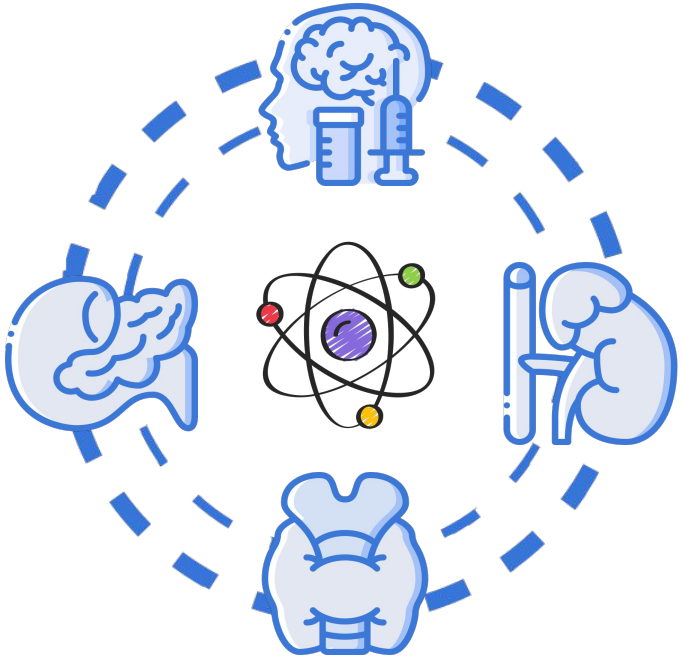
# Cushing Syndrome



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# Objectives:

- To identify physiological and biochemical characteristics of cortisol
- To understand the diagnostic algorithm for cushing's syndrome
- To understand the interpretation of laboratory and radiological investigation for diagnosis of cushing's syndrome


*best show ever*

# Adrenal Gland

Anatomically the gland is situated on the anterosuperior aspect of the kidney

**Adrenal Gland (Histology)**

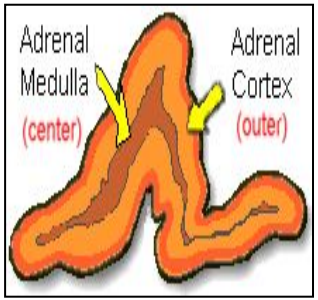
**Adrenal cortex**

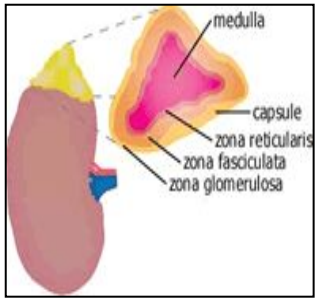
Based on cell type and function

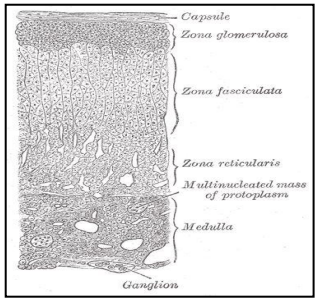
- Zona **G**lomerulsoa (outermost zone)→ Aldosterone (the principal mineralocorticoid)
- Zona **F**asciculata → Glucocorticoids, mainly cortisol (95%)
- Zona **R**eticularis → Sex hormones

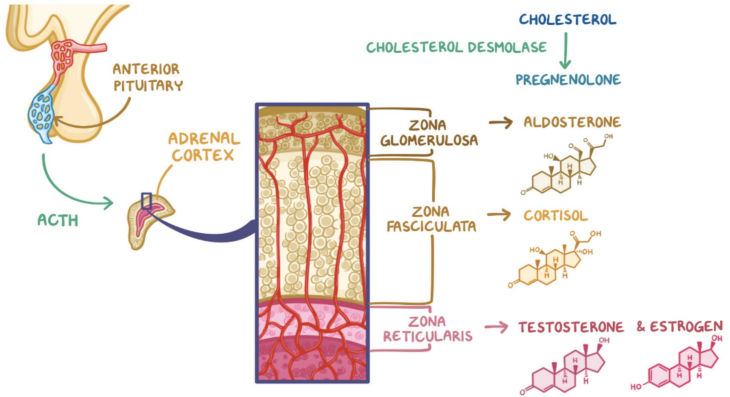
The Medulla and the Cortex differ in their embryological origin

**Adrenal medulla**



# Hypothalamic Pituitary-Adrenal (HPA) Axis

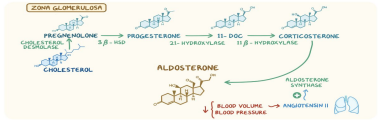
The hypothalamus secrete corticotropin releasing hormone (CRH)

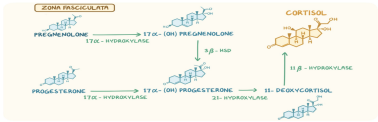
The CRH stimulate the anterior pituitary gland to secrete ACTH

ACTH acts on the Zona Fasciculata

Release of glucocorticoids (Cortisol)

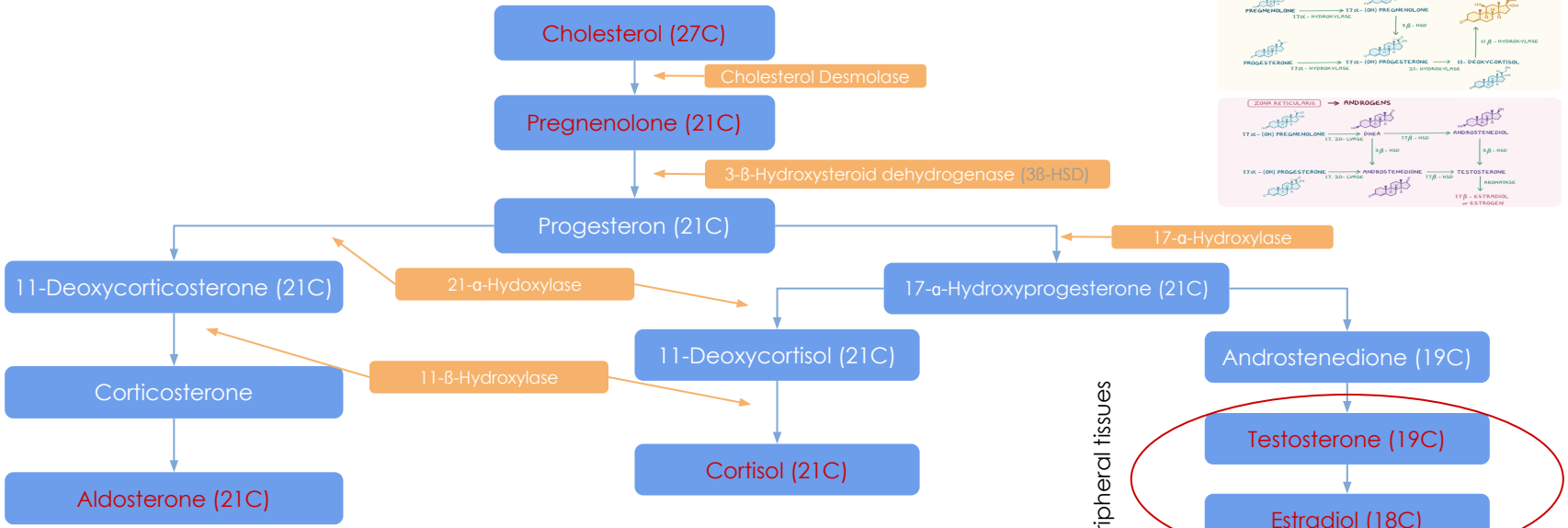
# Steroid Hormone Synthesis










Dr's note: It's is important to know the number of C and the precursor in particular

# Glucocorticoid Functions

- Glucocorticoids have widespread metabolic effects on carbohydrates, fats and protein metabolism
- Upon binding to its target, CORTISOL enhances metabolism in several ways:

| | |
|---|---|
| **In liver** | In the liver it's insulin antagonist[1] and has weak mineralocorticoid action:<br>1. ↑↑ Gluconeogenesis[2] → production of glucose from newly-released amino acids and lipids<br>2. ↑↑ Amino acid uptake and degradation<br>3. ↑↑ Ketogenesis |
| **In muscles** | • Cortisol → ↑↑ proteolysis and amino acids release |
| **In adipose tissue** [3] | • Cortisol → ↑↑ lipolysis through breakdown of fat |
| **Conserving glucose** | • Conserve glucose by inhibiting its uptake into muscle and fat cells. |

1-it will lower the level of insulin and increase glucose
2- The amino acid for gluconeogenesis are provided from the muscles and adipose tissue
3-The adipose tissue provide fats for both gluconeogenesis and ketogenesis

# Regulation of ACTH and Cortisol Secretion

- Highest cortisol level in the morning (8-9 AM)
- Lowest cortisol level in the late afternoon and evening (8-9 PM)

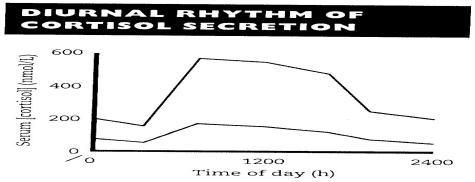
The diurnal rhythm of serum cortisol

**Negative feedback**

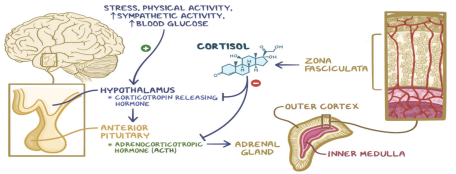
- ACTH release from the anterior pituitary is stimulated by hypothalamic secretion of CRH
- CRH → ↑ ACTH → ↑[cortisol]
- ↑[Cortisol] or synthetic steroid suppress CRH and ACTH secretion

**Stress**

- (e.g. major surgery, emotional stress) stress → ↑↑ CRH & ACTH → ↑↑ Cortisol




The diurnal rhythm of cortisol secretion the area between the curves represents values that lie within the reference range




# Plasma Cortisol Binding Globulin (CBG)

In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to CBG

The biologically active fraction of cortisol in plasma is the free(unbound) component[1]

- ↑↑ In pregnancy and with estrogen treatment (e.g. oral contraceptives)
- ↓↓ In hypoproteinemic states (e.g. nephrotic syndrome)

1- For investigation we look for the free form (The higher the level the higher the proteolysis)

# Cortisol and ACTH Measurements

**Serum Cortisol[1] and plasma (ACTH):**

- Sample must be collected (without venous stasis) between 8a.m and 9a.m. and between 10p.m. and 12a.m. because of the diurnal rhythm
- Temporary ↑ in these hormones may be observed as a response to emotional stress

**Urinary cortisol excretion:**

- Cortisol is removed from plasma by the liver → metabolically inactive compound → excreted in urine mainly as conjugated metabolite (e.g. glucuronide)
- A small amount of cortisol is excreted unchanged in the urine (UFC)[2]
- In normal individual: UFC is < 250 nmol/24 h

# Causes of Elevated Serum Cortisol

**Increased cortisol secretion**

- Cushing's syndrome
- Exercise
- Stress, anxiety and depression
- Obesity
- Alcohol abuse
- Chronic renal failure

**Increased CBG**

- Congenital
- Estrogen therapy
- Pregnancy

1-Plasma cortisol not used ALONE because there might be interference which can lead to false positive or false negative results

2- urinary free cortisol

# Signs and Symptoms of Cushing's Syndrome

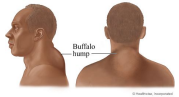
Helpful video for Cushing

## Symptoms

- Patients frequently suffers various psychological disturbances ranging from euphoria to frank psychosis
- ↓ Libido, amenorrhea and infertility
  "Excess cortisol may also affect other endocrine system"
- Atrophy of the skin and mucous membrane
- Weight gain and central obesity
- Purple stria on the trunk and legs


- Moon face

- Proximal muscle weakness
- Hirsutism
- Buffalo's hump




## Signs

- ↑ Protein metabolism
- Hypertension (due to aldosterone like effect)
- Hypokalemic alkalosis
- Hyperglycaemia or diabetes due to insulin resistance
- Loss of diurnal rhythm of cortisol and ACTH
- Impaired immunity

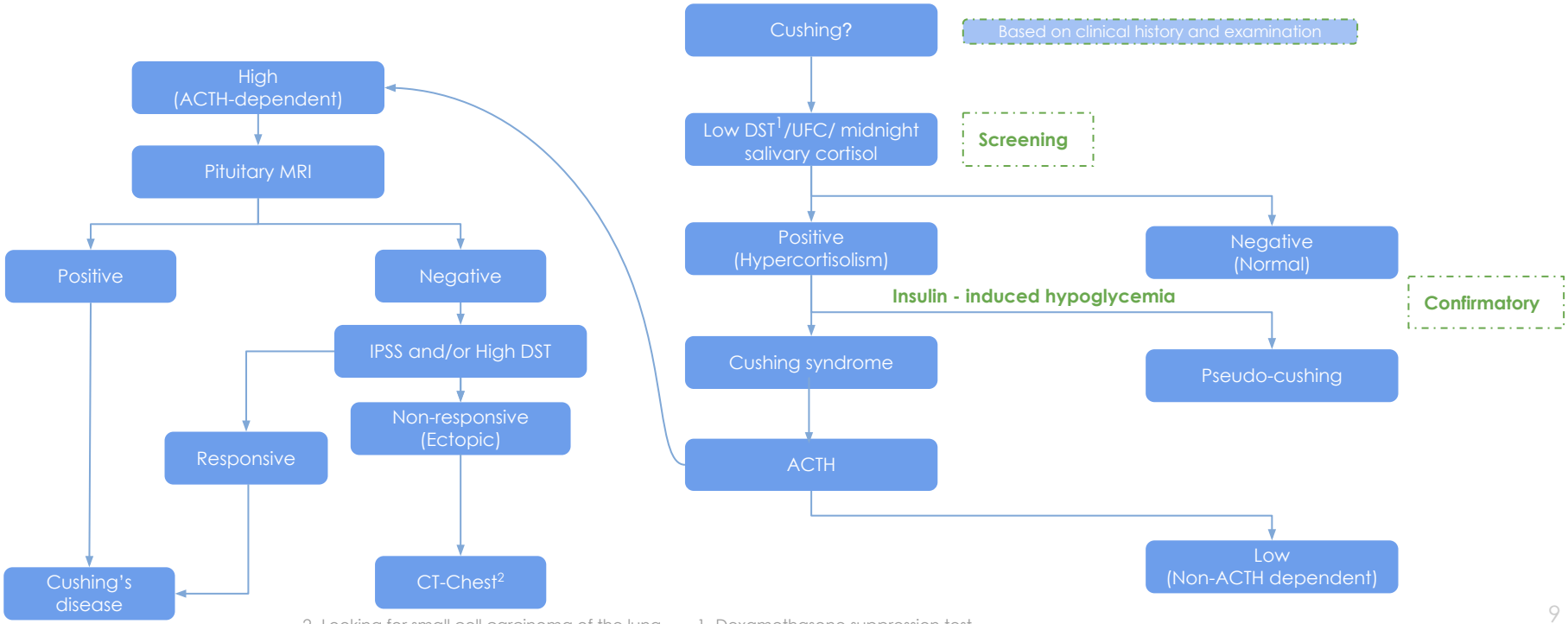
# Investigations of Suspected Adrenocortical Hyperfunction

**A. Screening and confirmatory tests**

- To assess the clinical diagnosis of adrenocortical hyperfunction

**B. Test to determine the cause:** to ascertain:

1) the site of the pathologic lesion
2) the nature of the pathologic lesion




2- Looking for small cell carcinoma of the lung

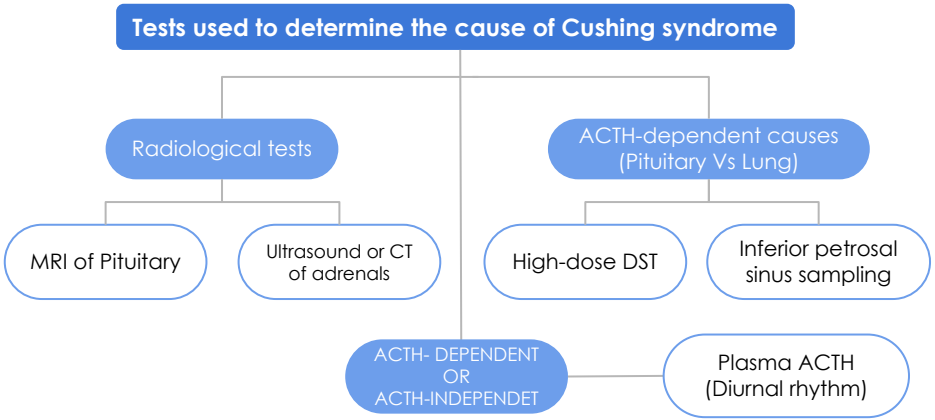
1- Dexamethasone suppression test

# Screening Tests

| | | |
|---|---|---|
| **LOW-dose DST** | **Procedure:** 1 mg dexamethasone (DXM) administered at 11 PM -12 AM the night before attending the clinic.<br>Serum cortisol is measured at 8-9 AM. | **Result:** Cortisol < 50 nmol/L (suppression) → exclude hypercortisolemia (Cushing Syndrome)<br>**Precautions:** enzyme inducers drugs (Phenobarbitone & phenytoin) → ↑ DXM metabolism and ↓ DXM blood level to achieve CRH suppression (false diagnosis of Cushing) |
| **24-hours urinary free cortisol** | **Procedure:** 24 hours urinary collection from the patient. | **Result:** Cortisol < 250 nmol/day → exclude Cushing Syndrome<br>**Disadvantage:** incomplete collection of urine → a false-negative result. |
| **Midnight Salivary Cortisol** | **Procedure:** sample from patient's saliva at Midnight. | **Result:** Cortisol < 100 ng/dL → exclude Cushing Syndrome. |

**Confirmatory Tests**

- Positive results of at least two screening tests would confirm the clinical diagnosis.
- Further investigation are required



## Causes of Adrenocortical Hyperfunction (Cushing's Syndrome)

- ACTH-dependent
  - ↑ Pituitary ACTH >90% (Cushing's disease)
  - Ectopic ACTH by neoplasm <10%
- ACTH-independent
  - Glucocorticoid therapy
  - Adrenal Tumor <20% (adenoma or carcinoma)

## High dose DST

- It is used to distinguish Cushing's disease from ectopic ACTH secretion.
- 2mg DXM six-hourly for 48 hours to suppress cortisol secretion.
- Basal (pre-DXM) serum cortisol or 24-hour urine free cortisol is compared with the results at the end of the 48-hour period.
- Suppression is defined as fall to less than 50% of basal value.
  - About 90% of patients with Cushing's disease show suppression of cortisol output.
- In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) show suppression. False positive

## PLASMA ACTH

It should be measured on Blood specimens at 8-9a.m and 8-9 p.m

**Plasma ACTH**

- Undetectable
  - Functional adrenal tumor → confirmed by an abdominal CT scan to detect an adrenal mass
- ↑↑ ACTH
  - Cushing's disease (pituitary-dependent)
- ↑↑↑↑ ACTH
  - Ectopic (non-endocrine) origin of ACTH

**Other Blood tests**
For patients suspected with Cushing

- Full blood count
- Blood glucose
- Blood electrolytes and pH
- Renal function tests
- Liver function tests

# Case Study

58 years old man was admitted with weight loss and Respiratory distress. He had increased pigmentation and BP was 140/80.

| Lab tests | Result | Normal Range |
|---|---|---|
| Urea | 8.6 | (2.5-7 mmol/L) |
| Sodium | 144 | (135-145 mmol/L) |
| Potassium | 2.0 | (3.5-4.5 mmol/L) |
| Cortisol | 1650 | (150-550 nmol/L) |
| Post overnight DXM | 1530 | (<50 nmol/L) |

Further investigation revealed the following:

| DXM suppression test | Basal | After 48h 0.5mg qid | After 48h 2.0mg qid |
|---|---|---|---|
| Serum Cortisol | 1350 | 1420 | 1100 (No suppression) [1] |

| | 8.00 am | 10.00 pm | |
|---|---|---|---|
| Plasma ACTH (ng/L) | 220 (sky high) | 180 [2] | Ref.range: 7-51ng/L |

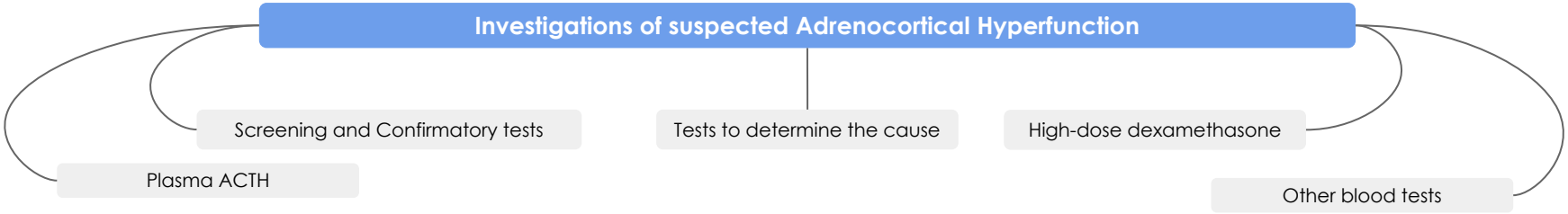
1. Didn't fall to less than 50% → Ectopic
2. Independent

# Take Home Messages

- Initial screening for Cushing by 24 h UFC, LOW Dose DSA suppression test or Midnight Salivary Cortisol.
- Confirmatory tests for Cushing by getting positive results of at least two of the screening tests.
- Tests to determine the cause of Cushing: Plasma ACTH, High-dose DXM suppression test, inferior petrosal sinus sampling and radiological investigations.
- ACTH-dependent Cushing: due to pituitary causes (Cushing's disease) and due to ectopic production of ACTH.
- ACTH-independent Cushing: due to adrenal carcinoma or carcinoma and due to steroid therapy.

# Summary

| | Glucocorticoids (Cortisol) |
|---|---|
| Function | • Anti insulin effect,<br>• Increase gluconeogenesis<br>• Proteolysis, lipolysis |
| Regulation | Highest in the morning, lowest in the evening<br>CRH → ACTH → Cortisol |
| Increase Cortisol | • Cushing Syndrome, Stress, Exercise, Chronic renal failure, Obesity<br>• Increased CBG: Congenital, Pregnancy, Estrogen therapy |
| Symptoms of Cushing | Moon face, Buffalo's hump, Central obesity, purple striae, Proximal limb weakness, Hirsutism |



# Quiz

## MCQs :

**Q1: How many carbon present in testosterone and estradiol respectively:**
**a)** 19,18 **b)** 18,19 **c)** 19,19 **d)** 17,18

**Q2: Which of the following is correct regarding cortisol function?**
**a)** Lower the rate of lipolysis **b)** Gluconeogenesis from new amino acids
**c)** Production of ketone bodies **d)** B & c

**Q3: During which of the following cortisol level will increase?**
**a)** Emotional stress **b)** 8-11pm **c)** Sleep

**Q4: Which of the following tests would confirm Ectopic type of Adrenocortical hyperfunction ?**
**a)** High-dose DSA **b)** Low-dose DSA
**c)** MRI of pituitary **d)** 24h Urine free cortisol

**Q5: Which of the following is common site of Ectopic ACTH secreting tumor:**
**a)** Breast **b)** Heart **c)** Pituitary gland **d)** Lungs

**Q6: What is the cause of Cushing disease:**
**a)** Adrenal tumor **b)** Pituitary tumor
**c)** Ectopic tumors **d)** Exogenous cortisol

## SAQs :

**Q1: Mention two conditions cause increase in CBG.**

**Q2: What if the effect of cortisol on the liver?**

**Q3: Mention two of the screening tests?**

**Q4: Mention four symptoms of Cushing Syndrome?**

★ **MCQs Answer key:**

1) a 2) d 3) a 4) a 5) d 6) b

★ **SAQs Answer key:**

1) 1- pregnancy 2- oral contraceptive
2) It's insulin antagonist and have weak mineralocorticoid action:
   - Gluconeogenesis from amino acids and lipids
   - Ketogenesis
   - Increase amino acid uptake and degradation
3) 1- 24h urine free cortisol 2- Midnight Salivary Cortisol
4) - Increase BP - Hyperglycemia - buffalo's hump -Weight gain

# Team members

**Girls Team:**

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

**Boys Team:**

- Alkassem Binobaid
- **Fares Aldokhayel**
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- **Yazen Bajeaifer**

# Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ **The best time for new beginning is NOW.**

438 BIOCHEMISTRY TEAM

We hear you