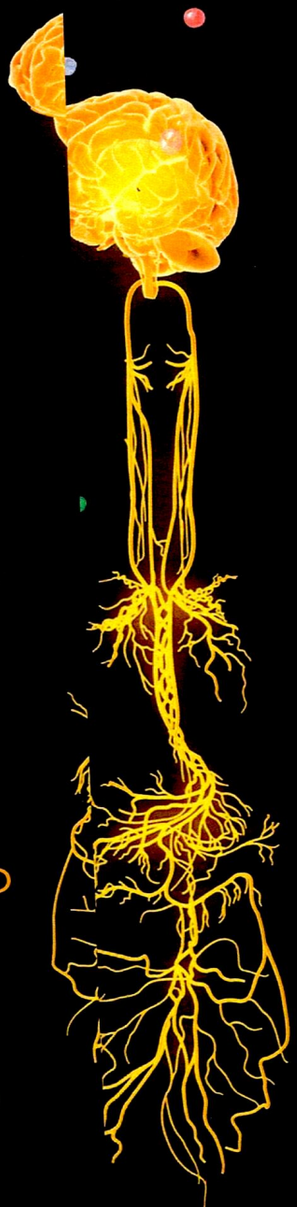
Medical

GROUP
NEET SS

Volume 6
2nd Edition

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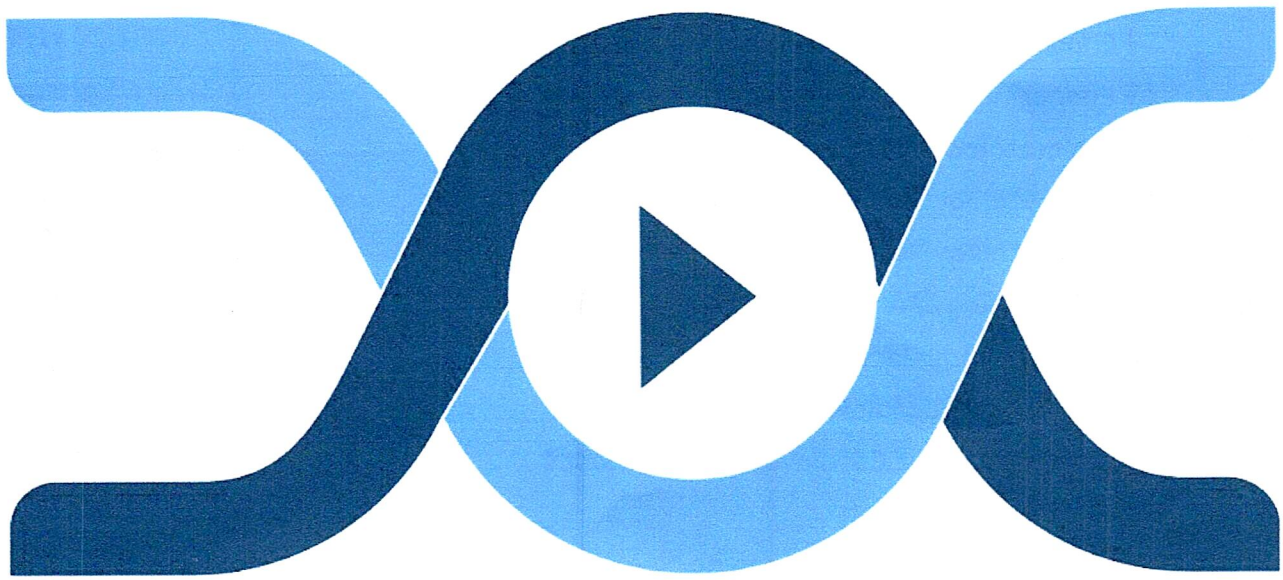
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ENDOCRINOLOGY PART-3

Basic Endocrine Physiology 00:00:10

Examples of Prevalent Endocrine and Metabolic Disorders in the Adult		
Disorder	Approximate Prevalence in adults	Screening/Testing recommendations
Obesity	40% Obese, BMI≥30 70% Overweight, BMI≥25	Calculate BMI Measure waist circumference Exclude secondary causes Consider comorbid complications
Type 2 diabetes mellitus	>10%	Beginning at age 45, screen every 3 years, or earlier in high-risk groups: FPG >126 mg/dL Random plasma glucose >200 mg/dL An elevated HbA_{1c} Consider comorbid complications
Hyperlipidemia	20-25%	Cholesterol screening at least every 5 years; more often in high-risk groups Lipoprotein analysis (LDL, HDL) for increased cholesterol, CAD, diabetes Consider secondary causes

- Prevalence of Type 2 Diabetes mellitus in India according to recent data: 8%
- ADA recommendation revised diabetes screening begin at 35 years, done every 3 years
- Prediabetes: Screening every year

Examples of Prevalent Endocrine and Metabolic Disorders in the Adult (Continued)		
Disorder	Approximate prevalence in adults	Screening/testing recommendations
Metabolic syndrome	35%	Measure waist circumference, FPG, BP, lipids
Hypothyroidism	5-10%, women 0.5-2%, men	TSH, confirm with free T_4
Graves' disease	1-3%, women 0.1%, men	TSH, free T_4
Thyroid nodules and neoplasia	2-5% palpable >25% by ultrasound	Physical examination or ultrasound of thyroid Fine-needle aspiration biopsy
Osteoporosis	5-10%, women 2-5%, men	Bone mineral density measurements in women>65 years or in postmenopausal women or men at risk

		Exclude secondary causes
Hyperparathyroidism	0.1–0.5%, women> men	Serum calcium PTH, if calcium is elevated Assess comorbid conditions
Infertility	10%, couples	Investigate both members of couple Semen analysis in male Assess ovulatory cycles in female Specific tests as indicated
Polycystic ovarian syndrome	5–10%, women	Free testosterone, DHEAS Consider comorbid conditions
Hirsutism	5–10%	Free testosterone, DHEAS Exclude secondary causes Additional tests as indicated
Menopause	Median age, 51	FSH
Hyperprolactinemia	15% in women with amenorrhea or galactorrhea	PRL level MRI, if not medication-related
Erectile dysfunction	10–25%	Careful history, PRL, testosterone Consider secondary causes (e.g., diabetes)
Hypogonadism, male	1–2%	Testosterone, LH
Gynecomastia	15%	Often, no tests are indicated Consider Klinefelter's syndrome Consider medications, hypogonadism, liver disease
Klinefelter's syndrome	0.2%, men	Karyotype Testosterone
Vitamin D deficiency	10%	Measure serum 25-OH vitamin D Consider secondary causes
Turner's syndrome	0.03%, women	Karyotype Consider comorbid conditions

- Prevalence of Vitamin D deficiency in India: >70%
- Prevalence of thyroid nodule by ultrasound method:50%

Examples of Membrane Receptor Families and Signaling Pathways		
Receptors	**Effectors**	**Signaling pathways**
G Protein–Coupled Seven-Transmembrane Receptor (GPCR)		
β-Adrenergic, LH, FSH, TSH	G_s, α, adenylate cyclase	Stimulation of cyclic AMP production, protein kinase A
Glucagon, PTH, PTHrP, ACTH, MSH, GHRH, CRH	Ca^{2+} channels	Calmodulin, Ca^{2+} -dependent kinases
α-Adrenergic, somatostatin	G_i, α	Inhibition of cyclic AMP production Activation of K^+, Ca^{2+} channels
TRH, GnRH	G_q, G_{11}	Phospholipase C, diacyl-glycerol, IP_3, protein kinase C,

		voltage-dependent Ca^{2+} channels
Receptor Tyrosine Kinase		
Insulin, IGF-I EGF, NGF	Tyrosine kinases, IRS Tyrosine kinases, ras	MAP kinases, PI 3-kinase; AKT Raf, MAP kinases, RSK
Cytokine Receptor-Linked Kinase		
GH, PRL	JAK, tyrosine kinases	STAT, MAP kinase, PI 3-kinase, IRS-1
Serine Kinase		
Activin, TGF-β, MIS	Serine kinase	Smads

G protein α: 3 Subunit:

1. $G_s\alpha$: Activates cAMP: Pituitary and Hypothalamic Hormones act via $G_s\alpha$
2. $G_i\alpha$: Inhibitory response
3. G_q, G_{11}
   - Somatostatin: Acts via $G_i\alpha$
   - α_2-Adrenergic: Acts via $G_i\alpha$
   - GHRH: Acts via ↑cAMP and Ca^{2+} channels
   - Cytokine Receptor-Linked Kinase: GH, PRL, Leptin, Erythropoietin: Acts via Cytokine Receptor-Linked Kinase
   - AMH: Acts via Serine kinase pathway

Genetic Causes of G protein Receptor Disorders		
RECEPTOR	**DISORDER**	**GENETICS**
LH	Leydig cell hypoplasia (male) Primary amenorrhea, resistance to LH (female) Familial male precocious puberty (male) Leydig cell adenoma, precocious puberty (male)	AR, inactivating AR, inactivating AD, activating Sporadic, activating
FSH	Hypergonadotropic ovarian failure (female) Hypospermia (male) Ovarian hyperstimulation (female)	AR, inactivating AR, inactivating Sporadic, activating
TSH	Congenital hypothyroidism, TSH resistance Nonautoimmune familial hyperthyroidism Hyperfunctioning thyroid adenoma	AR, AD, inactivating AD, activating Sporadic, activating
GARH	Hypogonadotropic hypogonadism	AR, inactivating
Kisspeptin	Hypogonadotropic hypogonadism precocious puberty	AR, inactivating AD, activating
Prokineticin	Precocious puberty	Sporadic, activating
TRH	Central hypothyroidism	AR, inactivating
GHRH	GH deficiency	AR, inactivating
PTH	Blomstrand chondrodysplasia	AR, inactivating

	Jansen metaphyseal chondrodysplasia	
Calcium sensing receptor	Familial hypocalciuric Hypercalcemia Neonatal severe hyperparathyroidism Familial hypocalcemia hypercalciuria	AD, inactivating AR, inactivating AD, activating
Arginine Vasopressin receptor 2	Nephrogenic diabetes insipidus Nephrogenic SIADH	XL, inactivating XL, activating
ACTH	Familial ACTH resistance ACTH-independent Cushing syndrome	AR, inactivating Sporadic, activating
Melanocortin 4	Severe obesity	Codominant, inactivating

- LH receptors: Activating mutation: Familial male precocious puberty: Testotoxicosis.
- TSH receptor: Activating mutation: Congenital Hyperthyroidism
  - Inactivating mutation: Congenital Hypothyroidism
- Kisspeptin: Activating mutation: Precocious puberty.
  - Inactivating mutation: Hypogonadotropic Hypogonadism
- PTH receptor: Activating mutation: Jansen metaphyseal chondrodysplasia.
  - Inactivating mutation: Blomstrand chondrodysplasia
- Ca sensing receptor: Activating mutation: Familial hypocalcemia hypercalciuria
  - Inactivating mutation: Familial hypocalciuric Hypercalcemia
- ACTH receptor: Inactivating mutation: Familial ACTH resistance: MC_2R mutation. It will lead to decrease in Glucocorticoids and Androgens and preserved Aldosterone.
- Melanocortin 4 receptor mutation: Inactivating Mutation: Severe obesity
- MSH: Induces satiety
- It is the most common cause for monogenic obesity
- Setmelanotide: Used in POMC deficiency

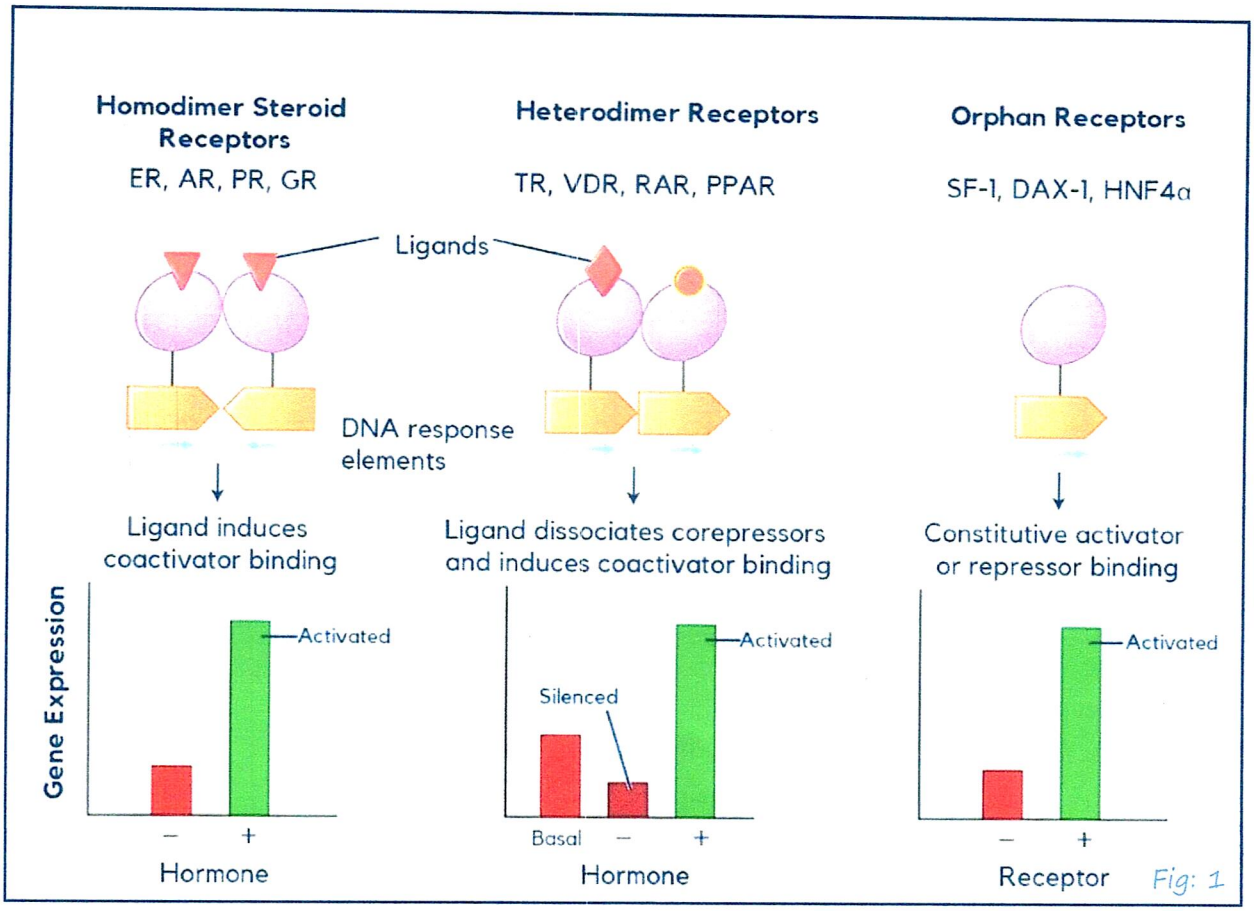


Fig: 1

- *Heterodimer Receptors: TR, VDR, RAR, PPAR*
- *HNF4 alpha: MODY-1 Diabetes*
- *SF-1: Adrenal insufficiency and Gonadal dysgenesis*
- *DAX-1: Adrenal hypoplasia congenita*
  - *: X-Linked dominant*
  - *: Hypogonadotropic hypogonadism*

Pituitary Gland

00:19:43

Anterior Pituitary Hormone Expression and Regulation					
Cell	Corticotrope	Somatotrope	Lactotrope	Thyrotrope	Gonadotrope
Tissue-specific transcription factor	T-Pit	Prop-1, Pit-1	Prop-1, Pit-1	Prop-1, Pit-1, TEF	SF-1, DAX-1
Fetal appearance	6 weeks	8 weeks	12 weeks	12 weeks	12 weeks
Hormone	POMC	GH	PRL	TSH	FSH, LH
Protein	Polypeptide	Polypeptide	Polypeptide	Glycoprotein α,β 3 subunits	Glycoprotein α,β 3 subunits
Amino acids	266 (ACTH 1-39)	191	198	211	210,204
Stimulators	CRH, AVP, gp-130 cytokines	GHRH, ghrelin	Estrogen, TRH, VIP	TRH	GnRH, activins, estrogen

Inhibitors	Glucocorticoids	Somatostatin, IGF-1	Dopamine	T_3, T_4, dopamine, somatostatin, glucocorticoids	Sex steroids, inhibin
Target gland	Adrenal	Liver, bone, other tissues	Breast, other tissues	Thyroid	Ovary, testis
Trophic effect	Steroid production	IGF-1 production, growth induction, insulin antagonism	Milk production	T_4 synthesis and secretion	Sex steroid production, follicle growth, germ cell maturation
Normal range	ACTH, 4-22 pg/L	<0.5 µg/L	M<15 µg/L; F <20 µg/L	0.1-5 mU/L	M, 5-20 IU/L, F (basal), 5-20 IU/L

- Earliest to develop: Corticotrophs
- Transcription factor for corticotrophs: T-Pit (TBX19)
- Pit-1 is not required for development of: Gonadotrophs, Corticotrophs
- Amino acids for GH, PRL: GH:191, PRL:198
- Inhibitors of TSH: T3, T4, Dopamine, Somatostatin, Glucocorticoids
- Stimulators of PRL: Estrogen, TRH, VIP

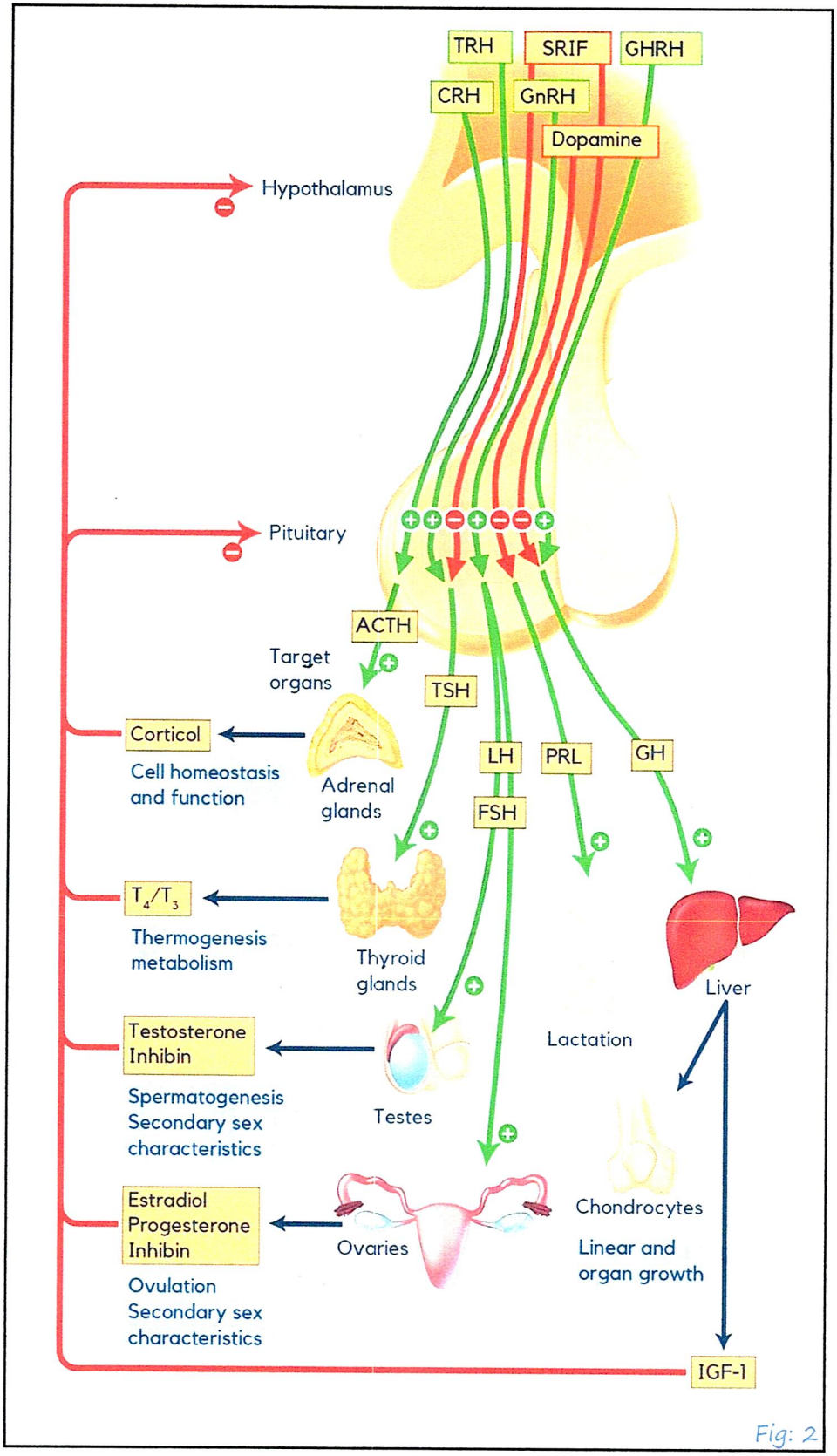


Fig: 2

- Inhibin is produced by Granulosa cells in females and Sertoli cell in males.
- Inhibin has negative feedback regulation on FSH.

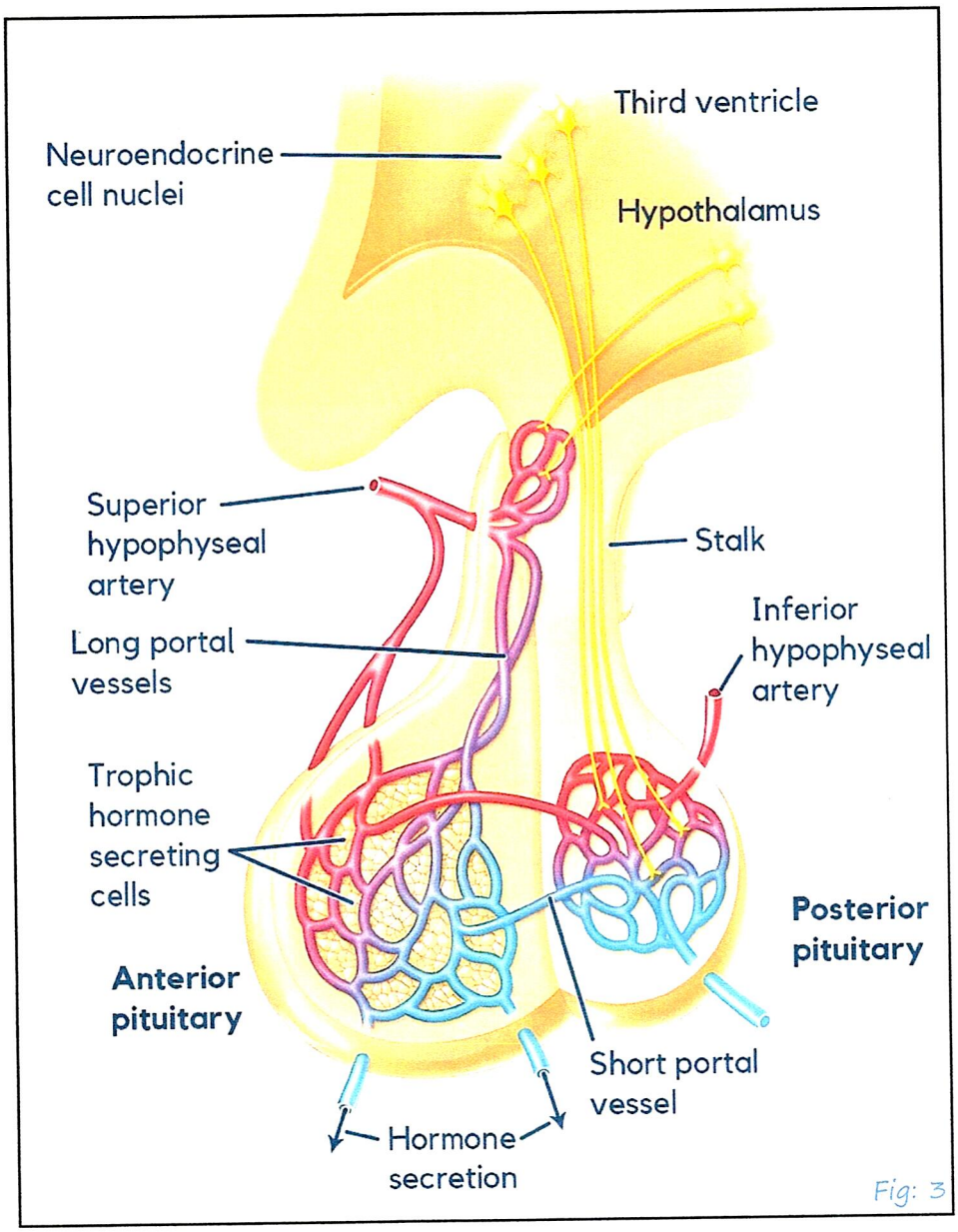
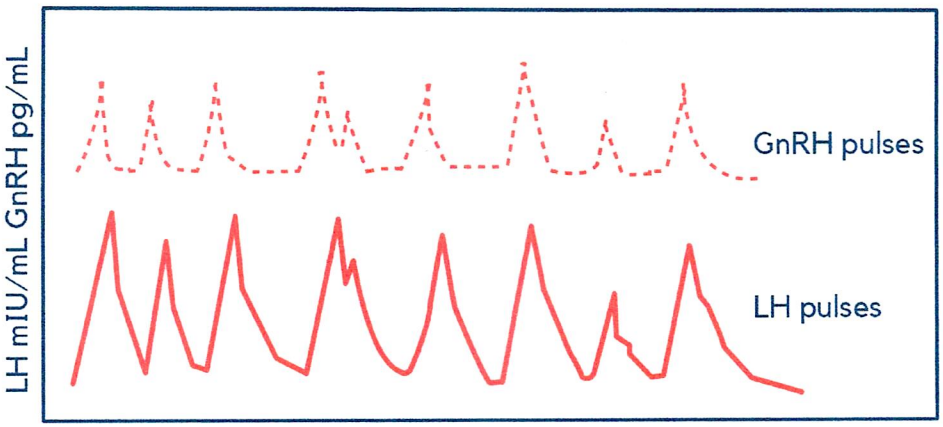


Fig: 3

Blood supply of Pituitary gland

- Anterior pituitary gland is supplied by superior hypophyseal artery which is a branch of cerebral part of internal carotid artery- forms the hypothalamic portal circulation.
- Posterior pituitary is supplied by inferior hypophyseal artery, a branch of cavernous portion of ICA.
- Metastasis reaches pituitary mainly from inferior hypophyseal artery which maintains the systemic arterial blood supply to pituitary.
- Most common site for primary in pituitary metastasis: Breast>lung
- Most common clinical manifestation of pituitary metastasis: Diabetes insipidus.
- Oxygen tension in portal circulation is low compared to posterior pituitary.
- In Sheehan syndrome least common manifestation is Diabetes Insipidus.



- GnRH: Located in medial pre-optic nucleus of Hypothalamus
- Frequency of GnRH pulse: 60-90 min
- When frequency is increased: stimulate LH
- When frequency is reduced: stimulate FSH
- In PCOD: ↑LH/FSH Ratio

Etiology of Hypopituitarism
Development/structural
Midline cerebral defect syndromes
Pituitary dysplasia/aplasia
Primary empty sella
Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Bardet-Biedl syndrome, Kallmann syndrome)
Congenital central nervous system mass, encephalocele
Genetic
Combined pituitary hormone deficiencies
Isolated primary hormone deficiencies
Traumatic
Surgical resection
Radiotherapy damage
Head injuries
Neoplastic
Pituitary adenoma
Parasellar mass (germinoma, ependymoma, glioma)
Rathke's cyst
Craniopharyngioma
Hypothalamic hamartoma, gangliocytoma
Pituitary metastases (breast, lung, colon carcinoma)
Lymphoma and leukaemia
Meningioma
Infiltrative/inflammatory
Lymphocytic hypophysitis

Hemochromatosis
Sarcoidosis
Histiocytosis X
Granulomatous hypophysitis
Transcription factor antibodies
Immunotherapy
Vascular
Pituitary apoplexy
Pregnancy-related (infarction with diabetes, postpartum necrosis)
Subarachnoid hemorrhage
Sickle cell disease
Arteritis
Infections
Fungal (histoplasmosis)
Parasitic (toxoplasmosis)
Tuberculosis
Pneumocystis jirovecii

- Most common genetic cause of the combined pituitary hormone deficiencies: PROP-1
- Most common neoplastic cause: Pituitary Adenoma
- Hypothalamic hamartoma is linked to precocious puberty.
- Pituitary apoplexy occurs in preexisting pituitary tumor but in pregnancy, sickle cell disease and in patients who are anti-coagulants, snake bite it will occurs in Normal pituitary also.
- Presentation of Infiltrative disease: Sarcoidosis/Langerhans cell histiocytosis: Diabetes Insipidus is most common.
  - Hypophysitis: ACTH>TSH
- Cell lines affected in Sheehan syndrome: Prolactin, GH most commonly involved.
- Hormone earliest involved in surgery and radiotherapy: GH>Gonadotropin.

Tests of Pituitary Sufficiency			
Hormone	Test	Blood samples	Interpretation
Growth hormone (GH)	Insulin tolerance test: Regular insulin (0.05-0.15 U/kg IV)	-30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL, GH should be >3µg/L
	GHRH test: 1 µg/kg IV	0,15, 30, 45, 60,120 min for GH	Normal response is GH >3µg/L
	L-Arginine test: 30 g IV over 30 min	0, 30, 60,120 min for GH	Normal response is GH >3µg/L
	L-Dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH >3µg/L
Prolactin	TRH test: 200-500 µg IV	0, 20, and 60 min for TSH and PRL	Normal prolactin is >2 µg/L and increase >200% of baseline
ACTH	Insulin tolerance test: regular insulin (0.05-0.15 U/kg IV)	-30, 0, 30, 60, 90 min for glucose and cortisol	Glucose <40 mg/dL Cortisol should increase by >7 µg/dL or to >20 pg./dL
	CRH test: 1µg/kg ovine CRH IV at 8 A.M.	0,15, 30, 60, 90,120 min for ACTH and cortisol	Basal ACTH increases 2- to 4-fold and peaks at 20-100 pg./mL Cortisol levels >20-25 pg./dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 AM; ACTH can also be measured	Plasma cortisol should be <4 g/dL to assure an adequate response. Normal response is 11-deoxycortisol >7.5 µg/dL or ACTH >75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (cosyntropin), 0.25 mg IM or IV	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol >21 g/dL and aldosterone response >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (cosyntropin), 1µg IV	0, 30, 60 min for cortisol	Cortisol should be >21 µg/dL
	3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8h each day		Cortisol >21 µg/dL

- Gold standard test for the GH and ACTH insufficiency: Insulin tolerance test and glucagon stimulation test.
- Metyrapone test: Secondary Adrenal insufficiency.
- ACTH stimulation test: Primary Adrenal insufficiency
- For Growth hormone test cut off value after test :7ng/mL in children and 5ng/mL in adults.

TSH	Basal thyroid function tests: T_4, T_3, TSH	Basal measurements	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased indicate pituitary insufficiency
	TRH test: 200–500 µg IV	0, 20, 60 min for TSH and PRL°	TSH should increase by >5 mU/L unless thyroid hormone levels are increased
LH, FSH	LH, FSH, testosterone, estrogen	Basal measurements	Basal LH and FSH should be increased in postmenopausal women. Low testosterone levels in the setting of low LH and FSH indicate pituitary insufficiency
	GnRH test: GnRH (100 µg) IV	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH (1 µg/kg), CRH (1 µg/kg), GnRH (100 µg). TRH (200 µg) are given IV	-30, 0,15, 30, 60, 90,120 min for GH, ACTH, cortisol, LH, FSH, and TSH	Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic

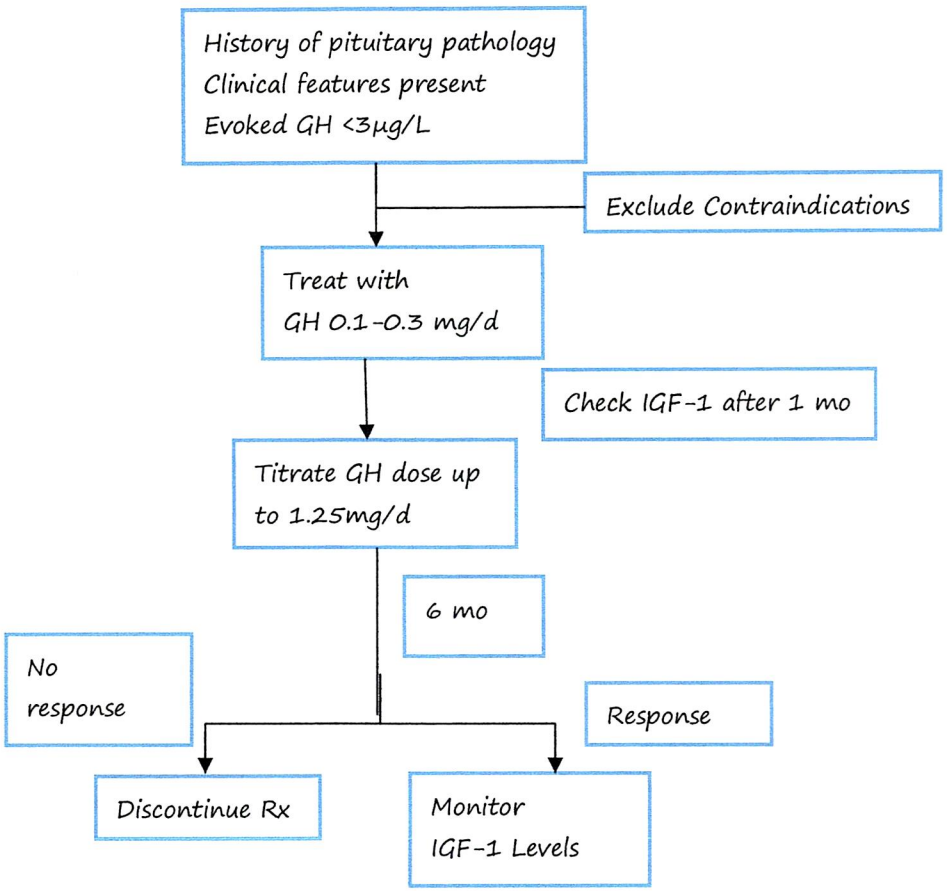
Hormone Replacement Therapy for Adult Hypopituitarism	
Hormone deficit	**Hormone replacement**
ACTH	Hydrocortisone (10–20 mg/d in divided doses)
	Cortisone acetate (15–25 mg/d in divided doses)
	Prednisone (5 mg A.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males
	Testosterone gel (5–10 g/d)
	Testosterone skin patch (5 mg/d)
	Testosterone enanthate (200 mg IM every 2 weeks)
	Females
	Conjugated estrogen (0.65–1.25 mg qd for 25 days)
	Progesterone (5–10 mg qd) on days 16–25
	Estradiol skin patch (0.025–0.1 mg every week), adding progesterone on days 16–25 if uterus intact
	For fertility: menopausal gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.1–1.25 mg SC qd) Children: Somatotropin (0.02–0.05 mg/kg per day)
Vasopressin	
	Intranasal desmopressin (5–20 g twice daily) Oral 300–600 µg qd

- Secondary Hypothyroidism: Always evaluate for HPA axis first. If multiple pituitary hormone deficiencies found give steroid first followed by Thyroxin.
  - Effect of GH replacement on other axis:
    1. Secondary Hypothyroidism: GH increase Somatostatin and Increase the peripheral conversion of T4 to T3 and ultimately leads to reduced TSH.
    2. Inhibit 11βHSD1 (Cortisone to cortisol)
- Effect of Estrogen supplementation on other axis:
  - Increase Thyroxine binding globulin.
  - Increase Cortisol binding globulin.
  - Increase Sex hormone binding globulin: reduce free available testosterone.
  - Inhibit IGF1 generation: ↑ GH doses:
  - Give Transdermal estrogen when both estrogen and growth hormone both supplementation is needed.s

Features of Adult Growth Hormone Deficiency
Clinical
Impaired quality of life
Decreased energy and drive
Poor concentration
Low self-esteem
Social isolation
Body composition changes
Increased body fat mass
Central fat deposition
Increased waist-to-hip ratio
Decreased lean body mass
Reduced exercise capacity
Reduced maximum O_2 uptake
Impaired cardiac function
Reduced muscle mass
Cardiovascular risk factors
Impaired cardiac structure and function
Abnormal lipid profile
Decreased fibrinolytic activity
Atherosclerosis
Omental obesity
Imaging
Pituitary, mass or structural damage
Bone: reduced bone mineral density
Abdomen: excess omental adiposity
Laboratory
Evoked GH <3 ng/mL
IGF-1 and IGFBP3 low or normal
Increased LDL cholesterol
Concomitant gonadotropin, TSH, and/or ACTH reserve deficits may be present

Adult Growth Hormone deficiency estimation test are:

- Insulin tolerance test: Risk for Hypoglycemia:5ng/mL
- Glucagon stimulation test: Preferred test:3ng/mL
- Macimorelin (Ghrelin analogue): 5ng/mL



- In Children GH given based on Weight based doses
- In adults IGF-1 Based.
- Women require higher dose of GH because estrogen inhibits the IGF generation of liver.
- 0.3mg: Women
- 0.2mg: Men
- 0.1mg: Old age