VOLUME-VI

PrepLadder



MEDICINE

NEET SS VERSION 4.0

PREFACE

Dear Dreamer,

Pat your back and reward yourself, today you've taken an important step towards reaching your dream. Mark Twain said, "the secret of getting ahead is getting started". You have started in the right direction.

The next few months until your targeted exam or exams are crucial. Every moment counts and each step you take now, will help you reach your goal, your dream.

PrepLadder is your partner in this journey. We are in this together. So, don't worry, do not stress. Just focus on your preparation and stay positive. Set daily targets, achievable and realistic ones. If you pass the target, celebrate. However, if you miss a daily target, forgive yourself, move on and do better the next day.

Always remember that you are special and unique. Do not compare your preparation, your speed, your abilities with others. Believe us, it doesn't help.

Practice a lot. Solve the QBank. Take Grand Tests. Review your performance. But don't let ranks and results drag you down. Rather use them as a guiding light to know your strengths and weaknesses, to increase your speed and accuracy, and to get yourself ready for the exam day.

If you have a doubt or a question, ask us. We are here.

Lastly and most importantly. take care of yourself. You and your health are precious. So, keep up with exercise, eat healthy, get enough sleep and care for yourself.

We're behind you, cheering you on to the finish line. You might be feeling stressed, overwhelmed, and so tired, but you're nearly there. Give it everything you've got, and know that whatever happens next, you've got what it takes for the life you want. You are a Champion.

Own Your Dream
Team PrepLadder

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ENDOCRINOLOGY

1 DIABETES INSIPIDUS PART-1

Physiology of Vasopressin (ADH)

00:01:43

- **Synthesis**
  - Synthesized in hypothalamus (Magnocellular neurons).
  - Through the HHT it gets stored in the posterior pituitary (storage organ).
- **Release and Action**
  - Depending upon the requirement, ADH is released and acts as vasopressin.
  - Acts on vasopressin receptors.

Vasopressin Receptors

- **Three Important Forms of Vasopressin Receptors**

1. **V1 receptors**
   → They are present on blood vessels.
   → V1 receptors cause vasoconstriction when stimulated.
   → Used in the treatment of hypovolemic shock and esophageal varices.
   - Surgical treatment for bleeding esophageal varices: Variceal band ligation.
   - Non-bleeding esophageal varices: Propranolol is used to prevent Portal HTN and bleeding.
     - Octreotide and vasopressin are also used.
2. **V2 Receptors**
   → **Distribution:** Located in the collecting ducts of kidney and endothelial cells of blood vessels.
   → **Effects:** Stimulation of V2 receptors
   - In Collecting Ducts: Results in the absorption of water.
   - In Endothelial Cells: Results in the release of Von Willebrand factor and factor 8.

   → **V2 Receptors in Treatment**
   - Used in the treatment of Diabetes insipidus and Nocturnal enuresis in children.
   - Also used in Von Willebrand disease and hemophilia.
3. **V3 Receptors**
   → Distributed across anterior pituitary (corticotroph cells).
   → Stimulates the release of ACTH.

Regulation of ADH Secretion

- **Serum osmolality** regulates ADH secretion.
  - Normal value: 285-295 mosm/L.
  - Increased serum osmolality stimulates ADH secretion:
  - Once serum osmolarity is increased, two events occur
    → Stimulation of Osmoreceptor: Initiate the synthesis of ADH, causes reabsorption of water, resulting in increased fluid volume increases, affecting serum osmolality
    → Stimulates thirst center → Polydipsia (increased water intake).

Clinical Characteristics: Definition

00:13:28

- Either there is ADH deficiency or resistance.
  - It is characterized by the excretion of abnormally large volumes of water in the form of dilute urine.
  - **Polyuria:**
    → In Diabetes insipidus 24-hour urine volume > 40 ml/kg.
    → 24-hour urine osmolality < 280 mosm/L.
    → Average value: 500-800 mosm/kg.
- These patients will have polyuria, which produces increase in urinary frequency

- It will cause enuresis or nocturia
- Serum osmolality will be increased. This stimulates the thirst centre causing polydipsia
- There will be no signs of dehydration even with polyuria because, there is an excessive stimulation of thirst centre leading to increased water intake

Etiology of Diabetes Insipidus (DI)

00:19:24

- **Four Types of DI**
  1. Central DI
  2. Primary polydipsia DI
  3. Gestational DI
  4. Nephrogenic DI

Central DI

- **Most Common Cause**
  - Primary deficiency of arginine vasopressin secretion, seen in Central DI aka Neurogenic DI aka Pituitary DI aka Cranial DI aka Neurohypophyseal DI.
- **Etiology of Central DI**
  - Congenital
  - Acquired
  - Genetic disorders

Genetic Disorders

00:21:04

- **Six Genetic Forms**
  - Autosomal dominant mode (most common).
    → Mutations in AVP-neurophysin 2 gene.
  - Autosomal recessive forms
    → Type A: AVP-neurophysin gene mutation
    → Type B: AVP- neurophysin gene mutation
    → Type C/Wolfram syndrome: 4P-WFS 1 gene mutation
  - X-linked recessive: PCSK1 gene mutation.

Autosomal Dominant DI

- Diverse mutations in the coding region of one allele of AVP2 gene, altering one or more amino acids.
- This results in abnormal folding of prohormone, interfering with trafficking through the ER.
- The misfolded mutant precursor accumulates and interferes with the production of AVP
- Eventually, it destroys the magnocellular neuron
- Histological studies in a few patients shows fibrosis and lack of AVP containing neurons in the posterior pituitary
- Magnocellular neurons are present in the supraoptic nucleus and the PVN nucleus of the hypothalamus
- AVP deficiency is not present at birth but it develops gradually over a period of months to years
- Once established, the deficiency of AVP is permanent, but due to unknown reasons, in the late middle age, DI improves

Autosomal Recessive DI

- Due to an inactivating mutation in the AVP portion gene, producing biologically inactive AVP.
- Another mutation involves the majority of the AVP gene.
- WFS1 gene mutation causes Wolfram syndrome aka DI DM OA D syndrome:
  - DI - Diabetes Insipidus
  - DM - Diabetes Mellitus
  - OA - Optic Atrophy
  - D - Deafness

X-linked Recessive DI

- Mutation in the Xq28 gene.
  - PCSK1 gene mutations present with severe malabsorptive diarrhea, leading to polyuria and polydipsia. Presents before 5 years of age.

Acquired Causes of DI 00:34:34

- **Head Trauma:** Closed / penetrating head trauma to the pituitary gland
- **Neoplasms:** Craniopharyngioma (Tumors originating from Rathke's pouch) or pituitary adenoma.
- Granulomas like sarcoidosis or histiocytosis and xanthoma disseminatum
- Infections:
  - Chronic meningitis
  - Viral encephalitis
  - Toxoplasmosis
- **Inflammatory Disorders:**
  - SLE
  - Wegener's granulomatosis
  - Lymphocytic infundibulo-neuro-hypophysitis
- Vascular conditions
  - Sheehans syndrome
  - Aneurysms origination from the ICA

Primary Polydipsia DI

- Due to a suppression of AVP or due to excessive fluid consumption, lowering serum osmolality and reducing AVP production.
- Three subtypes:
  1. **Dipsogenic DI:**
     → Due to excessive fluid intake because of increased thirst.
     → Occur following head trauma or in association with multifocal diseases (Neuro sarcoidosis / TB meningitis/ Multiple sclerosis) in the brain
  2. **Psychogenic DI**
     → Not associated with increased thirst
     → Polydipsia is associated with psychosis/ OCD
  3. **Iatrogenic DI**
     → Due to increased water intake which is motivated by health benefits

Gestational DI

- Due to a deficiency of AVP caused by increased degradation of AVP.
- Caused by N-terminal aminopeptidase produced in the placenta.
- Manifests during pregnancy.
- Remission after a few weeks post-delivery.

Nephrogenic DI

- **Renal insensitivity** to ADH.
- Common causes:
  - Drugs:
    → Lithium
    → Demeclocycline
    → Amphotericin B
    → Aminoglycosides (effective against gram-negative bacteria)
    → Cisplatin
    → Rifampicin
    → Foscarnet

- Metabolic conditions:
  → Hypercalcemia
  → Hypercalciuria
- Infiltrative conditions like amyloidosis.
- Vascular conditions like sickle cell disease.

- **Genetic Nephrogenic DI:**
  - **Genetic form**: The most common genetic form is transmitted in a semi recessive X-linked manner and is due to mutation gen on chromosome Xq28, encoding V2 receptor.
  - Autosomal recessive or dominant forms due to mutations in chromosome 20 that encodes Aquaporin 2 channel, responsible for water reabsorption in the collecting duct.

Pathophysiology

00:48:12

- In pituitary and nephrogenic DI, the defect in urine concentration results in:
  - 1-2% decrease in plasma fluid.
  - Increased plasma osmolality and sodium levels.
  - Stimulation of thirst center, causing polydipsia.
- The severity of ADH dysfunction varies from patient to patient.
- In some cases, the defect is nearly complete and cannot be overcome by the intense stimulus due to severe dehydration
- In others, the defect in AVP secretion or action is incomplete, even with modest stimulus with few hours of fluid deprivation, Smoking and Vasovagal reactions, concentration of urine will occur

2 DIABETES INSIPIDUS PART-2

Primary Polydipsia

Pathophysiology of Primary Polydipsia

00:00:04

- It is opposite to pituitary and nephrogenic diabetes insipidus.
- Increased fluid intake in primary polydipsia reduces:
  - Plasma osmolality
  - Plasma sodium
  - ADH secretion
  - Urine osmolality
- In these patients fluid deprivation or hypertonic saline infusion increases serum osmolality, ADH secretion, and urine osmolality.

Differential Diagnosis

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- If symptoms like urinary frequency, enuresis, or persistent thirst are present, we can suspect

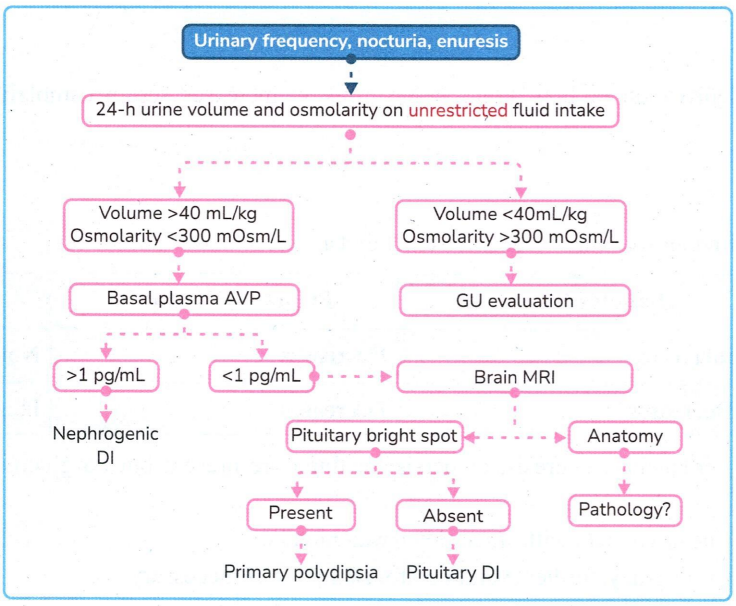
	Diabetes Insipidus	Primary Polydipsia	Diabetes Mellitus
Plasma osmolality	Increases	Decreases	Normal / increased in HONK
Urine osmolality	Decreases	Decreases	Increases

- If symptoms like urinary frequency, enuresis, or persistent thirst are present but no glucosuria, we can suspect Diabetes insipidus
- Workup for DI: 24-hour urine in a patient with unrestricted water intake
  - If urine osmolality is 50 ml/kg/day, further evaluation for DI subtype is necessary.
  - Basal plasma osmolality and sodium above normal range indicate fluid deprivation test should not be done due to risk.
- To differentiate subtypes of DI: Arginine Vasopressin Test
  - Injection of AVP (0.5 IU) or desmopressin (2 mcg) is given.
  - If urine osmolality increases: central or pituitary DI.
  - If the basal plasma osmolarity and sodium are within the normal limits as they usually are: alternative methord is used in determining the subtype of DI
  - The traditional approach is to stop all fluid intake for 4 -6 hrs and Closely Monitor Changes in: Body weight, Plasma osmolality, Plasma sodium, Urine osmolality

Water Deprivation Test

- Polyuria and decreased urine osmolality.
- Serum osmolality and sodium are normal.
- Hold fluid intake for 4-6 hours and monitor urine osmolality.
- **Interpretation:**
  - If urine osmolality increases: primary or psychogenic polydipsia.
  - If it remains low, despite fluid restriction: DI suspected.
    - → Central or nephrogenic DI:
      - In central DI: Urine osmolality increases after ADH injection.
      - In nephrogenic DI: Urine osmolality decreases.
- A simpler and less stressful but equally reliable way to differentiate among pituitary DI, nephrogenic DI and Primary polydipsia is to start by measuring the basal plasma AVP and urine osmolarity
- **Nephrogenic DI:**
  - AVP normal or elevated (>1 pg/ml), concurrent urine osmolality low (<280 mOsm/L), indicating resistance to ADH.

- **Plasma AVP Levels:**
  - If basal AVP is low or undetectable (<1 pg/ml): Nephrogenic DI unlikely.
  - It can be either Central DI or Primary polydipsia
  - In these patients brain MRI can be performed
    - → Hyperintense signal on T_1 W MRI indicates AVP presence.
    - → Bright spot is always present in primary polydipsia
    - → Bright spot absent in Pituitary DI, AVP is deficient.
    - → MRI doesn't distinguish between pituitary and nephrogenic DI as it is also faint or absent in nephrogenic DI
    - → Pituitary bright spot is also absent in Empty sella syndrome



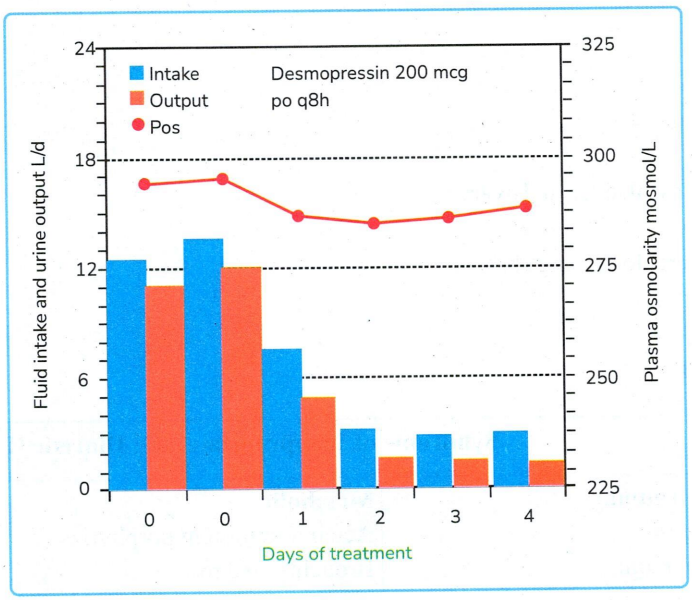
- MRI is not reliable for differentiating central and long-standing nephrogenic DI.
- Bright spot in MRI may be absent, small, or faint in this condition
- If MRI and/or AVP assays with the requisite sensitivity and specificity are unavailable and a fluid deprivation test is impractical or undesirable, a third way to differentiate: is by giving a properly dosed, closely monitored trial of desmopressin
  - In Nephrogenic DI, fluid restriction and desmopressin therapy are ineffective
  - In Pituitary DI, desmopressin abolishes polyuria and polydipsia. Reduces serum osmolarity and sodium by 1-2%
  - However, in primary polydipsia, antidiuretic therapy eliminates polyuria but does not eliminate the urge for polydipsia
  - In primary polydipsia, patients may develop moderate to severe hyponatremia within 8-24 hours.
- **Copeptin Test:**
  - Differentiates central from nephrogenic DI.
  - Copeptin is co-secreted with AVP.
  - Hypertonic 3% saline is administered IV as 250ml bolus f/b a continuous infusion ate a rate of 0.15ml/Kg/min. plasma sodium is measured stat every 30 minutes. When it reaches 150mmol/L, measure plasma copeptin.
    - → If plasma copeptin level is < 4.9Pmol/L: Pituitary DI

Treatment

00:30:50

- The signs and symptoms of uncomplicated pituitary DI can be eliminated by giving Desmopressin:
  - Desmopressin (DDAVP): An analogue of arginine vasopressin that selectively acts at V2 receptors to increase urine concentration.
  - Desmopressin has a longer duration of action and is less prone to degradation than AVP.

- **Dosage:**
  - 1-2 μg via injection, or 10-20 μg nasally 2-3 times per day or 100-400 μg bid or tid orally
  - The onset of antidiuresis is rapid, ranging from 15min after injection or 60 minutes after oral supplementation
  - Effectiveness results in 24-hour urine osmolality normalization (400-800 mosm/L) and urine volume reduction (15-30 ml/kg/day).
- **Treatment Impact:**
  - Increases total body water.
  - Reduces polydipsia and thirst within a few hours.
- **Hyponatremia:** Rarely develops
  - Occurs if urine volume does not reduce to <10 ml/kg/day, leading to fluid overload.



  - Treatment with Desmopressin shows a rapid decrease in fluid intake and output over a few days, normalizing plasma osmolality.
- Desmopressin (DDAVP) should not be given in patients with primary polydipsia.
- Psychogenic and Iatrogenic DI treatment includes:
  - Psychological counseling.
  - Patient education.
- To minimize the risk of water intoxication, Thiazide diuretics or Carbamazepine may be used to impair urinary free water excretion.

Nephrogenic DI Treatment 00:40:36

- Drug of choice: Thiazide diuretics.
  - Impair free water excretion and increase sodium reabsorption at the proximal convoluted tubule (PCT), leading to a paradoxical effect in managing nephrogenic DI.
- Hydrochlorothiazide acts at the level of the distal convoluted tubule (DCT).
  - Diabetes insipidus pathology primarily affects the collecting duct.
- **Partial Resistance to V2 Receptors:**
  - In cases of partial resistance, higher doses of ADH (10 times the normal dose) can overcome this, but DDAVP may be too expensive and inconvenient for long-term use.
- **Conventional Treatment for Nephrogenic DI:**
  - Use of Amiloride with a low sodium diet and a prostaglandin synthesis inhibitor like Indomethacin.
  - This combination can reduce polyuria and polydipsia by 30-70%, though there is a risk of hypokalemia and gastric irritation.
- **Enhancing ADH Action in Central DI:**
  - Drugs like Carbamazepine, Clofibrate, and Chlorpropamide may enhance ADH action in central diabetes insipidus.

3 SIADH

SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion)

00:00:56

- Clinical condition characterized by excessive production of ADH (antidiuretic hormone).
- **Effects:**
  - Reduced plasma osmolality due to increased water reabsorption across tubules → Excessive dilution of plasma.
  - Hypo-osmolar hyponatremia: Normal serum sodium levels: 135-145 mEq/L.
  - Impaired urinary dilution with decreased urine concentration, not due to hypovolemia or hypotension but due to an increase in ADH levels.

Etiology

00:03:09

- **Malignancy**:
  - Bronchogenic carcinoma
  - Duodenal carcinoma
  - Carcinoma of the pancreas, bladder, and ovary.
- **Head Trauma**
- Infections: Pneumonia, tuberculosis, lung abscess
- **Metabolic conditions**
- **CNS pathology**
- **Drugs** that can cause SIADH.

Etiology	Syndrome of Inappropriate Anti Diuretic Hormone		
Neoplasm: Carcinomas • Lung • Duodenum • Pancreas • Ovary • Bladder, Ureter	**Head trauma:** **Infections** • Pneumonia • Abscess (lung or brain) • Cavitation (aspergillosis) • Tuberculosis, lung or brain • Meningitis, bacterial or viral • Encephalitis • AIDS	**Metabolic** Acute intermittent porphyrias Bronchial asthma Pneumothorax Pneumonia, bacterial or viral Positive-pressure respiration	**Vascular** • Cerebrovascular occlusion, hemorrhage • Cavernous sinus thrombosis
Other Neoplasms • Thymoma • Mesothelioma • Bronchial adenoma • Carcinoid • Gangliocytoma • Ewing sarcoma		**Drugs** Vasopressin or desmopressin Chlorpropamide Oxytocin, high dose Vincristine Cyclophosphamide Tricyclic antidepressants Monoamine Oxidase Inhibitors Serotonin Reuptake inhibitors	**Neurologic** Guillain - barre-syndrome Multiple sclerosis Delirium tremens Amyotrophic lateral sclerosis Hydrocephalus Psychosis Peripheral neuropathy

Subtypes of SIADH

- **Nephrogenic SIADH**:
  - In about 10% of cases
  - AVP secretion occurs normally, but there is a failure to dilute urine due to excessive action of AVP on tubules.
- **Familial SIADH**:
  - Rare condition caused by a mutation in the V2 receptor or due to a stimulatory G-α protein mutation.

Effects of Excessive ADH Production

- Increased water reabsorption leading to an increase in plasma fluid volume.
- Highly concentrated urine and decreased urinary output.
- The body activates compensatory mechanisms like natriuresis to flush out excess water.

Important Compensatory Mechanisms in SIADH

00:12:38

1. Inhibition of RAAS (Renin-Angiotensin-Aldosterone System)
2. Decrease in sympathetic activity
3. Increased secretion of ANF (Atrial Natriuretic Factor)

1. Inhibition of RAAS

- SIADH leads to an increased fluid volume and renal perfusion.
- This causes an Increase in GFR (glomerular filtration rate) causing inhibition of RAAS, leading to decreased aldosterone levels and increased natriuresis (excretion of sodium and water).

2. Decrease in Sympathetic Activity

- In SIADH, there is an increase in water retention, causing BP to rise, which is sensed by baroreceptors, and results in vasomotor center inhibition, causing decreased sympathetic outflow, normalizing BP.

3. Increased Secretion of ANF

- In SIADH, increased reabsorption of water leads to atrial distention, which stimulates the release of ANF.
- ANF causes natriuresis and sodium excretion, balancing fluid, and sodium levels.

Outcome:

- These compensatory mechanisms lead to decreased serum sodium level, Increase in urinary sodium, decrease in serum osmolality, and increased urine osmolality.

Once compensatory mechanisms start:

- Euvolemia (normal blood volume).
- No ascites or edema.
- Induces hyponatremia (low sodium).

Important Information

Q. What is the problem when the mechanism starts even if it does everything properly?

Ans. It induces hyponatremia.

- **Clinical Features of Hyponatremia:**
  - **Gradual onset:** If it persists for a few days, patients are often asymptomatic.
  - **Abrupt onset:** Symptoms are severe and include:
    - → Headache, Confusion, Seizures, Coma, and Projectile vomiting due to cerebral edema.
    - → **Reason:** Sodium in the extracellular compartment decreases, raising intracranial pressure.

Laboratory Investigations of SIADH

00:23:03

- **Serum Sodium**: Decreased
- **Urinary Sodium**: Increased
- **Blood Urea Nitrogen / Serum Uric Acid**: Decreased due to dilution.
- **Osmolality**:
  - **Serum osmolality**: Decreased
  - **Urine osmolality**: Increased
- **Serum Potassium**: Normal

	Serum Osmolality	Urine Osmolality	Serum Sodium
SIADH	Decreased	Increased	Decreased
DI	Increased	Decreased	Increased

IOC of SIADH

- **Water Loading Test**:

- Normal individuals excrete 90% of water within 4 hours.
- SIADH patients excrete only 20-30% of water.

Treatment of SIADH

00:27:02

- **Fluid restriction**: 800 ml-1 liter per 24 hours.
- Supplementation of VAPTANs (Vasopressin receptor antagonists).
- If euvolemic hyponatremia is present: treat the underlying cause
  - Restrict water intake
  - Neutralize excess water
- For Mild Hyponatremia:
  - If the patient is asymptomatic, restriction of total water intake until remission of SIADH
  - Normal water intake: 30ml/kg/day
- **Severe and symptomatic Hyponatremia**:

  → Administer 3% NaCl or AVP antagonist (Start Tolvaptan or Conivaptan)

  → 3% NaCl should be given at 0.05 ml/kg/min to increase sodium at the rate of 1-2meq/L/hr. this promote solute diuresis leading to decrease in TBW

  → Both Serum sodium and plasma osmolality have to be tested every 1-2 hours, until serum sodium reaches 130meq/L, when giving 3% NaCl

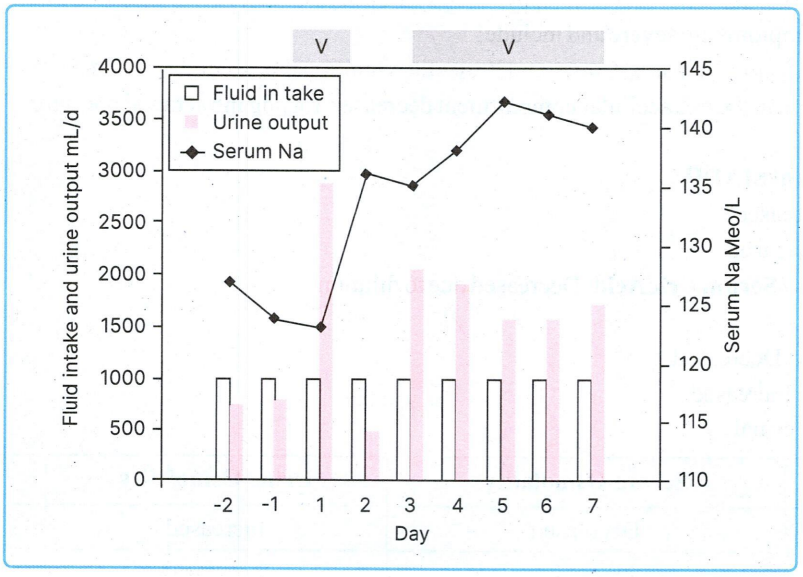
  → Faster correction of Serum sodium will cause central pontine myelinolysis
- **CPM (Central Pontine Myelinolysis):**
  - It is a fatal neurological syndrome caused by rapid correction of serum sodium.
  - Features include quadriparesis, ataxia, and abnormal extraocular movements.
- **DOC:** Vaptans
  - **Tolvaptan**:

    → 15 mg/day PO, max dose 30-50 mg.

    → Produces a brisk diuresis.
  - **Conivaptan**:

    → Given IV (acts on V1 and V2 receptors antagonist).

    → Starting dose: 20 mg over 30 mins followed by 20 mg/24 hours.
- **Effect of VAPTAN Therapy:**



  - Once VAPTAN is given, urine output increases, and peak effect is seen by day 1.
  - Serum sodium increases gradually with VAPTAN therapy.
  - Fluid intake should be restricted to 800-1000 ml.

- **Familial SIADH:**
  - Caused by mutations of the V2 receptor.
  - VAPTANs do not block the antidiuresis mechanism.
  - Osmotic diuretic (urea) can be effective for long-term management of SIADH.
  - Furosemide should not be given to SIADH patients unless there is dangerous pulmonary edema.

Hyponatremia

00:43:17

Types of Hyponatremias

1. **Hypervolemic Hyponatremia (Type I)**:
   - Seen in CHF (congestive heart failure) or cirrhosis.
   - Generalized edema develops.
2. **Hypovolemic Hyponatremia (Type II)**:
   - Due to loss of sodium and water caused by diarrhea, vomiting, or primary adrenal insufficiency.
   - Results in low GFR and increased plasma renin activity.
3. **Euvolemic Hyponatremia (Type III)**:
   - Seen in patients with severe deficiency of cortisol or thyroxine and in patients with SIADH.
   - Edema is absent in both conditions, but urinary sodium levels are slightly elevated
   - Plasma renin activity will be reduced

Differential Diagnosis of Hyponatremia based on Extracellular Fluid Volume

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Clinical Findings	Type 1 Hypervolemic	Type 2 Hypovolemic	Type 3 Euvolemic	SIADH Euvolemic
History	-	Vomiting, Diarrhea	-	-
CHF & Cirrhosis	Yes	No	No	No
Salt and Water Loss	No	Yes	No	No
ACTH- Cortisol	No	No	↓	No
Edema and Ascites	Yes	No	No	No
Postural Hypotension	Maybe	Maybe	Maybe	No
BUN & Serum Creatinine	↑	↑	Low-Normal	Low-Normal
Uric Acid	↑	↑ (High-Normal)	Low-Normal	Low-Normal
Serum K^+	Low-Normal	Low-Normal	Normal	Normal
Urate	High	High	Low	Low
Albumin	Low-Normal	High-Normal	Normal	Normal
Serum Cortisol	Normal	Normal	↓	Normal
Plasma Renin	↑	↑	↓	↓
Urinary Na^+	Low	Low	↑	↑

Treatment of Hyponatremia

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- Management differs based on the type, severity, and duration of hyponatremia.
- For **hypervolemic hyponatremia**
  - Objective is to reduce total body water and normalize sodium levels.
  - If hyponatremia is mild, restrict fluid intake.
  - Tolvaptan or Conivaptan can be used, if the urine output is very low or the hyponatremia is severe.
    → It is given to increase the rate of urinary water excretion.
    → Given only for 30 days.
    → If given beyond 30 days, the individual will have abnormal LFT

- Infusion of Hypertonic Saline is contraindicated in hypervolemic hyponatremia as it worsens edema and causes cardiovascular decompensation.

- **Hypovolemic Hyponatremia**
  - Fluid restriction and Vaptans: absolutely contraindicated
  - Treatment: Isotonic and hypertonic saline
- **Euvolemic hyponatremia**
  - For euvolemic hyponatremia, treat the underlying cause. If it is due to Cortisol or Thyroxine deficiency, Cortisol or Thyroxine replacement should be used.

Hypodipsic Hypernatremia

01:02:30

- Sequel of diabetes insipidus.
- Due to decrease in TBW or an increase in Total body sodium. This results from decreased fluid intake.

Clinical Characteristics

- Hypodipsic Hypernatremia is a syndrome characterized by chronic or recurrent hypertonic dehydration.
- Associated with hypovolemia, resulting in:
  - Decrease in BP (postural hypotension).
  - Increased heart rate.
  - Azotemia and increased Uric Acid levels.
  - Decreased potassium (K^+)
- Secondary hypoaldosteronism causes potassium excretion leading to hypokalemia.
- **Other Features**:
  - Severe muscle weakness
  - Severe pain (leading to rhabdomyolysis)
  - Hyperglycemia
  - Hyperlipidemia
  - Acute renal failure, coma
- At presentation, plasma AVP is usually subnormal

Etiology

01:10:49

- Hypodipsia is caused by damage to the hypothalamus or osmoreceptors.
- Can result from:
  - Congenital malformations of midline brain structures.
  - May be acquired due to surgeries or aneurysms of the ACA
  - Primary or metastatic tumors in the hypothalamus.
  - Granulomatous diseases (sarcoidosis, histiocytosis).
  - AIDS, cytomegalovirus encephalitis.

Important Information

- Adipsic Hypernatremia can occur without demonstrable hypothalamic lesions and is associated with autoimmune antibodies against subfornical regions.

- Also seen in certain psychological conditions like depression.

Pathophysiology

01:14:25

- Failure to drink sufficient water leads to increased plasma osmolality and serum sodium levels.
- Plasma AVP levels are subnormal.
- **Differential Diagnosis**: Differentiated from other causes of inadequate fluid intake:
  - Coma
  - Paralysis

- Restraints
- Lack of access to fresh water

Treatment 01:16:42

- Corrected by administering water orally if the patient is alert.
- If not alert, supplement with hypotonic salt (0.45% NaCl, 5% dextrose).
- The free water deficit is calculated using the formula:
  - FW = 0.5*BW8(S.Na-140)/140
- If serum glucose is elevated then serum sodium is corrected using another formula
  - Serum sodium = Sr. Na^+ = Sr. Na^+ + $\frac{(\text{Serum glucose} - 90)}{36}$
- Monitor plasma urea / creatinine for signs of acute renal failure.
- MRI of the brain and anterior pituitary function tests are performed once the patient is rehydrated.

4 HYPERPROLACTINEMIA

HYPERPROLACTINEMIA

00:00:37

Physiology of Prolactin

- Secreted by lactotrophs of anterior pituitary
- Anterior pituitary has various types of cells
  - Lactotrophs, Somatotrophs, Corticotrophs, Thyrotrophs
- Every hormone needs stimulus from hypothalamus for production of hormone from anterior pituitary
- Prolactin secretion is inhibited by Dopamine

Hypothalamus produces substance - Dopamine

↓

Dopamine acts on anterior pituitary

↓ ↓

No Prolactin produced | If dopamine doesn't act on anterior pituitary

↓

Prolactin is produced

- Dopamine agonist are used in treatment of hyperprolactinemia
- Dopamine synthesis inhibitor/receptor blocker
  - Increase prolactin level

Males	Females
• Prolactin Inhibits testosterone o Decreased libido, Impotency, Inhibit spermatogenesis	• Prolactin Helps in lactation o Inhibits estrogen and progesterone secretions o Amenorrhea, Inhibits ovulation, Infertility

Etiology

- MC cause: Prolactinoma (Tumor)
  - Most common secretory tumor
- Level of prolactin in Prolactinoma
  - Normal levels - <20 mcg/dl
  - Prolactinomas - >200 mcg/dl
- Physiological
  - Pregnancy, Lactation, Chest wall stimulation, sexual orgasm, Stress, Nipple stimulation, Sleep (returns to normal within 1 hr of awakening)
- Hypothalamic Pituitary stalk damage
  - Tumors causing compression - Craniopharyngiomas, Meningioma, Dysgerminoma
  - Others - Empty Sella, Adenoma, Irradiation, Trauma

Hypothalamo-hypophyseal tract is present between hypothalamus and Pituitary gland

↓

Compression in tract

↓

Dopamine released from hypothalamus will not act on anterior pituitary

↓

Hyperprolactinemia

- Pituitary hypersecretion
  - Prolactinoma, Acromegaly

- Systemic disorders
  - Chronic renal failure
  - Cirrhosis of liver
  - Hypothyroidism, Epileptics seizures
- Drugs

Dopamine receptor blockers	• Risperidone (Atypical antipsychotic drug) • Chlorpromazine (Phenothiazine group) • Haloperidol (Butyrophenones)
Dopamine synthesis inhibitors	Alpha methyldopa
H2 antagonists	Ranitidine, Cimitidine
Imipramine	Amitriptyline, Amoxapine
SSRIs	Fluoxetine
CCBs	Verapamil

Chronic renal failure

Chronic renal failure
↓
Decrease in peripheral clearance
↓
Increase in Prolactin levels

Primary hypothyroidism

- Primary hypothyroidism is associated with mild hyperprolactinemia

Excessive stimulation of TSH and TRH
↓
Increase in Prolactin levels

Mutation of prolactin receptors

- Rare cause of hyperprolactinemia

Hypothalamic Pituitary stalk

Lesion in hypo thalamic pituitary region
↓
Disruption of dopamine synthesis and passage of dopamine
↓
Inhibition in dopamine synthesis
↓
Increase in Prolactin levels

- Infiltrative disorders
  - Granuloma

Plurihormonal adenomas

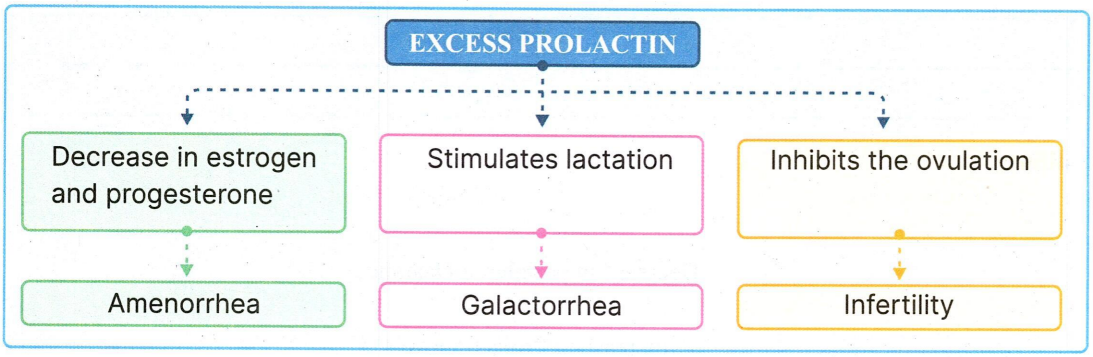
- Type of pituitary adenoma secreting more than two hormones
  - Somatotroph type of pituitary adenoma: Increased GH
  - Lactotroph type of pituitary adenoma: Increased prolactin
  - Corticotroph type of pituitary adenoma: Increase in ACTH

- Pituitary mass will cause compression of pituitary stalk
- Drug induced inhibition/disruption of dopaminergic receptor causes an increase in Prolactin
- Antipsychotics and Antidepressants: Causes mild rise in prolactin

Risperidone	Increase serum prolactin levels >200mcg/l
Methyldopa	Inhibits dopamine synthesis
Verapamil	Block dopamine release, lead to hyperprolactinemia
Hormonal agents	Estrogen and thyroid releasing hormone supplements causes increase in prolactin levels

Presentation and diagnosis of Hyperprolactinemia

- Hallmark in females: Amenorrhea, galactorrhea, and infertility



- If hyperprolactinemia develops before menarche → primary amenorrhea
- Hyperprolactinemia in later ages: Oligomenorrhea, amenorrhea
- Sustained hyperprolactinemia: Osteoporosis
  - Vertebral bone mineral density is decreased
- Galactorrhea
  - In 80% females with Hyperprolactinemia
  - Bilateral and spontaneous
  - Occasionally unilateral and manual

Other presentations

- Complaints of decreased libido, weight gain
- Mild hirsutism

Increased dihydroxy epiandrosterone acetate
↓
Enters the tissues
↓
Converts into testosterone
↓
Mild Hirsutism

- Men with hyperprolactinemia
  - Decreased libido, Infertility
  - Visual loss
    → Pituitary adenoma causes compression of optic nerves
- Gonadotropin suppression → Decreased testosterone → Development of impotence and oligospermia

Important Information

- Males and females with hyperprolactinemia suffers with infertility

Secondary effects of hypogonadism

- If longstanding, then patients may have Osteopenia, Reduced muscle mass, Decreased growth of beard

Galactorrhea

- Inappropriate discharge of milk containing fluid from breast
- Abnormal discharge > 6 months after stoppage of breastfeeding
- Postpartum galactorrhea
  - Also associated with amenorrhea
  - Self-Limiting disorder
  - D/t ↑ prolactin levels
- May occur spontaneously/due to nipple stimulation
- Galactorrhea may vary in color and consistency in male and women
  - Color – Transparent, Milky, bloody
  - Consistency – Unilateral, Bilateral
- Mammography or ultrasonography – for bloody discharge from single nipple
  - Suspicious of breast cancer
- Acromegaly is associated with galactorrhea - ⅓ of patients.
  - Hyperplasia of somatotrophs and lactotrophs

Treatment

- Goal: Discontinuation of drugs
- Prolactinoma: Dopamine agonist
- Hyperthyroidism: T4 (Thyroxine)

Laboratory Investigation

- Assess hypersecretion
  - Basal fasting morning prolactin levels
  - Normal Values 250 mcg/l
- False positive and false negative results may be encountered

False elevated values

Aggregated forms of circulating prolactin

↓

Contribute to macroprolactinoma

- Hypothyroidism should be excluded
  - Increase TSH/TRH level in hyperprolactinemia d/t hypothyroidism

Treatment of Hyperprolactinemia

- Depends on cause of Hyperprolactinemia
- Regardless of etiology, treatment should be aimed at normalizing prolactin levels
  - Reduction/suppressive effects of gonadal functions
  - Halt of galactorrhea
  - Preservation of bone mineral density

Dopamine agonist	• Most effective treatment • Includes Bromocriptine, Cabergoline • Stop the drugs which causes hyperprolactinemia
Thyroid hormone replacement	• Adequate Thyroxine is supplemented • Chronic renal failure: Dialysis/renal transplantation • Resection of hypothalamic/sellar mass lesion
Granulomatous infiltrates	• DOC: Glucocorticoids

Prolactinoma

- Most common secretory tumor of anterior pituitary
- Classified into Macro adenoma, Microadenoma

Etiology and prevalence

- Tumors arising from lactotroph type of cells
- Account for half of all functioning tumors
- Common in females than in males
- Prevalence: 10 in 1,000,00 in men
  - 30 in 1,000,00 in women
- Mixed tumors secrete combination of
  - Growth hormone and prolactin
  - ACTH and prolactin
  - Rarely TSH and prolactin

Plurihormonal tumors

- Secrete More than two hormones simultaneously
- Recognized by immunohistochemistry

Microadenoma	Macroadenoma
• Size of tumor: <1 cm or <10 mm • Increased prolactin • Minimal impingement on the surrounding structures • Female to male ratio: 20:1	• Size of tumor: >1 cm or >10 mm • Increased prolactin and mass effect on the surrounding structure • Female to male ratio: 1:1

- Tumor size correlates directly with prolactin concentration
  - Increased tumor size, increased prolactin concentration
- Macroadenoma: Prolactin levels >250 mcg/l
- Prolactinomas are slow growing tumors (prolactin levels remain stable in most patients)
- 5% microadenomas progress to macroadenomas, if left untreated

Presentation of Prolactinoma

Women	Men

• Present with
  ○ Amenorrhea
  ○ Galactorrhea
  ○ Infertility
• Tumor extends outside sella: Visual field abnormality
  ○ Early: Bi-temporal superior quadrantanopia
  ○ Late: Bi-temporal hemianopia
	• Present with
	  ○ Impotence, Loss of libido
	  ○ Infertility
	  ○ Signs of CNS compression
	  → Headache (raised intracranial pressure)
	  → Visual field defects

Diagnosis of Prolactinoma

- In prolactinoma - prolactin levels >200 mcg/l
- Prolactin levels <100 mcg/l caused by -
  - Microadenoma
  - Other sellar lesions inhibit dopamine synthesis.
  - Non neoplastic causes
    - → Drugs, Systemic causes
    - → Compression of hypothalamo-hypophyseal tract

Craniopharyngioma	Role of MRI
• Contribute to increase prolactin levels. • Tumor originates from Rathke's pouch. • Mass effect: Compression of optic chiasma • Patient will develop - o Bi-temporal inferior quadrantanopia o Progress to bi-temporal hemianopia • Close differential diagnosis for prolactinoma	• Done in all patients of hyperprolactinemia • To determine size of tumor • To differentiate micro/macro adenoma • To determine other causes of hyperprolactinemia • Hyperprolactinemia caused secondarily by mass effect of non-lactotroph lesions - o Treatment: Dopamine agonists

Treatment of Prolactinoma

- Micro adenomas rarely progress to become macroadenomas

Asymptomatic microadenomas	Symptomatic microadenomas
• Fertility is not desired - o No treatment is required o Monitoring of serial prolactin levels is important o Monitoring done by MRI	• Therapeutic goals include - o Normalize increased prolactin levels. o Reduced tumor size o Restoration of infertility o Resolution of galactorrhea

- Dopamine agonist dose should be titrated to achieve -
  - Maximal prolactin suppression
  - To restore reproductive function

For Macroadenomas -

- Formal visual field testing is performed before start of dopamine agonists
- MRI and visual fields should be assessed for every to 6 - 12 months interval until the mass shrinks
- After Maximum reduction in size of tumors - Annual assessment done

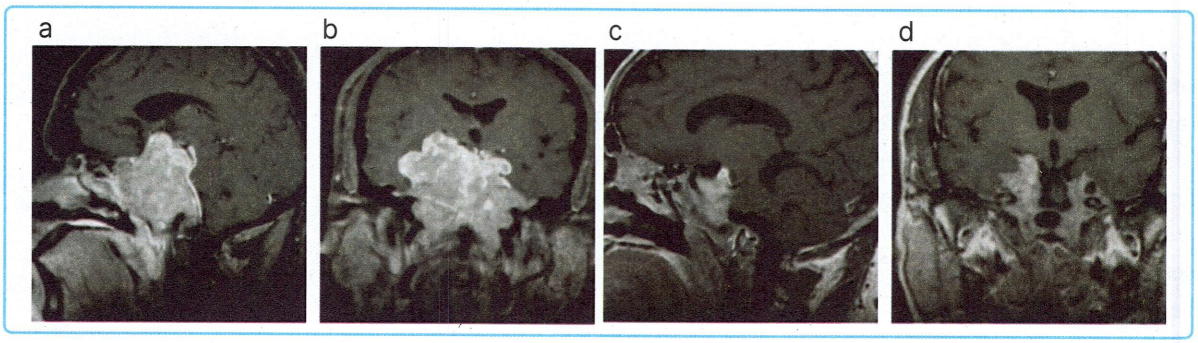
Oral dopamine agonists

- Cabergoline, Bromocriptine
- Considered as mainstay of treatment
- Either micro/macro adenoma – oral dopamine agonist are mainstay of treatment
- Suppresses prolactin secretion
- Reduces lactotroph cell proliferation
- Withdrawn after 2 years
  - In Microadenomas
    - → Significant Reduction in size
    - → Normal prolactin levels
  - Monitored carefully for evidence of recurrence
- 20% of males are resistant to dopaminergic treatment

- Decreased dopamine receptors
- A post receptor defect

Cabergoline

- Ergoline derivative
- Long-acting dopamine agonist
- High affinity to D2 receptor
- Suppresses prolactin levels >14 days (Single oral dose)
- Induces tumor shrinkage
- Dose: 0.5 to 1.0 mg twice weekly
  - Achieve normal prolactin levels
  - Resumption of Gonadal functions
    → In 80% patients with microadenomas
  - Reduction of galactorrhea in 90% of patients
- In Macroadenomas
  - Shrinkage of tumor in 70% of patients
  - Mass effect symptoms like Headache, Visual disorders
    → Improve dramatically within a few days
  - Improvement of sexual functions requires several weeks of treatment
  - MRI should be repeated within 16 weeks after initial therapy (Shrinkage)
  - After initial control is achieved, levels of cabergoline are reduced to lowest effective maintenance dose
- Cabergoline is effective in patients resistant to bromocriptine
- Case scenario - Large invasive prolactinoma successfully treated with cabergoline.
- A - B
  - Prolactin-secreting macroadenoma in a 32-year-old male measuring 5.6 x 6.9 cm invading the skull base, PRL level was 122,260 mcg/L
  - Four days after cabergoline was started, PRL was 10,823 g/L and dropped to 772 mcg/L after 3 weeks.
- C-D
  - Substantial tumor regression after 40 months of treatment, with PRL levels stable at 25 mcg/L.



Bromocriptine

- Ergot alkaloid bromocriptine mesylate
- Short acting dopamine receptor agonist
- Suppress prolactin secretion
- Preferred in pregnancy
- Therapy is initiated with a low bromocriptine dose.
  - Dose: 0.625 - 1.25 mg at bedtime
  - Gradually dose is increased depending on clinical response of patient
- Controlled with a daily dose of <7.5 mg (2.5 mg TID)

Side effects of Dopamine Agonists

- Bromocriptine - Constipation, Nasal stuffiness, Dry mouth, Nightmares, Vertigo, Insomnia
- Side effects will be reduced by decreasing dose
- 25% of patients after the initial dose developed
  - Nausea progressing to vomiting
  - Postural hypotension → Progress to faintness
- Patients intolerant to oral bromocriptine, then cabergoline is preferred
- Intravaginal administration of bromocriptine is efficacious in intractable GI side effects

Important Information

- Side effects of Cabergoline is less than compared to bromocriptine.

- In 5% patients it has
  - Auditory hallucinations, Delusions, Mood swings
  - Due to dopamine agonist or lysergic acid derivative properties
- Rare ADRs of Bromocriptine
  - Leukopenia, Thrombocytopenia
  - Pleural fibrosis, Cardiac arrhythmias, Hepatitis
- Cabergoline is recommended in Parkinson's disease patients
  - 3 mg of cabergoline causes cardiac valve regurgitation.
  - No evidence of valvular regurgitation in patients with 2 mg/week of cabergoline
  - Before the start of cabergoline, echocardiogram is performed

Surgery

- Rarely, surgical adenoma debulking may be indicated in
  - Dopamine resistance/intolerance
  - Presence of invasive macroadenoma with Decrease in vision
- Prolactin normalization is achieved in
  - 70% of patients with microprolactinoma after surgical resection
  - 30% of patients with macroprolactinoma

Recurrence of Hyperprolactinemia

- In 20% of patients within first year after the surgery
- Chance of recurrence in Microadenomas: 20%
- Chance of recurrence in Macroadenomas: 50%

Radiotherapy

- Reserved for patients with aggressive tumors
- No response to dopamine agonists
- No response to surgery

Pregnancy and Prolactinoma

- Size of pituitary gland is increased during pregnancy due to
  - Estrogen, Increased pituitary vascularity, Lactotroph cell hyperplasia
- Microadenomas: 5% increase in size during pregnancy
- Macroadenomas: 15 to 30% increase in size during pregnancy
- Bromocriptine is recommended
  - Used >30 years to restore fertility of individual
  - No teratogenicity

- In women with macroadenomas - Bromocriptine will reduce size of tumor
  → Regular visual field monitoring is done
- Pituitary MRI is safe during pregnancy, but reserved for
  - Symptomatic individuals With severe headache and visual field abnormality
- Compromise of vision: Surgical decompression indicated
- Cabergoline is not recommended for women when fertility is desired
  - It is a long acting with high D2 receptor affinity

