PIPADOR REVISION

# MRCOG Part 1 Revision Notes

## *Proteins: Haemoglobin*

BIOCHEMISTRY • LECTURE 226

VISUAL EXAMINATION REVISION NOTES

*2026 Edition*

MRCOG PART 1 REVISION NOTES | BIOCHEMISTRY

# 226 Proteins: Haemoglobin

*Structure, haem synthesis, oxygen binding, developmental haemoglobins, haemoglobinopathies and haemoglobin breakdown*

| $\alpha_2\beta_2$ | $Fe^{2+}$ | P50 3.5 kPa | 1.34 mL |
|---|---|---|---|
| HbA tetramer (4 haem, 4 $O_2$) | Ferrous iron binds $O_2$ ($Fe^{3+}$ = MetHb) | Adult; HbF ≈ 2.5 | $O_2$ per g Hb (fully saturated) |

**■ KEY FACTS: Learning objectives**

- Describe the structure of haemoglobin, haem synthesis and globin genes.
- Describe oxygen binding (cooperativity, ODC, Bohr and Haldane effects) and $CO_2$ carriage.
- Describe haemoglobin types through development, abnormal haemoglobins and haemoglobin breakdown.
- Relate to haemoglobinopathies, porphyrias and screening in pregnancy.

## 226.1 Structure

| Component | Details |
|---|---|
| **Globin chains** | Four polypeptides — HbA = 2 α + 2 β; α-like genes on chromosome 16 (ζ, α — duplicated), β-like on chromosome 11 (ε, γ, δ, β) — expressed in developmental order |
| **Haem** | Protoporphyrin IX + $Fe^{2+}$, held in a hydrophobic pocket; proximal histidine binds iron |
| **Quaternary states** | T (tense, deoxy) — low affinity, stabilised by 2,3-BPG and salt bridges; R (relaxed, oxy) — high affinity |

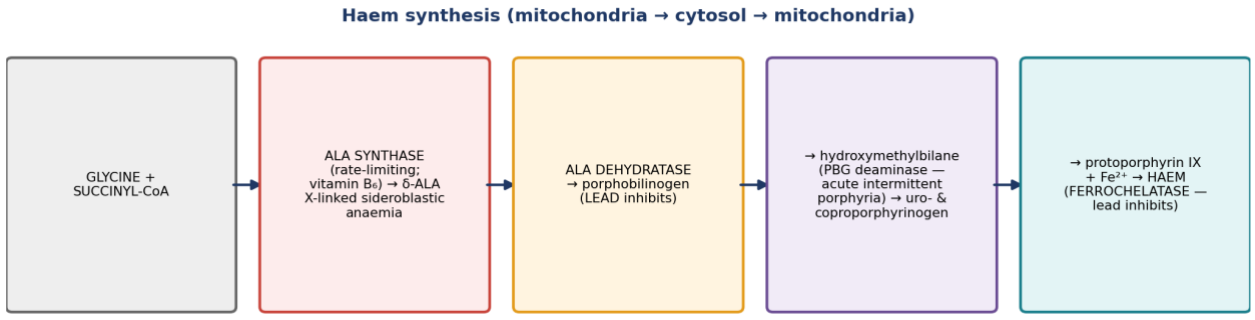



*Figure 226.1 — Haem synthesis*

| Haem synthesis disorder | Features |
|---|---|
| **Iron deficiency** | ↓ Haem → microcytic anaemia; ↑ zinc protoporphyrin |
| **Lead poisoning** | Inhibits ALA dehydratase and ferrochelatase → microcytic anaemia, basophilic stippling, neuropathy; ↑ ALA, protoporphyrin |
| **Sideroblastic anaemia** | ALA synthase (X-linked; $B_6$-responsive), alcohol, isoniazid → ring sideroblasts |
| **Acute intermittent porphyria** | PBG deaminase (autosomal dominant): abdominal pain, neuropsychiatric symptoms, hyponatraemia, dark urine; precipitated by progesterone, oral contraceptives, enzyme-inducing drugs, fasting, pregnancy; treat with haem arginate and glucose |

## 226.2 Oxygen binding and transport

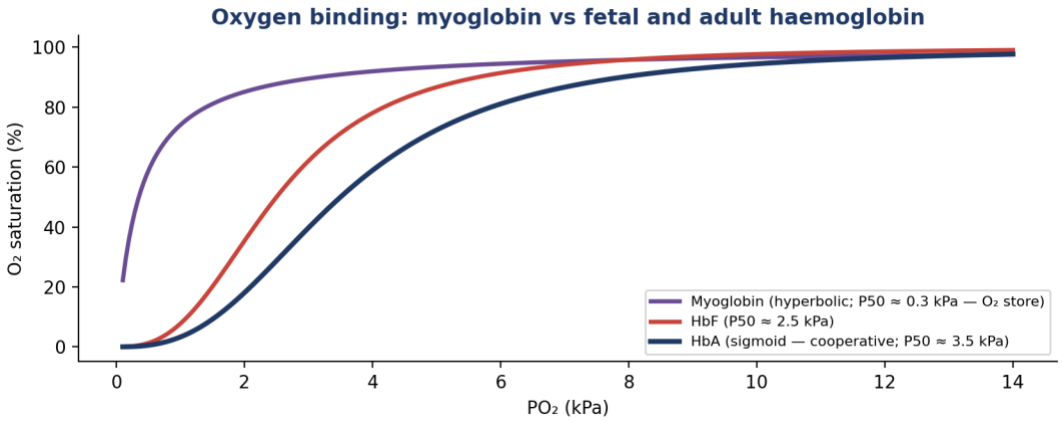



*Figure 226.2 — Oxygen binding curves of myoglobin and haemoglobins*

- **Cooperativity**: binding of one $O_2$ increases affinity of the remaining haems → **sigmoid** curve — loads in lungs, unloads in tissues. **Myoglobin** (monomer) has a hyperbolic curve — an $O_2$ store.
- **Right shift** (↓ affinity, ↑ unloading): ↑ $CO_2$, ↑ $H^+$ (**Bohr effect**), ↑ **2,3-BPG**, ↑ temperature, exercise; **left shift**: HbF, CO, methaemoglobin, alkalosis, stored blood (Lecture 130).
- **$CO_2$ carriage**: ≈ 60–70% bicarbonate, ≈ 20–30% **carbamino-Hb**, 10% dissolved; **Haldane effect** — deoxy-Hb carries more $CO_2/H^+$ (histidine buffering).
- **$O_2$ content** = 1.34 × Hb (g/dL) × $SaO_2$ + 0.023 × $PaO_2$ (kPa).

## 226.3 Haemoglobins through development

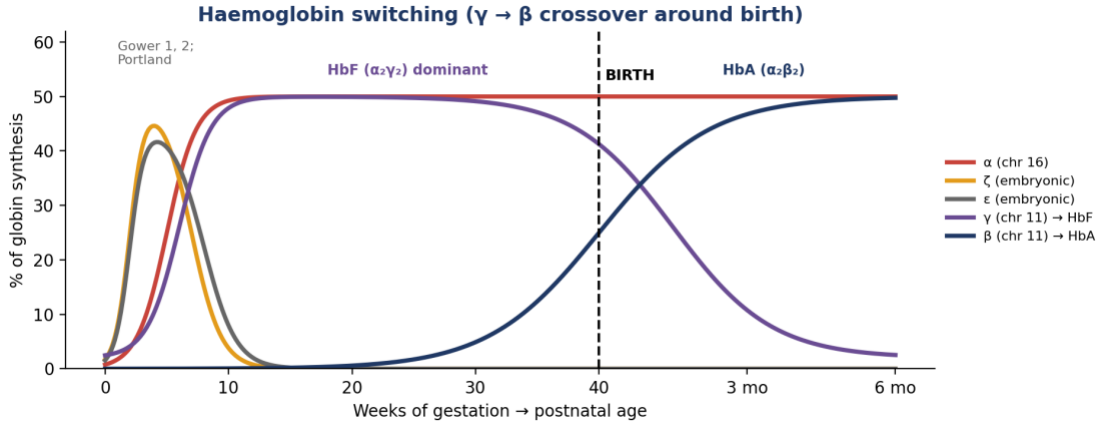



*Figure 226.3 — Globin switching*

| Haemoglobin | Chains | Period / notes |
|---|---|---|
| **Gower 1, Gower 2, Portland** | $\zeta_2\varepsilon_2$, $\alpha_2\varepsilon_2$, $\zeta_2\gamma_2$ | Embryonic (yolk sac) |
| **HbF** | $\alpha_2\gamma_2$ | Fetal; binds 2,3-BPG poorly → left shift (P50 ≈ 2.5 kPa); 60–80% at birth; Kleihauer test (acid-resistant) |
| **HbA** | $\alpha_2\beta_2$ | ≈ 97% adult |
| **$HbA_2$** | $\alpha_2\delta_2$ | 2–3%; ↑ > 3.5% in β-thalassaemia trait |
| **HbA1c** | Glycated HbA | Glycaemic control (falls in pregnancy — ↑ RBC turnover) |

## 226.4 Abnormal haemoglobins and breakdown

| Condition | Mechanism | Pregnancy relevance |
|---|---|---|
| **Sickle cell disease (HbSS, HbSC)** | β6 Glu → Val; deoxy-HbS polymerises | Crises, VTE, pre-eclampsia, FGR, stillbirth; antenatal screening and partner testing (Lecture 135) |
| **β-thalassaemia** | ↓/absent β-chain synthesis | Trait: microcytosis with normal ferritin, ↑ $HbA_2$; major: transfusion, iron overload |
| **α-thalassaemia** | α-gene deletions (1–4) | $\alpha^0$ (--/--) = Hb Bart's ($\gamma_4$) → hydrops fetalis; HbH ($\beta_4$) disease |
| **Methaemoglobinaemia** | $Fe^{3+}$ cannot bind $O_2$ (prilocaine, nitrites, dapsone; NADH-cytochrome b5 reductase deficiency) | Cyanosis with normal $PaO_2$; methylene blue (not in G6PD deficiency) |
| **Carbon monoxide** | Binds ≈ 240× more avidly than $O_2$; left shift | Fetal HbF binds CO even more; hyperbaric $O_2$ considered in pregnancy |

Senescent RBC (120 days) → splenic macrophages ▶ Haem oxygenase → biliverdin + $Fe^{2+}$ (recycled) + CO ▶ Biliverdin → **unconjugated bilirubin** (albumin-bound) ▶ Liver **UGT1A1** conjugation → bile → urobilinogen ▶ Neonatal jaundice: ↑ RBC turnover, immature UGT1A1 (fetal bilirubin cleared by placenta)

## 226.5 Must-know summary

■ **EXAM TIP**

- HbA $\alpha_2\beta_2$; α genes chr 16, β-like chr 11; haem = protoporphyrin IX + **$Fe^{2+}$**.
- Haem synthesis: **ALA synthase ($B_6$, rate-limiting)**; lead inhibits ALA dehydratase and ferrochelatase; AIP precipitated by progesterone/pregnancy.
- Cooperative sigmoid ODC; Bohr ($H^+/CO_2$) and 2,3-BPG right-shift; HbF left-shifted.
- HbS Glu → Val; ↑ $HbA_2$ in β-thal trait; Hb Bart's → hydrops; methaemoglobin → methylene blue.
- Breakdown → unconjugated bilirubin → UGT1A1 conjugation.

■ **MNEMONIC / MEMORY AID**

**Right shift — 'CADET, face Right'**: $CO_2$, Acid, 2,3-DPG, Exercise, Temperature.