📘 The Respiratory System

🟢 Formation of the Lung Buds

- At ~4 weeks of development, the respiratory diverticulum (lung bud) appears as a ventral outgrowth from the foregut.

- Its *appearance and position* are dependent on:

  - ⬆️ Retinoic acid (RA) produced by adjacent mesoderm
  - Upregulation of TBX4 transcription factor in the endoderm of the gut tube.
  - TBX4 → induces formation, growth, and differentiation of the developing lung.

🔍 Important MCQ Point

TBX4 is the key transcription factor responsible for initiating lung development.

- Germ layer origins:

  - Endoderm → epithelium of larynx, trachea, bronchi, and lungs.
  - Splanchnic mesoderm → cartilage, muscle, and connective tissue of trachea and lungs.

🟡 Separation of Lung Bud from the Foregut

- Initially lung bud is in open communication with the foregut.

- As the diverticulum grows caudally, two longitudinal ridges form → tracheoesophageal ridges.

- Fusion of these ridges forms the tracheoesophageal septum, which divides the foregut into:

  - Dorsal part → esophagus
  - Ventral part → trachea + lung buds

- Communication with pharynx remains through the laryngeal orifice.

🔴 Clinical Correlates

Tracheoesophageal Fistulas (TEFs) & Esophageal Atresia

- Cause: Abnormal partitioning of esophagus and trachea by tracheoesophageal septum.

- Incidence: ~1/3,000 births.

- Most common type (~90%):

  - Upper esophagus ends blindly
  - Lower segment forms a fistula with trachea

- Other types:

- Isolated esophageal atresia → 4%
- H-type TEF without esophageal atresia → 4%
- Remaining rare variations → ~1% each

Associated Conditions

- Frequently associated with other congenital anomalies (33% have cardiac defects).

- Part of VACTERL association:

- Vertebral anomalies
- Anal atresia
- Cardiac defects
- Tracheoesophageal fistula
- Esophageal atresia
- Renal anomalies
- Limb defects

Complications

- Polyhydramnios:

- Swallowed amniotic fluid cannot reach the stomach/intestines in some TEF types.

- Postnatal risks:

- Gastric contents / amniotic fluid may enter trachea via fistula → pneumonitis, pneumonia

---

🟢 Development of the Larynx

Germ Layer Origins

- Endoderm → internal *epithelial lining* of the larynx

- Mesenchyme of 4th & 6th pharyngeal arches → cartilages + muscles of larynx

Morphological Changes

- Rapid proliferation of arch mesenchyme causes the laryngeal opening to change:

- Initially → sagittal slit
- Later → becomes T-shaped

- Mesenchyme differentiates into thyroid, cricoid, and arytenoid cartilages, resulting in the adult appearance of the laryngeal orifice.

Recanalization Phase

- Laryngeal epithelium proliferates → temporarily occludes lumen

- Vacuolization & recanalization form laryngeal ventricles

- These are bordered by folds → become false and true vocal cords

Innervation (Frequently Asked)

- All laryngeal muscles derive from 4th & 6th arches → supplied by Vagus nerve (CN X)

- Superior laryngeal nerve → derivatives of 4th arch
- Recurrent laryngeal nerve → derivatives of 6th arch

🟡 Trachea, Bronchi, and Early Lung Development

- As the lung bud separates from the foregut → forms trachea + two bronchial buds

- Week 5:

- Each bronchial bud enlarges → right & left main bronchi
- Right → forms 3 secondary bronchi (→ 3 lobes)
- Left → forms 2 secondary bronchi (→ 2 lobes)

Expansion of Lung Buds

- Grow caudally & laterally into pericardioperitoneal canals

- These canals gradually narrow and become separated by:

  - Pleuroperitoneal folds (→ separates from peritoneal cavity)
  - Pleuropericardial folds (→ separates from pericardial cavity)

- Remaining space → primitive pleural cavities

Pleura Formation

Structure	Germ Layer Origin	Fate
Mesoderm covering lung surface	Splanchnic mesoderm	Visceral pleura
Mesoderm lining the body wall	Somatic mesoderm	Parietal pleura

Space between them	—	Pleural cavity

🔵 Branching of Bronchial Tree

- Secondary bronchi → divide dichotomously

- Form:

  - 10 segmental (tertiary) bronchi in right lung
  - 8 segmental bronchi in left lung
  - → basis of bronchopulmonary segments

- By 6th month → ≈17 generations of branches formed

- After birth → ~6 more generations occur

🧠 Regulation of branching = epithelial–mesenchymal interactions

Signals originate in splanchnic mesoderm (e.g. FGF family)

- As branching continues, lungs gradually shift caudally → at birth, tracheal bifurcation is at T4 level

---

📊 Maturation of the Lungs

Stage	Weeks	Key Features
Pseudoglandular	5–16 wk	Formation of terminal bronchioles only; no respiratory bronchioles or alveoli
Canalicular	16–26 wk	Respiratory bronchioles form → divide into alveolar ducts
Terminal sac period	26 wk – birth	Terminal sacs (primitive alveoli) develop; capillaries contact epithelium
Alveolar period	8 months – childhood	Formation of mature alveoli with well-developed epithelium–capillary contacts

🟢 Maturation of the Lungs

Canalicular Phase (up to 7th month)

- Bronchioles continuously divide into smaller respiratory bronchioles
- Vascular supply increases steadily
- Each respiratory bronchiole → 3–6 alveolar ducts
- Ducts terminate in terminal sacs (primitive alveoli) → lined by flat alveolar cells closely associated with capillaries
- End of 7th month → enough terminal sacs & capillaries present → premature infant can survive

Late Fetal / Terminal Sac Period (last 2 months + postnatal years)

- Number of terminal sacs increases steadily
- Type I alveolar epithelial cells become thinner → capillaries protrude into sacs
- Formation of blood-air barrier (thin epithelium + capillary endothelium)
- Type II alveolar epithelial cells appear (~end of 6th month)
  - Function → produce surfactant
  - Surfactant = phospholipid-rich fluid → ↓ surface tension at air-alveolar interface

---

Before Birth

- Lungs are filled with fluid containing:

- High chloride, little protein
- Mucus from bronchial glands
- Surfactant (from type II cells)

- ↑ surfactant production near 34th week

- Small amount enters amniotic fluid → activates macrophages
- Macrophages migrate → produce IL-1β
- → ↑ prostaglandin production → initiates uterine contractions

- *Fetal surfactant may help trigger labor*

Fetal Breathing Movements

- Begin before birth

- Cause aspiration of amniotic fluid

- Help stimulate lung development and train respiratory muscles

---

At Birth

- Fluid in alveoli is rapidly absorbed (blood/lymph vessels)
- Surfactant remains on alveolar surface → prevents collapse during expiration
- First breath → lungs expand and fill pleural cavities

🔴 Clinical Correlate – Surfactant and RDS

Condition	Mechanism / Feature

Respiratory Distress Syndrome (RDS)	Insufficient surfactant → ↑ surface tension → alveoli collapse (atelectasis) during expiration
Frequency	~20% of deaths in premature newborns
Histology	Alveoli partially collapsed, contain protein-rich fluid, hyaline membranes, lamellar bodies
Management	Artificial surfactant therapy + Maternal glucocorticoids (stimulate fetal surfactant production)

🟡 Congenital Lung Abnormalities

Abnormality	Description / Significance
Blind-ending trachea / absence of lungs / lung agenesis	Very rare
Abnormal bronchial branching	More common; may → supernumerary lobules (usually clinically insignificant, but may complicate bronchoscopy)
Ectopic lung lobes	Arise from trachea or esophagus → due to extra respiratory buds

Congenital lung cysts	Dilated terminal or larger bronchi → honeycomb appearance on imaging; drain poorly, often → chronic infections

---

🔵 Postnatal Lung Development

- Respiratory movements at birth → air enters lungs → expands alveoli

- Lung growth after birth:

  - Mainly due to increase in number of respiratory bronchioles and alveoli
  - Only ~1/6 of adult alveoli are present at birth
  - Remaining alveoli form over the first ~10 years of life

-> The End <-