Hypopituitarism

Chapter 391 | Harrison's 22e

KEY CLINICAL POINTS

1. Hypopituitarism can be caused by developmental/structural defects, genetic mutations, trauma, neoplasm, infiltration, vascular events, or drug-induced injury.
2. Pit-1 mutations lead to combined GH, PRL, and TSH deficiencies; PROP1 mutations cause GH, PRL, TSH, and gonadotropin deficiency (ACTH deficiency may follow).
3. Kallmann Syndrome is a specific hypothalamic disorder characterized by GnRH deficiency and anosmia/hyposmia.
4. Diagnosis of pituitary sufficiency involves various stimulation tests (e.g., Insulin tolerance, CRH, Metyrapone) to assess GH, ACTH, and LH/FSH levels.
5. Adult growth hormone (GH) deficiency is characterized by impaired quality of life, increased body fat, and reduced muscle mass.
6. Management of GH deficiency involves a titration period starting at 0.1–0.3 mg/d with evaluation at 6 months.
7. ACTH replacement options include Hydrocortisone, Cortisone acetate, or Prednisone.
8. AVP deficiency is treated with intranasal desmopressin (5–20 µg twice daily) or oral desmopressin (300–600 µg qd).
9. Pituitary apoplexy and pregnancy-related events are significant causes of acute pituitary failure.
10. Newer immunotherapies (CTLA-4, PD-1/PD-L1 inhibitors) are identified as potential causes of drug-induced hypopituitarism.

DEFINITION & CLASSIFICATION

- **Definition (Harrison's 22e):** *Impaired production of one or more of the anterior pituitary trophic hormones can result from inherited disorders; more commonly, adult hypopituitarism is acquired and reflects the compressive mass effects of tumors or the consequences of local pituitary or hypothalamic traumatic, autoimmune, inflammatory, or vascular damage.*

ETIOLOGY & PATHOPHYSIOLOGY

Developmental and Structural Causes

- **Structural Defects:** Pituitary dysplasia may result in aplastic, hypoplastic, or ectopic development due to midline cell migration issues.
- **Midline Cerebral Defect Syndromes:** Associated with craniofacial disorders; includes septo-optic dysplasia, Prader-Willi syndrome, Bardet-Biedl syndrome, and Kallmann syndrome.
- **Genetic Mutations:**
  - Pit-1 mutations → combined GH, PRL, and TSH deficiencies (often with growth failure).

– PROP1 mutations → combined GH, PRL, TSH, and gonadotropin deficiency; ACTH deficiency usually occurs sequentially (GH → FSH/LH → TSH → ACTH).

CLINICAL FEATURES

Adult Growth Hormone (GH) Deficiency (Table 391-4)

- **Clinical Features:**
  – Impaired quality of life: decreased energy/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.
  – Physical capacity: reduced exercise capacity, reduced maximum O_2 uptake, reduced muscle mass.
  – Cardiovascular risk: impaired cardiac structure/function, abnormal lipid profile (increased LDL), decreased fibrinolytic activity, atherosclerosis, omental obesity.
- **Imaging Findings:**
  – Pituitary: mass or structural damage.
  – Bone: reduced bone mineral density.
  – Abdomen: excess omental adiposity.
- **Laboratory Findings:**
  – Evoked GH < 30 ng/mL.
  – IGF-1 and IGFBP-3 low or normal.
  – Increased LDL cholesterol.
  – Potential concurrent gonadotropin, TSH, and/or ACTH reserve deficits.

Hypothalamic Endocrine Dysfunction

- **Kallmann Syndrome:**
  – Cause: Defective GnRH synthesis and GnRH deficiency.
  – Clinical Presentation: Anosmia or hyposmia (due to olfactory bulb agenesis/hypoplasia), potentially with color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism, and neurologic abnormalities.

DIAGNOSTIC APPROACH

1. **GH Assessment (Table 391-2):**
   - Insulin tolerance test: (0.05–0.15 U/kg IV) → Glucose <40 mg/dL; GH should be >3 µg/L.
   - GHRH/L-arginine test: (GHRH 1 µg/kg IV, arginine 30 g IV over 30 min) → Normal response is BMI dependent (11 µg/L if BMI <25; 8 µg/L if BMI 25–30; 4 µg/L if BMI ≥30).
   - Ghrelin receptor agonist test: (0.5 mg/kg PO) → Normal response is GH >2.8 µg/L.
   - Glucagon test: (1 mg IM; 1.5 mg if weight >90 kg) → Normal response is GH >3.0 µg/L (if BMI <25); GH >1.0 µg/L (if BMI ≥30 and high pretest probability).
   - l-Dopa test: (500 mg PO) → Normal response is GH >3 µg/L.
   - TRH test: (200–500 µg IV) → Used for TSH and PRL.
2. **ACTH Assessment (Table 391-2):**

- Insulin tolerance test: (0.05–0.15 U/kg IV) → Glucose <40 mg/dL; Cortisol should increase by >7 µg/dL or to >20 µg/dL.
- CRH test: (1 µg/kg CRH IV at 8 a.m.) → Basal ACTH increases 2–4 fold (peak 20–100 pg/mL); Cortisol >20–25 µg/dL.
- Metyrapone test: (30 mg/kg at midnight) → Plasma cortisol <4 g/dL; Normal response is 11-deoxycortisol >7.5 µg/dL or ACTH >75 pg/mL.
- Standard ACTH stimulation test: (ACTH 1-24, 0.25 mg IM or IV) → Cortisol >21 µg/dL and aldosterone response >4 ng/dL above baseline.
- Low-dose ACTH test: (ACTH 1-24, 1 µg IV) → Cortisol should be >21 µg/dL.
- 3-day ACTH stimulation test: (0.25 mg ACTH 1-24 given IV over 8 h each day) → Cortisol >21 µg/dL.
- Basal thyroid function tests: T, T3, TSH.
- TRH test: (200–500 µg IV) → Used for TSH and PRLa.

3. **LH/FSH Assessment (Table 391-2):**
   - Basal measurements: LH, FSH, testosterone, estrogen.
   - GnRH test: (GnRH 100 µg IV) → LH should increase by 10 IU/L and FSH by 2 IU/L.
4. **Multiple Hormones (Table 391-2):**
   - Combined anterior pituitary test: GHRH, CRH, GnRH, TRH administered sequentially to assess multiple hormones.

MANAGEMENT & TREATMENT

Growth Hormone (GH) Management (Flowchart 1)

1. **Initial Screening:** Identify patients with history of pituitary pathology, clinical features, or evoked GH <3 µg/L.
2. **Pre-treatment:** Exclude contraindications.
3. **Initiation:** Treat with GH 0.1–0.3 mg/d.
4. **Short-term Monitoring:** Check IGF-1 after 1 month.
5. **Titration:** Titrate GH dose up to 1.25 mg/d.
6. **Evaluation (at 6 months):**
   - If Response → Monitor IGF-1 Levels.
   - If No response → Discontinue Rx.

Hormone Replacement Therapy (Table 391-3)

1. **ACTH Deficiency:**
   - Hydrocortisone (10–20 mg/d in divided doses)
   - Cortisone acetate (15–25 mg/d in divided doses)
   - Prednisone (5 mg a.m.)
2. **FSH/LH Deficiency:**
   - 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); OR Estradiol skin patch (0.025–0.1 mg every week) + Progesterone (if uterus intact).

3. **AVP Deficiency:**

- Intranasal desmopressin (5–20 μg twice daily)
- Oral desmopressin (300–600 μg qd).

COMPLICATIONS & PROGNOSIS

- **Pituitary Apoplexy:** Acute vascular event leading to pituitary failure.
- **Pregnancy-related complications:** Inclusion of infarction with diabetes and postpartum necrosis as causes of acute failure.

KEY PEARLS & HIGH-YIELD POINTS

- **Etiology Overview (Table 391-1):**
- Developmental: Midline defects, Pituitary dysplasia/aplasia, Primary empty sella.
- 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, Pituitary metastases, Lymphoma/leukemia, 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, Snake bite venom.
- Infections: Fungal (histoplasmosis), Parasitic (toxoplasmosis), Tuberculosis, Pneumocystis jirovecii.
- Drug-induced: CTLA-4 inhibitors, PD-1/PD-L1 inhibitors.

REFERENCE TABLES

TABLE 391-1

Etiology of Hypopituitarism a Development/structural

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TABLE 391-1

Etiology of Hypopituitarisma

- 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 leukemia 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 Snake bite venom Infections Fungal (histoplasmosis) Parasitic (toxoplasmosis) Tuberculosis Pneumocystis jirovecii Drug-induced CTLA-4 inhibitors PD-1/PD-L1 inhibitors

TABLE 391-2

Tests of Pituitary Sufficiency HORMONE GH

HORMONE	TEST	BLOOD SAMPLES	INTERPRETATION
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 >3 µg/L
	GHRH/L-arginine test: GHRH 1 µg/kg IV and arginine 30 g IV over 30 min	0, 15, 30, 45, 60, 120 min for GH	Normal GH response is BMI dependent: 11 µg/L if BMI <25 kg/m2, 8 µg/L if BMI 25-20, and 4 µg/L if BMI ≥30 Not available in the United States
	Ghrelin receptor agonist test: 0.5 mg/kg PO	0, 30, 45, 60, 90 min for GH	Normal response is GH >2.8 µg/L
	Glucagon test: 1 mg IM (1.5 mg if body weight >90 kg)	0, 30, 60, 90, 120, 150, 180, 210, 240 for GH	Normal response is GH >3.0 µg/L if BMI <25 kg/m2 or if BMI 25-30 and low pretest probability, and GH >1.0 µg/L if BMI 25-30 and high pretest probability or if BMI >30
	l-Dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH >3 µg/L
	TRH test: 200–500 µg IV	0, 20, and 60 min for TSH and PRL	
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 µg/dL
	CRH test: 1 µg/kg 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 µg/dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 a.m.; 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

HORMONE	TEST	BLOOD SAMPLES	INTERPRETATION
	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 µg/dL and aldosterone response >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (cosyntropin), 1 µg 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 8 h each day		Cortisol >21 µg/dL
	Basal thyroid function tests: T, T, TSH 4 3	Basal measurements	
	TRH test: 200–500 µg IV	0, 20, 60 min for TSH and PRLa	
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 (see text)

TABLE 391-3

Hormone Replacement Therapy for Adult Hypopituitarism a

HORMONE DEFICIT	HORMONE REPLACEMENT
ACTH	Hydrocortisone (10–20 mg/d in divided doses)
	Cortisone acetate (15–25 mg/d in divided doses)

HORMONE DEFICIT	HORMONE REPLACEMENT
	Prednisone (5 mg a.m.)

TABLE 391-4

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 uptake 2 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 IGFBP-3 low or normal Increased LDL cholesterol Concomitant gonadotropin, TSH, and/or ACTH reserve deficits may be present	
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
AVP	Intranasal desmopressin (5–20 g twice daily) Oral 300–600 μg qd