Pituitary Causes of Infertility: A Case Based Approach to Ovulatory Dysfunction

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Associate Professor
Harvard Medical School
Boston, Massachusetts
Pituitary Tumor Types

Thyrotroph (1%)
Hyperthyroidism

Corticotroph (10-15%)
Cushing's Disease

Somatotroph (10-20%)
Acromegaly

Gonadotroph (15-40%)
“Clinically nonfunctioning”
Visual field loss
Hypopituitarism

Lactotroph (40-50%)
Hyperprolactinemia

“Clinically nonfunctioning”


Hypopituitarism


Visual field loss


Hypopituitarism
Case 1

• A 38 y/o woman presented with infertility, galactorrhea and headaches and a pituitary adenoma
Case 1: HPI

- 5 years ago: dx with PCOS
  - irregular menses, acne, hirsutism & infertility.
  - conceived with clomiphene citrate
- Post partum glucose intolerance persisted
- After discontinuation of nursing, she had amenorrhea and lactation for over 1 year
- Oral contraceptives were begun
Case 1: HPI

- HCG negative
- Intermittent headaches
- Severe “ice pick” headache on an air flight lead to MRI
Brain MRI

- Sellar and suprasellar mass lesion
- Widened remodeled sella
- Mild patchy enhancement
- No hemorrhage
- Questionable right cavernous sinus invasion
- Mild mass effect on the optic chiasm
- Diffusely thickened skull
- Prominent frontal sinuses
## Preoperative Biochemical Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin</td>
<td>40.0</td>
<td>0-20 ng/ml</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.8</td>
<td>0.9-1.8 ng/dl</td>
</tr>
<tr>
<td>TSH</td>
<td>1.6</td>
<td>0.4-5.0 uU/ml</td>
</tr>
<tr>
<td>Stimulated cortisol*</td>
<td>25</td>
<td>≥18 ug/dl</td>
</tr>
<tr>
<td>LH</td>
<td>0.8</td>
<td>.6-19 U/L</td>
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<td>FSH</td>
<td>3.4</td>
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</tr>
<tr>
<td>Estradiol</td>
<td>&lt; 20</td>
<td></td>
</tr>
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</table>
Physical exam

- 74.8 kg, 162.6 cm, 116/70, 68 beats per minute
- Broad nose and face, prominent brow
- Slight underbite, no macroglossia
- Facial acne, skin tags, acanthosis nigricans
- Large, thick fingers
Upon further questioning she notes increase in her shoe and her ring size
# Biochemical Evaluation

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<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tr>
<td>IGF-1</td>
<td>969</td>
<td>114-492 ng/ml</td>
</tr>
<tr>
<td>Prolactin</td>
<td>40.0</td>
<td>0-20 ng/ml</td>
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<td>&lt; 20</td>
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<tr>
<td>Hemoglobin AIC</td>
<td>6.5</td>
<td>3.8-6.5 %</td>
</tr>
<tr>
<td>GH after OGGT</td>
<td>72</td>
<td>&lt;1 ng/ml</td>
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</table>
Diagnoses

• Acromegaly
  – Central Hypothyroidism
  – Hypogonadotrophic Hypogonadism
  – Normal Adrenal Reserve

• Neuro-ophthalmology Referral
  – Visual Field Examination: Normal

• Neurosurgery Referral
  – Trans-sphenoid Resection
Pathology

- Final Diagnosis: Growth Hormone Producing Pituitary Adenoma
  Moderately Pleomorphic
  Low Ki-67 Proliferation Index (0.9%)
GH/IGF-I Actions on Multiple Targets

- GH
  - Anterior Pituitary
  - GH/IGF-I Actions on Multiple Targets
  - GHRH
  - Hypothalamus Somatostatin
  - Lipolysis
  - Amino Acid Transport Protein Synthesis
  - Bone
  - Fat
  - Muscle
  - Liver
  - IGF-I
  - Anabolic Effects

References:
The 3 Most Common Initial Reasons Leading to Diagnosis of Acromegaly

<table>
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<tr>
<th>Initial Presentation</th>
<th>(N = 3173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmorphic feature</td>
<td>22%</td>
</tr>
<tr>
<td>Acral Changes</td>
<td>14%</td>
</tr>
<tr>
<td>Headache</td>
<td>8%</td>
</tr>
</tbody>
</table>

8.4% of women presented with menstrual disorder

Petrossians P et al Endocrine Related Cancer 2017
Prevalence of Clinical Features

- Acral enlargement and/or coarse features
- Sweating
- Menstrual disorder
- Headache
- Arthritis
- Carpal tunnel syndrome
- Diabetes or impaired glucose tolerance
- Impaired potency and/or libido
- Hypertension
- Visual field defect
- Obstructive sleep apnea
- Galactorrhea
- Coronary artery disease

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Diagnosis Frequently Delayed Due to Gradual Development of Acromegaly
Random GH Measurements Result in False-Positive and False-Negative Diagnoses

GH and IGF-I levels vary with method used

Diagnosis of Acromegaly

Inability to suppress serum GH during an oral glucose tolerance test (OGTT) to less than 1 ng/ml

Elevated serum IGF-I levels
  - Age - matched normal range required
Baseline Evaluation of Acromegaly

- Pituitary function testing (if macroadenoma)
- PRL
- Pituitary MRI
- Visual fields (if compression of optic chiasm)
Evaluation of Acromegaly: Screening for Co-morbidities

- Colonoscopy
- Sleep tests if sxs of sleep apnea
- Fasting Glucose and Hemoglobin A1C
- Echocardiogram if cardiac symptoms
Acromegaly: Therapy

- Surgical
- Medical
- Radiation
# Acromegaly and Ovarian Dysfunction

<table>
<thead>
<tr>
<th>Causes</th>
<th>Treatment</th>
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<tr>
<td>Hyperprolactinemia</td>
<td>Cabergoline or bromocriptine</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>Ovulation induction: clomiphene, gonadotropins</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>Metformin Reverse high PRL or GH</td>
</tr>
<tr>
<td>GH excess</td>
<td>Acromegaly treatments</td>
</tr>
</tbody>
</table>
Changes in IGF-I & GH levels during the 1st trimester pregnancy in acromegaly (N=12)

Caron P et al J Clin Endocrinol Metab 2010
Acromegaly and Pregnancy

- GH excess may improve with high E2
- Risk of gestational DM (4/64) & HTN (8/64) assoc with poor control GH/IGF1
- Rare tumor enlargement in macros 3/27
- GH-suppressive therapy can be safely withdrawn after conception in most

Caron P et al J Clin Endocrinol Metab 2010
Acromegaly Therapy During Pregnancy

- Dopamine agonists and somatostatin analogs cross the placenta - but safety evidence in several studies
- Octreotide? assoc with microsomia; try to use short acting preconception and stop
- Pegvisomant reported retrospectively in 27 maternal exposures only 3 continued throughout pregnancy; one preterm delivery

Van Der Lily Aj et al Endocrine 2015
Cheng S Pituitary 2012
Brian SR et al J Clin Endocrinol Metab 2007
Physiological Causes of Hyperprolactinemia

- Sleep
- Physical exertion
- Food
- Stress
- Coitus
- Pregnancy and postpartum state
- Nursing

Anterior pituitary

Third Ventricle

Optic chiasm
Regulation of Prolactin Secretion

PRL secretion regulated by the inhibitory tone exerted by dopamine
Pathological Causes of Hyperprolactinemia

- Prolactinoma
- Acromegaly
- Other pituitary tumors
- Infiltrative disorders
- Hypothalamic and pituitary stalk disease or damage

Other
- Primary hypothyroidism
- Seizures
- PCO
- Neurogenic causes (chest wall trauma, herpes zoster)
- Renal insufficiency
- Cirrhosis
# Pituitary Sella Lesion Differential Diagnosis

<table>
<thead>
<tr>
<th>Neoplastic:</th>
<th>Inflammatory / Infiltrative:</th>
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<tbody>
<tr>
<td>• Adenoma</td>
<td>• Hypophysitis</td>
</tr>
<tr>
<td>• Craniopharyngioma</td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td>• Meningioma</td>
<td>• Langerhans’ cell histiocytosis</td>
</tr>
<tr>
<td>• Metastasis (lymphoma, breast, lung)</td>
<td>• Wegener’s granulomatosis</td>
</tr>
<tr>
<td>• Germinoma</td>
<td>• Hemochromatosis</td>
</tr>
<tr>
<td>• Chordoma</td>
<td></td>
</tr>
<tr>
<td>• Chondrosarcoma</td>
<td></td>
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<tr>
<td>• Glioma</td>
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<tr>
<td>• Schwannoma</td>
<td></td>
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<tr>
<td>• Esthaesioneuroblastoma</td>
<td></td>
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<tr>
<td>• Pituitary carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Pituicytoma</td>
<td></td>
</tr>
<tr>
<td>• Plasmacytoma</td>
<td></td>
</tr>
<tr>
<td>• Hypothalamic hamartoma</td>
<td></td>
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<tr>
<td>• Lipoma</td>
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<th>Cysts:</th>
<th>Vascular:</th>
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<tbody>
<tr>
<td>• Rathke’s cleft cyst</td>
<td>• Carotid aneurysm</td>
</tr>
<tr>
<td>• Arachnoid cyst</td>
<td>• Cavernous malformation</td>
</tr>
<tr>
<td>• Epidermoid or dermoid</td>
<td>• Hemorrhage, infarction</td>
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<th>Other:</th>
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<tr>
<td>• Tuberculosis</td>
<td>• Empty sella</td>
</tr>
<tr>
<td>• Abscess</td>
<td>• Congenital abnormalities</td>
</tr>
<tr>
<td>• Fungal</td>
<td>• Trauma / surgery</td>
</tr>
<tr>
<td>• Neurocysticercosis</td>
<td>• Cranial irradiation</td>
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<td>• Syphilis</td>
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<td>• Hemochromatosis</td>
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Pharmacological Causes of hyperprolactinemia

- **Antihypertensives** (α-methyldopa, verapamil)
- **Psychotropics**
  - antidepressants: tricyclics, SSRIs, MAOIs
  - antipsychotics: phenothiazines, haloperidol, atypical (risperidone)
- **Metoclopramide**
- **Opiates**
- **Cocaine**
- **Protease Inhibitors**
Hyperprolactinemia due to Psychotropic Medications

- Increasingly common
- Use extends to headaches, mood stabilization, ADHD, depression
- Atypical neuroleptics such as Risperidal can cause PRL > 100ng/ml
- Elevations more common in women than men
Prolactinomas: Epidemiology

- Prevalence 100 per million
- Occurs more commonly in women of childbearing age (20-50 yrs)
- 10:1 female/male ratio but equal after age 50
- 90% microadenomas and 10% macroadenomas
- 80% of macroadenomas occur in men
Clinical Manifestations of Hyperprolactinemia

Galactorrhea
Infertility
Osteopenia
Decreased libido

Women
- Oligo-amenorrhea
- Acne/hirsutism
- Estrogen deficiency sx/s dyspareunia

Men
- Erectile dysfunction
- Gynecomastia
GnRH Mediated Effects on Bone

Brain
- Hypothalamus
- GnRH

Anterior pituitary
- LH/FSH

Prolactin

Bone
- Estrogen

Ovaries
Case 2: History

- 33 Y/O woman
- Amenorrhea
- Galactorrhea
- Headache
- No meds or supplements
Case 2: Exam

- Galactorrhea
- Mild acne
- Normal neurologic exam
- Normal visual fields
Which labs should be ordered?

Diluted prolactin, IGF-1, HCG and TFTS should be obtained.
Case 2: Test Results

- Normal TSH and Free T4
- HCG negative
- Prolactin 60 (1-20 ng/ml)
- MRI 9mm adenoma w/o compression of chiasm
Evaluation

RADIOLOGY:

MRI of the pituitary with and without gadolidium

If suprasellar extension, obtain visual fields
If macroadenoma, perform anterior pituitary testing for GH, thyroid and adrenal insufficiency
Management of Prolactinomas

• Treatment indications include:
  – tumor growth
  – oligo or amenorrhea/ hypogonadism
  – bothersome galactorrhea
  – infertility

• Hyperprolactinemic patients with a microadenoma may be followed without treatment if they are:
  – Asymptomatic
  – Eugonadal
  – Have stable MRI scans
Prolactinomas: Therapy

- Dopamine agonists – first choice in most patients
  - Cabergoline
  - Bromocriptine
- Surgery
- Radiation
Prolactinomas: Indications for Surgery

- Visual field defects unresponsive to medical therapy
- Macroadenomas unresponsive to medical therapy
- Tumor growth while on medical therapy
- Intolerance to dopamine agonist therapy
- Pituitary apoplexy (rare)
- Cerebrospinal rhinorrhea due to prolactinoma erosion into sphenoid sinus (rare)
Hyperprolactinemia: Goals for Dopamine Agonist Therapy

• Normalize prolactin levels and achieve remission of associated symptoms
• Reduce or stabilize tumor size, thereby preserving or restoring anterior pituitary function
• Prevent disease progression
Dopamine agonist safety during pregnancy

- No significantly higher frequency of complications was found in pregnancies and/or offspring exposed than in the normal population.
- Class B
- More patients with bromocriptine have been studied and for longer f/u period than cabergoline (> 2000 vs < 400’s)

Stalldecker G et al Pituitary 2011; Krupp Klin Wochenschr. 1987
Case 3

- A 24 y/o female presents with galactorrhea
- She had onset of menses at age 12 but menses were irregular since age 14
- She had minimal hirsitism and acne with no recent progression
- Reported mild swelling in hands and feet with no other specific features of acromegaly
- Normal exam except for galactorrhea
  - BP 100/80 HT 5ft 5inches  Weight 136 BMI 22.6
Case 3: Labs

Slightly high T4, free T4 and TSH were normal

Slightly high IGF-1

PRL 56 ng/ml (1-20)

FSH and LH were low

Androgens were normal

E2 was high

HCG was positive
Case 3

- MRI may show pituitary enlargement in normal pregnancy
- IGF-1 may be elevated in normal pregnancy
- Prolactin may be elevated in normal pregnancy
- Total T4 might be high with normal free T4 due to increased TBG
Cushing’s Syndrome

Morbidities
- HTN
- DM
- Osteoporosis

Screening: 24 hr urine cortisol, pm salivary cortisol, 1 mg dexamethasone suppression test

Normal or high ACTH
- Pituitary
- Ectopic

Low ACTH
- Adrenal
- Exogenous
Cushing’s Syndrome and pregnancy

- Fertility impaired low gonadotropins, higher androgens
- Avoid fertility in active Cushing’s
- Poor maternal and fetal outcomes in active Cushing’s
- Difficult to diagnose during pregnancy
- Rare reports of medical therapy for Cushing’s during pregnancy
- Aim for surgery in early 2nd trimester
Case 4: A 30 year old woman with infertility, irregular menses and headaches

PRL 60
TSH 1424

PRL 15
TSH 2.4

on thyroid x 6 months
Pituitary Enlargement: Causes

Hyperplasia

- Physiologic
  - Pregnancy and lactation
  - Youth

- Pathologic
  - Primary hypothyroidism
  - Ectopic GHRH
  - Ectopic CRH
A 32 y/o woman regular menses and desire to conceive

PRL 36 TFTS normal HCG negative IGF-1 normal

Aneurysm
Conceived on bromocriptine after coiling
Hypogonadotropic Hypogonadism: Functional

Low FSH, Low LH & Low E2

- Physical or Psychological stress
- Weight loss
- Excessive exercise
- Anorexia nervosa
- Starvation
Case 5

- A 37 y/o was referred to Neuroendocrine for amenorrhea x 8 months
- Prior regular menses- one child spontaneously conceived 10 years ago
- Diagnosed with “idiopathic” central diabetes insipidus and started on DDAVP 1 year ago
- 1 month ago began having severe headaches
Case 5

• Exam: no evidence of acromegaly or crushing's
• Labs: diluted prolactin was 70 (nl >20), TFTs, cort stim and IGF-1 were normal
• Outside MRI done for headaches was reported as “normal”.
Diffuse linear and nodular leptomeningeal enhancement involving the entire brain and spinal cord with thickening of the pituitary stalk.
diffuse linear and nodular leptomeningeal enhancement involving the entire brain and spinal cord with thickening of the pituitary stalk
CSF Results

- **Ace**: 4 (<10 units)
- **Glu**: 30 (50-70 mg/dl)
- **TP**: 127 (5-55 mg/dl)
- **Cell cont**: 3 RBC 81 WBC (95L4 M1E)
- **Cytology**
  - **ATYPICAL**: An increased number of lymphocytes, including occasional reactive forms
Case 5: Diagnosis

- Extensive evaluation for malignancy was negative.
- Sarcoidosis suspected based on imaging parameters with negative transbronchial biopsy and serum ACE.
- Flexible bronchoscopy with mediastinoscopy
  Pathology: confluent nonnecrotizing granulomas with extensive hyalinization c/w sarcoidosis
- Responded to steroids
Case 5: Concluding Points

• An outside “negative” MRI report does not definitively indicate a negative scan
• Central DI should be evaluated with cranial imaging and designated pituitary views on MRI
• Mild hyperprolactinemia may be associated with stalk lesions and may cause reproductive dysfunction (via inhibition of GnRH)
Summary Points

• Acromegaly: if clinical features, obtain IGF-1
• In hyperprolactinemia: obtain TFTS, HCG and MRI to exude other tumors, hypothyroidism or infiltrative lesions
• Prolactiomas: treat with dopamine agonists until conception
• Cushing’s: avoid pregnancy until in remission