolic
Infectious/inflammatory
Neoplasm
Drug
Vascular
Trauma
Sudden onset
Neurologic signs and symptoms
Change in the level of consciousness
Older >40y
Meningeal signs
Recent trauma
Hx of hypertension
Hx of endocrine disease

Mandate further assessment:
neurological, endocrine, lab, imaging
Chief complaint

27 yo, with PMC @ 31+3w, BCBA twins
Complaints of severe rt parietal and retrobulbar headaches

Medical background

Healthy until 24yo
Headaches, galactorrhea and irregular menses
Hyperprolactinemia up 6000mIU/L (285 ng/dl)
MRI: pituitary microadenoma – 3mm
Started on bromocriptine
Moved to cabergoline due to GI upset

Prolactin levels decreased to 1200 (57 ng/dl)
Galactorrhea ceased, headaches lessened
Menses still irregular
Current pregnancy

Cessation of Dostinex followed by IVF due to unovulation

Resulted in BCBA twins pregnancy

NT, UST1, UST2 - normal

On admission: PMC, 1.5cm dilated, Vx-Br, 1400/1600

Conventional treatment with hydration, betamethasone, nifedipine

At the HRP unit

4th post-admission day:

Complaints of severe headache on the right side. Parietal and retrobulbar

Increasing in intensity. Not alleviated by medications

No visual disturbances, no nausea or vomiting
**Physical and labs**

- Normal vital signs including BP and temperature
- Normal general physical examination
- Normal ophthalmological examination including – fundus and visual fields
- No neurological deficits
- Normal HGB, lytes, chemistry, urine, PRL=1010ng/dl (21000mIU/L)

**Imaging**

- MRI showed a pituitary macroadenoma 11mm in diameter
- Engulfing the rt cavernous sinus
- Not pressing on the optic chiasm
- An area suspected of a small hemorrhage in the middle (apoplexy??)
Consultations

Endocrinology consult:

Tests of pituitary function including: TSH, Free cortisol, ACTH test, lytes, PRL

Start bromocriptine 2.5mg per day with increments of 2.5mg

Neurosurgery consult:

Headaches related to dural pressure around the cavernous sinus

No signs of neurological deficits

No signs of pressure on the optic chiasm

No indication to intervene immediately

Delivery should be timed by obstetrical indications
Working diagnosis

Pituitary adenoma increasing in size
Apoplexy?

Issued to be addressed

Do prolactinomas increase in size during pregnancy?
Recommended follow up and management
The safety of the pharmacological treatment
What is apoplexy of tumor?
The effects of lactation on the course of the disease
The effects of pregnancy on the course of the disease
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**Gestational physiologic changes**

**Pituitary increases up to 136%**

Enlargement due to:

- lactotroph hyperplasia
- vascular congestion

Increase in serum prolactin levels up to 450 ng/ml (9450 mIU/L)
Prolactinomas and Pregnancy

Prevalence: 500 cases/1,000,000

Pituitary tumors: 10 to 15% of intracranial tumors

Classified as:
- microadenomas (diameter <10 mm)
- macroadenomas (>10 mm)

Microadenoma/Macroadenoma 3:1
Major symptoms:

- Headaches
- Galactorrhea
- Amenorrhea
- Visual disturbances

Prolactin-secreting adenomas (prolactinomas) are the most common

Account for 50% of all pituitary adenomas

Prolactinomas F/M – 4:1
Pregnancy and microprolactinoma’s growth

1979, Gemzell & Wang

Questionnaire sent to interested doctors

Symptoms of tumor enlargement in

4.7% with microprolactinomas

Questionable methodology
246 pts with microprolactinoma
Untreated during pregnancy
Symptoms of tumor enlargement - 1.6%
Asymptomatic enlargement by CT - 4.5%

More recent studies show similar results

Microprolactinomas do grow but the risk of symptoms is low

Macrophotactinomas growth during pregnancy

1979, Gemzell & Wang

Symptoms of tumor enlargement in 41% with macroprolactinomas


Symptoms related to tumor enlargement in 15.5%
Determinants of growth of macroprolactinomas during pregnancy

1. Tumors expanding outside sellar borders tend to grow

1986, Holmgren et al

2. No tumor enlargement in 14 patients treated with BRCP > 1y before pregnancy

3. The duration of BRCP Tx prior to conception may be a prognostic of tumor enlargement during pregnancy
Do prolactinomas increase in size during pregnancy?

**Recommended follow up and management**

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Management during pregnancy

MRI should be done before conception to:

- document tumor size
- serve as a baseline for comparison with MRIs done during pregnancy

Not enough safety data are available to recommend the routine use of DA during pregnancy.

The endocrine society recommend the **discontinuation of DAs** shortly after confirmation of pregnancy for microprolactinomas.
Follow-up plan during pregnancy - microprolactinomas

- Low risk of tumor growth
- Tx is effective
- No correlation between PRL elevation and clinical complications

- Discontinue DA's once pregnancy is confirmed
- Clinical assessment of tumor growth q 3 months
- PRL assessment usually is not required
- Further work-up (MRI) only with complaints suggesting tumor growth
- Educate pt for symptoms of enlargement
- Baseline visual field testing at the time of diagnosis
Who should be offered treatment?

Symptoms of tumor growth

Imaging showing compression of intracranial structures

Recommended treatment

Bromocriptine is very effective – drug of choice

Surgery for non-responders

Delivery for obstetrical indications
Follow-up plan during pregnancy- macroprolactinomas

Look for symptoms related to tumor enlargement q 1 month

Serum PRL does not add information

If tumor growth is suspected:

- imaging investigation (preferably MRI)
- neuro-ophtalmological examination
Continued bromocriptine treatment during pregnancy

BRCP is safe though is crosses the placenta

The risk of symptoms related to tumor enlargement >15%

This risk is lower in longer tx before pregnancy

Reinstituting BRCP with symptoms related to tumor enlargement is effective in most cases

Discontinue medication in macroadenomas:

Treated for >1y before getting pregnant

Presenting tumor restricted to sellar boundaries
Indications for surgical treatment during pregnancy

Bromocriptine and other DA are ineffective

Life threatening situations: brain compression

Acute and severe apoplexy
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Bromocriptine is an ergoline derivative and a dopamine D2 receptor agonist.

Taken during early pregnancy, the incidence of abortions, ectopic pregnancies, or congenital malformations is no higher than that in the general population. 


DA’s did not affect post-natal development.

Long-term follow-up to 9 years: bromocriptine did not cause detrimental effects on fetal outcomes in terms of physical development and psychomotor development.

Alternatives to bromocriptine

10% cannot tolerate BRCP

Nausea, headache and faintness (orthostatic hypotension)

Hallucinations in <1%

Dizziness, fatigue, nasal congestion

Side effects can be minimize by:

1. building tolerance by a smaller dose at bed time (1.25mg)

2. vaginal administration

Alternatives to BRCP are now available

- Cabergoline
- Quinagolide
Cabergoline

Higher affinity and selectivity for D2 dopamine receptors
Long duration of action
Allowing administration once or twice weekly
Better tolerability and patient compliance


No significant difference in the frequency of spontaneous abortion, premature delivery, multiple pregnancy, or neonatal malformations

Data of 12 years follow-up in the children born from mother treated with cabergoline showed no influence on their post-natal development
Quinagolide

- Long-lasting prolactin lowering effect
- Taken once daily and has better tolerability than bromocriptine
- Limited safety compared with bromocriptine
- No apparent adverse effects on pregnancy or fetal development in 200 pregnancies
Meanwhile....

Headaches worsen

Bromocriptine followed by nausea and vomiting

Bromocriptine discontinued, Cabergoline started

Repeated MRI due to susp apoplexy – no change

Neurosurgery and endocrinology consult:

No change of plans
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Pituitary Tumor Apoplexy

Clinical syndrome characterized by:

- sudden headache
- vomiting
- visual impairment
- meningismus
Caused by rapid enlargement of a pituitary adenoma

Usually due to hemorrhagic infarction of the tumor

Pituitary apoplexy is a clinical definition

Should be distinguished from ischemic changes in pituitary after prolonged hypotensive episodes e.g. Excessive postpartum bleeding: Sheehan’s syndrome
Around 5% apoplexy in pituitary adenomas

Mean age: 46.7 years

Null-cell adenomas have highest incidence of apoplexy

Size, apparently, does not matter
Signs and Symptoms

Headache 100% (often retro-orbital)
Nausea 80%
Reduction in visual field 71%
Ocular paresis 69%
Third nerve palsy 67%
Reduction in visual acuity 66%
Vomiting 57%
Photophobia 49%
Decreased level of consciousness 11%
Diagnosis

**Biochemical:**

- Gonadotropin deficiency 79%
- Hypocortisolism 76%
- Testosterone deficiency 73%
- TSH deficiency 50%
- Hyponatremia (<135) 44%

**Radiological:**

- CT scan revealed tumor in 93% and hemorrhage in 21%
- MRI revealed tumor in 100% and hemorrhage in 88%

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**Blood Test** | **Purpose**
---|---
PRL (w/ dilution) | diagnose prolactinoma; dilutions needed to correlate PRL level & tumor size for accurate diagnosis
IGF-I (reflects overall GH production) | diagnose acromegaly (randomly tested GH level may be normal)
ACTH | diagnose adrenal insufficiency; ACTH-dependent Cushing syndrome
cortisol (8 a.m.) | diagnose adrenal insufficiency; not adequate to diagnose Cushing syndrome
T₄ | diagnose hypothyroidism (TSH level may be normal in secondary hypothyroidism)
TSH | diagnose TSH-producing adenoma
LH | diagnose gonadotroph adenoma (tumor marker)
FSH | diagnose gonadotroph adenoma (tumor marker)
α-subunit | diagnose gonadotroph adenoma (tumor marker)
testosterone (male patients) | diagnose hypogonadism

* These blood tests are usually adequate to diagnose all but Cushing disease.

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Source: Neurosurg Focus © 2004 American Association of Neurological Surgeons
Management focused on two aspects:

- Acute neurologic deficits from tumor mass
- Endocrinopathy

Medical stabilization
High-dose steroids
Pituitary panel and electrolytes
Imaging
Emergent surgical decompression
Endocrinologic consultation
5 days later @ 34+5 weeks:
Spontaneous delivery ensued
Followed by CS for pt request
Two healthy newborns 1900/1800 gr
Headache disappeared in the immediate post partum period
PRL decreased to 760ng/ml
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The effects of pregnancy on the course of the disease
The effects of lactation

Should breastfeeding be discontinued?

DAs will decrease serum PRL levels, subsequently impairing lactation

Suckling stimulates PRL secretion in normal women for the first few weeks or months postpartum

No data to suggest that breast-feeding can cause tumor growth

No reason to discourage nursing in women with prolactinomas.

PRL measurements after birth

If symptom-free throughout pregnancy - PRL measurement 2 months after delivery or cessation of nursing
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The effects of pregnancy on the course of the disease
The effect of pregnancy on tumor progression

Pregnancy induces remission of hyperprolactinemia in 66% of women after discontinuation of DA

Post-partum Remission %

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<tr>
<th>Study #</th>
<th>Non-tumoral hyperPRL</th>
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<th>MacroPRLemia</th>
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<tr>
<td>1</td>
<td>76</td>
<td>70</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>66</td>
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Underlying mechanisms are uncertain

Generally attributed to the autoinfarction of the tumor

Growth is uncommon (more in macro)

DA’s may be discontinued

DA’s are safe and very effective in symptomatic growth

Surgery – for intractable cases or compression

Post-partum prognosis is excellent