

Prematurity and Fetal Growth Restriction

Definitions, etiologic mechanisms, pathologic correlates, and consequences

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Learning objectives

- Distinguish gestational immaturity from impaired fetal growth.
- Explain membrane rupture, infection, structural factors, and multiple gestation as causes of prematurity.
- Classify maternal, fetal, and placental determinants of growth restriction.
- Link causal mechanisms with neonatal hazards and growth patterns.

Clinicopathologic perspective

Two related clinical problems; Different causal questions

Two distinct questions in perinatal pathology

Gestational age

- Was delivery before 37 completed weeks?
- Immaturity creates organ-system vulnerability.
- A preterm infant can be appropriate in size for gestational age.

Fetal growth

- Did the fetus achieve expected growth?
- Growth reflects maternal supply, intrinsic fetal potential, and placental function.
- An undergrown infant may be born at term.

Birthweight alone does not answer either question completely.

Prematurity is defined by gestational age

<37

Completed weeks of gestation

- An age-based category—not a weight-based diagnosis.
- Prematurity contributes neonatal illness related to organ immaturity.
- Always interpret neonatal weight in the context of gestational age.

Birthweight is not a surrogate for gestational age



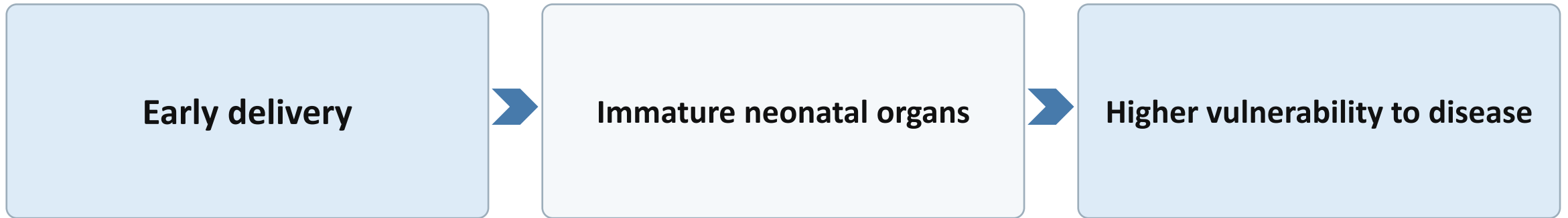
- Premature newborns may weigh less simply because fetal growth time was shortened.
- At term, low birthweight may instead signal restricted fetal growth.

Two dimensions: Gestation and attained size

Gestation	Appropriate size	Undergrown / SGA
Preterm	Shorter intrauterine maturation; weight may match age	Prematurity and undergrowth can coexist
Term	Completed gestational maturation with expected size	Low weight may reflect growth restriction

Schematic categories; No invented percentile threshold.

Prematurity: A pathologic cascade



- Timing of birth is the upstream event.
- Clinical effects depend on maturity and superimposed complications.

Clinical significance of preterm birth

- Prematurity as the second most common cause of neonatal mortality after congenital anomalies.
- The burden includes respiratory, intestinal, infectious, and intracranial complications.
- Gestational age is central to risk assessment.

Clinicopathologic perspective

Source statement refers to
the textbook context.

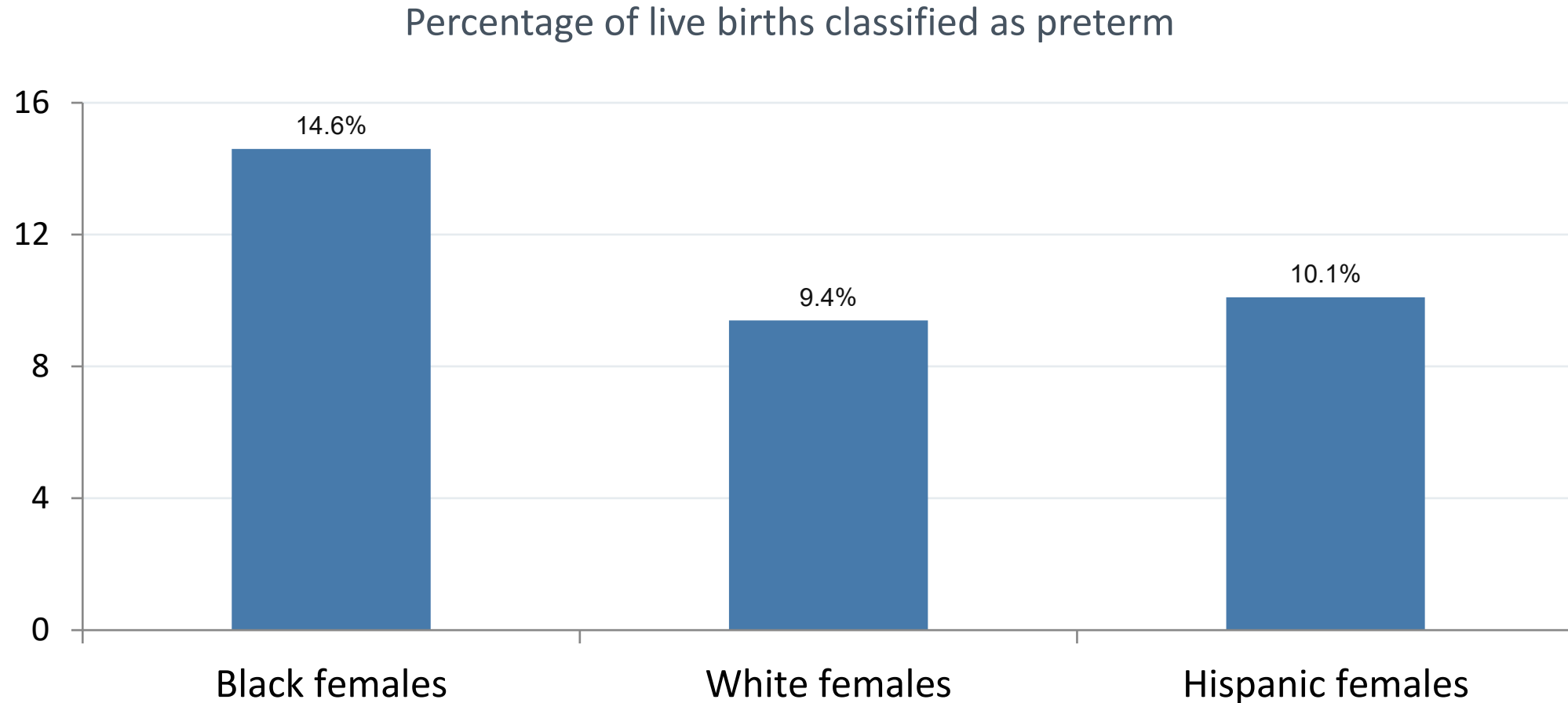
U.S. Preterm birth in 2022

10.4%

Of infants born in the United
States

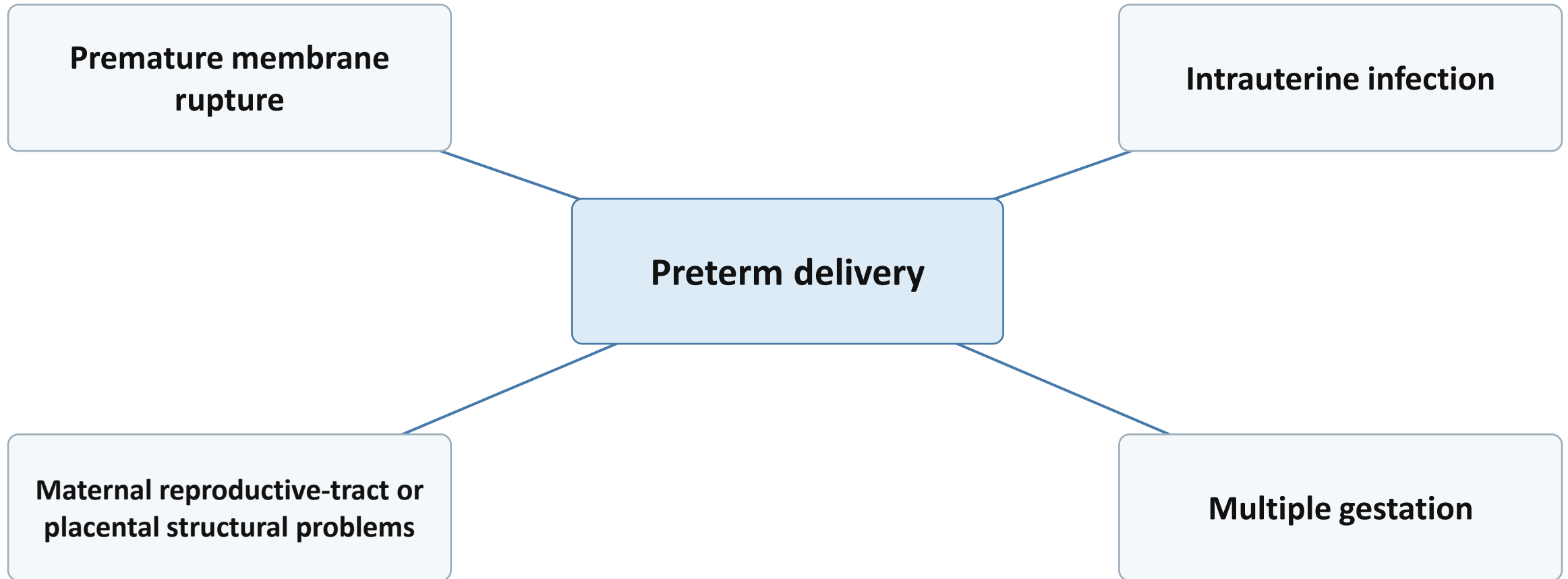
- CDC figures quoted by Robbins, 11th edition.
- The source describes a 1% decrease compared with 2021.
- These are historical 2022 figures—not a current prevalence estimate.

Preterm birth rates differed between population groups (2022)



Historical 2022 figures. Group differences are descriptive and do not establish an individual causal mechanism.

Four etiologic domains of prematurity



These factors can overlap rather than forming mutually exclusive diagnoses.

PPROM: Failure of membranes before term



- Preterm prelabor rupture of membranes (PPROM) exposes the amniotic cavity.
- Timing distinguishes PPRom from rupture after 37 weeks.

PPROM versus PROM

PPROM

- Spontaneous membrane rupture before labor.
- Occurs before 37 weeks of gestation.
- Fetal immaturity is a major additional concern.

PROM after 37 weeks

- Spontaneous rupture before labor.
- Occurs after 37 weeks terminology.
- Risks related to extreme prematurity are reduced.

Use gestational age and labor status together to classify rupture.

PPROM: Contribution to preterm delivery

$\approx 3\%$

Of all pregnancies
complicated by PPRM

- The book attributes as many as one-third of preterm deliveries to PPRM.
- Frequency in all pregnancies is not the same denominator as fraction of preterm births.
- Data are approximate figures as presented.

Recognized clinical risk factors for PPRM

History during pregnancy	Maternal / social context
Previous preterm delivery	Maternal smoking
Current preterm labor	Low socioeconomic status
Vaginal bleeding in current pregnancy	Poor maternal nutrition

Risk factors are associations; None determines outcome alone.

Antecedent obstetric history matters

- Prior preterm delivery is a recognized risk factor for PPRM.
- Preterm labor during the current pregnancy is also associated with rupture.
- Current-pregnancy vaginal bleeding is another warning context.

Clinicopathologic perspective

Clinical history helps identify susceptibility, not a single mechanism.

Maternal context and PPRM

- Smoking, low socioeconomic status, and poor nutrition are associated with PPRM.
- These exposures can coexist with obstetric risk factors.
- The Robbins excerpt lists associations without assigning an individual causal effect size.

Clinicopathologic perspective

Avoid treating one
association as sufficient
proof of cause.

PPROM prognosis is strongly dependent on timing



- Second-trimester PPRom is described as having a very poor prognosis.
- Risk changes as gestational maturity increases.

PPROM also opens a route to intra-amniotic infection



- Prevention of infection in the exposed amniotic cavity contributes to outcome.
- The source emphasizes infection prophylaxis alongside gestational maturity.

Intrauterine infection and prematurity

$\approx 25\%$

Of preterm births implicated

- Intrauterine infection as a major cause of preterm labor.
- This approximate contribution is not restricted to one pathogen.
- Placental inflammatory morphology provides pathologic corroboration.

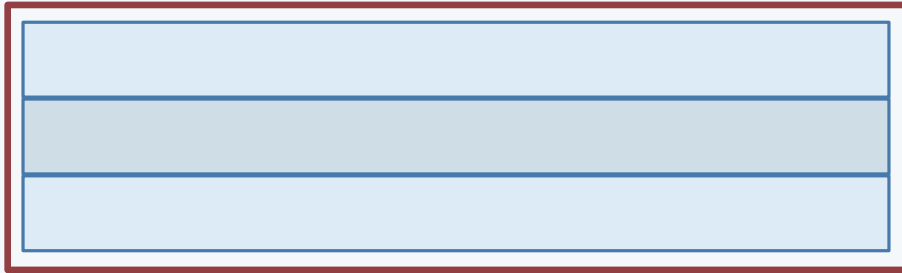
Earlier preterm births: Infection becomes more prominent



- The association is qualitative; The source does not provide an age-stratified risk curve.
- Do not interpret it as proof that all very early births are infectious.

Placental inflammation has an anatomic location

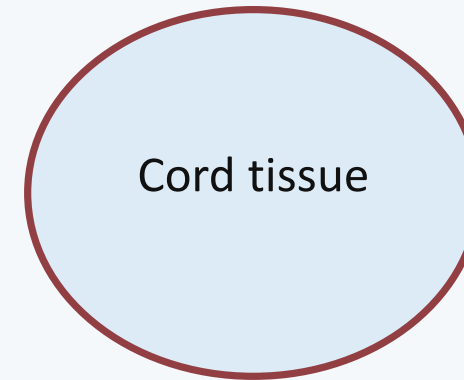
PLACENTAL MEMBRANES



Chorioamnionitis

Inflammation involving the placental membranes

UMBILICAL CORD



Funisitis

Inflammation involving the fetal umbilical cord

Simplified anatomic localization — schematic only, not a histologic specimen.

Chorioamnionitis and funisitis

Chorioamnionitis

- Inflammation of placental membranes.
- Maternal–fetal interface is affected.
- Histologic correlate of intrauterine infection.

Funisitis

- Inflammation of the fetal umbilical cord.
- Evidence that the fetal cord is involved.
- May accompany infection-associated preterm labor.

Anatomic distinction is more useful than treating these terms as synonyms.

How to read an inflammation-related placental report



- Membranes → chorioamnionitis.
- Umbilical cord → funisitis.

Organisms implicated in intrauterine infection

Organism or infection	Textbook context
Ureaplasma urealyticum	Genital-tract organism implicated in preterm labor
Mycoplasma hominis	Implicated in intrauterine infection
Gardnerella vaginalis	Associated with bacterial vaginosis
Trichomonas	Protozoal infection listed among contributors

The list is illustrative, not a diagnostic ranking.

Bacterial vaginosis: A polymicrobial context

- *Gardnerella vaginalis* as a dominant organism found in bacterial vaginosis.
- Bacterial vaginosis is described as polymicrobial.
- Its placement in the source links genital-tract ecology with infection-associated prematurity.

Clinicopathologic perspective

Do not equate one isolated species with every case of bacterial vaginosis.

Additional genital infections implicated in preterm labor

- The source lists gonorrhea and Chlamydia among implicated infections.
- Trichomonas is also listed in the relevant infectious spectrum.
- The presence of a listed organism is not proof of causation in any individual delivery.

Clinicopathologic perspective

Infection is one cause
among several.

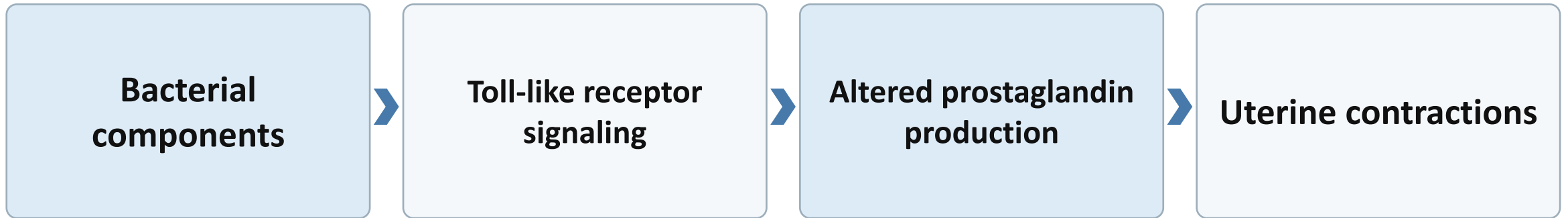
Global variation in infectious contributors

- Malaria and HIV as important contributors in developing countries.
- The epidemiologic context therefore differs across settings.
- The source does not specify comparable country-level prevalence or relative risks.

Clinicopathologic perspective

Interpret population
attribution in its
geographic context.

Proposed inflammation-to-contraction pathway



- This chain as a proposed molecular mechanism.
- TLRs recognize microbial ligands and may initiate signaling that changes uterine activity.

Mechanistic uncertainty must remain visible

- The TLR–prostaglandin model in the source is explicitly postulated.
- Inflammation-associated preterm labor can be mechanistically plausible without being demonstrated in every case.
- Histologic inflammation, organism detection, and clinical labor are distinct observations.

Clinicopathologic perspective

Hypothesis ≠ universal
causal proof.

Uterine distortion versus cervical support failure

Uterine distortion

- Uterine fibroids can distort uterine architecture.
- Anatomic abnormality is associated with prematurity.

Cervical structural weakness

- Compromised cervical support is termed cervical incompetence.
- Mechanical competence of pregnancy support is reduced.

Both belong to structural, rather than infectious, predisposition.

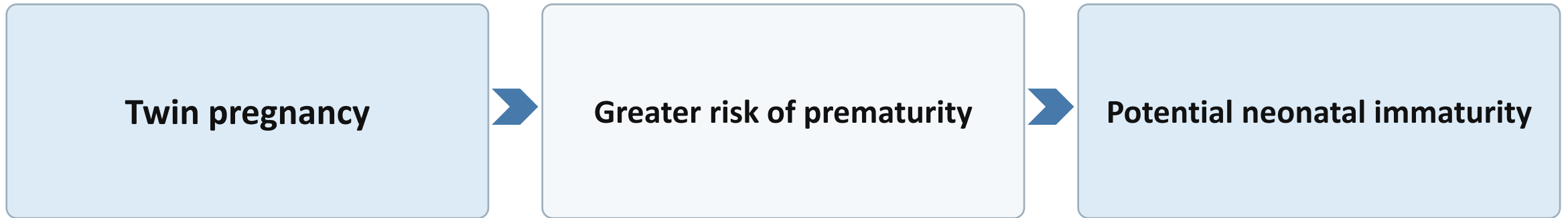
Placental structural conditions linked with prematurity

- Placenta previa is associated with an increased risk of preterm delivery.
- Placental abruption (abruptio placentae) is another recognized association.
- These complications are considered separately from infections and membrane rupture.

Clinicopathologic perspective

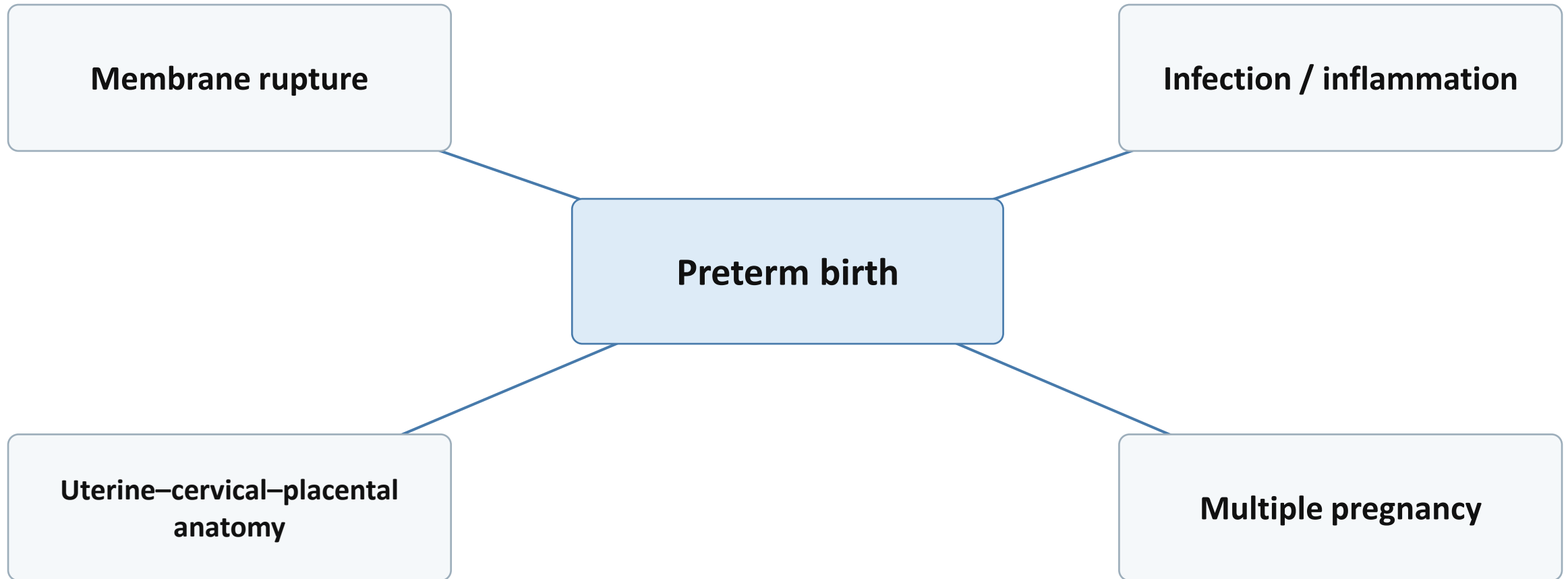
Some placental disorders also influence fetal growth.

Multiple gestation and preterm delivery



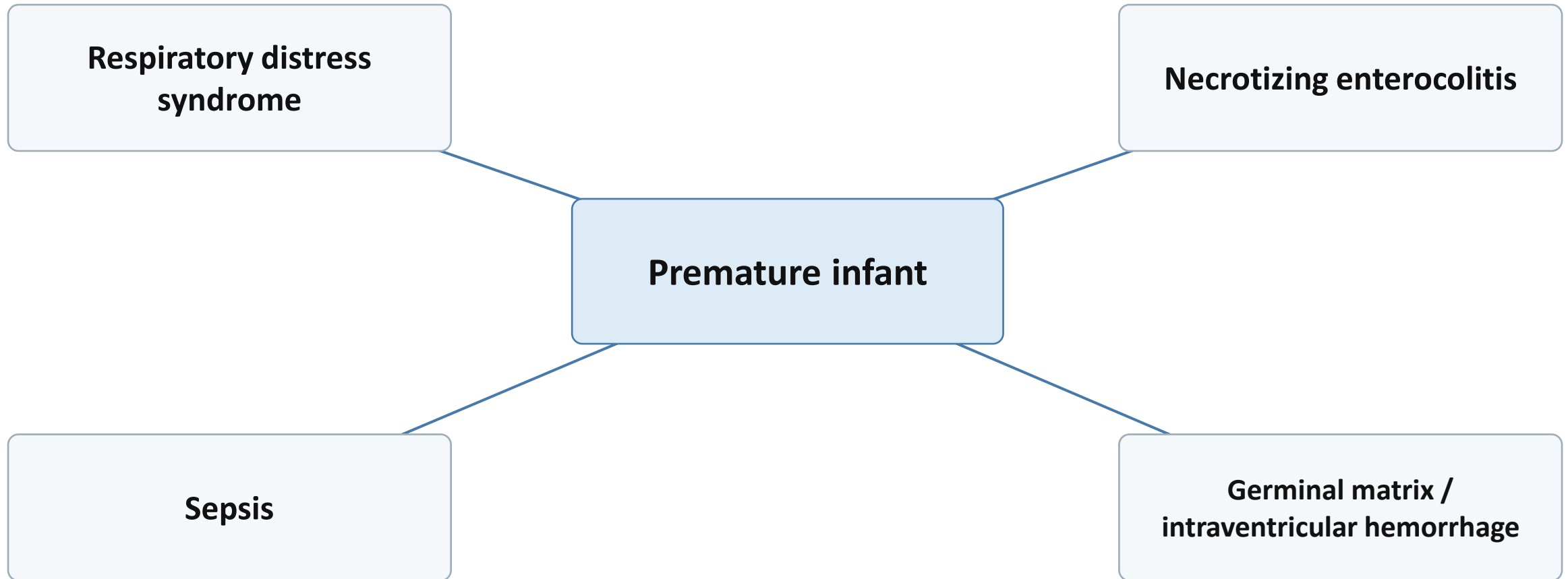
- Multiple gestation appears among Robbins' major risk factors.
- It may also contribute to growth restriction by placental mechanisms.

A mechanistic map of prematurity



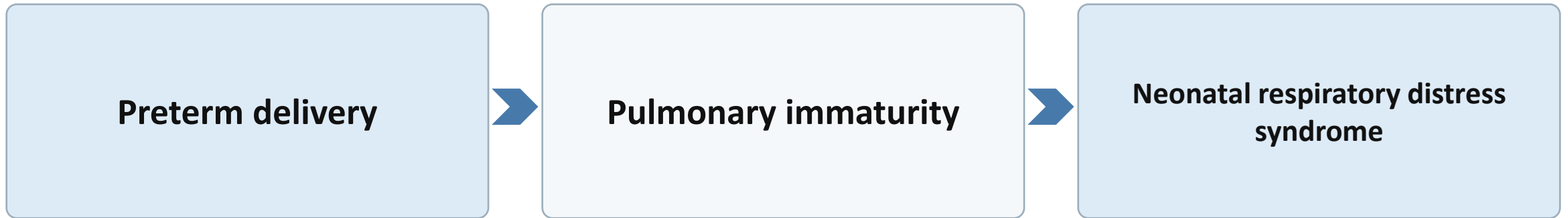
The unifying result is delivery before completion of gestation.

Neonatal hazards of prematurity



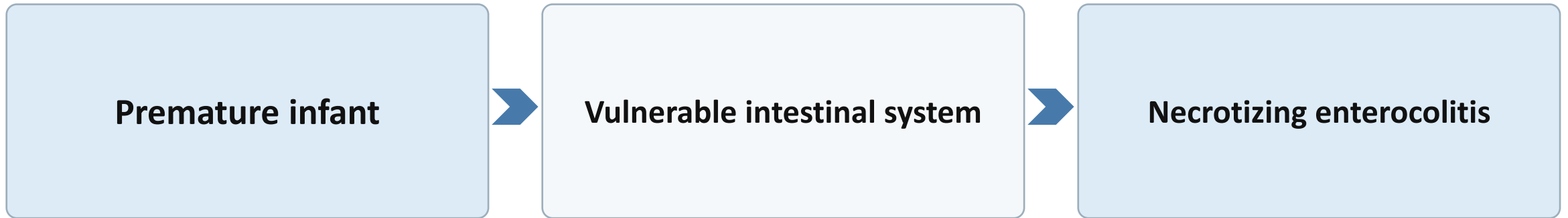
These complications are specifically named.

Respiratory distress: An immature lung



- Robbins also calls this hyaline membrane disease.
- The immediately following textbook section discusses surfactant deficiency in detail.

Necrotizing enterocolitis as a neonatal hazard



- The condition is a recognized complication of prematurity.
- Detailed NEC pathogenesis belongs to the adjacent Robbins topic.

Sepsis in the premature newborn



- Sepsis among the principal hazards of prematurity.
- Intrauterine infection and neonatal sepsis should not be conflated as identical events.

Germinal matrix and intraventricular bleeding



- Bleeding in and around the germinal matrix is a named major hazard.
- It exemplifies neurologic susceptibility associated with prematurity.

Different hazards involve different organ systems

Complication	Dominant affected system	Teaching distinction
Respiratory distress syndrome	Lung	Respiratory immaturity
Necrotizing enterocolitis	Intestine	Necrotizing bowel disease
Sepsis	Systemic infection	Infectious complication
Germinal matrix hemorrhage	Central nervous system	Intracranial bleeding

Not a ranking of frequency or severity.

Prematurity and restricted fetal growth can coexist

Prematurity

- Age at birth is the defining variable.
- Immaturity explains many neonatal vulnerabilities.
- Size may be normal for gestational age.

Fetal growth restriction

- Inadequate attainment of growth potential is the central issue.
- Can occur in an infant delivered at term.
- Causes are maternal, fetal, and placental.

Classification should consider both dimensions simultaneously.

Low birthweight does not always imply prematurity

<2500 g

Includes a substantial term-born subgroup

- As many as one-third of infants under 2500 g are born at term.
- Such infants may be undergrown rather than gestationally immature.
- Always assess age-appropriate size.

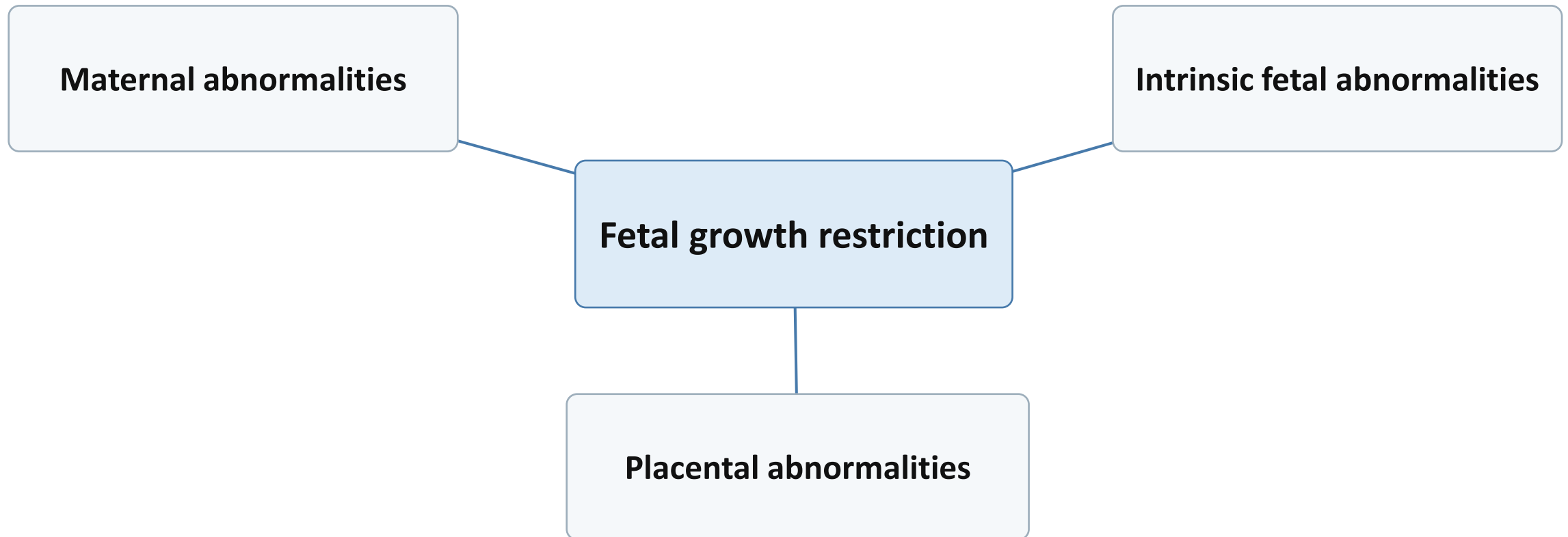
FGR: The underlying problem is failed growth

- An infant can be small because gestation ended early or because fetal growth was restricted.
- , the undergrown term infant is considered in the small-for-gestational-age (SGA) context.
- An underlying cause is sometimes unidentified despite evaluation.

Clinicopathologic perspective

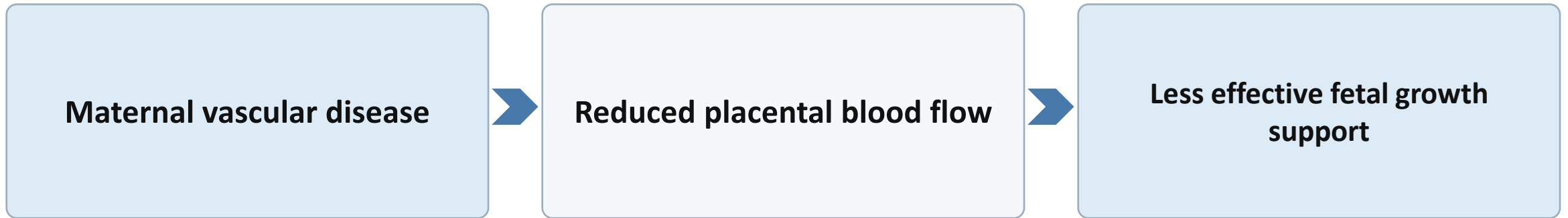
Cause and phenotype
should not be confused.

Three major sources of fetal growth restriction



Grouping by compartment helps organize the diagnostic explanation. An unspecified cause remains possible.

Maternal vascular disease: The common pathway



- Maternal conditions that decrease placental blood flow are common among SGA infants.
- This is an extrinsic limitation of fetal growth.

Preeclampsia and chronic hypertension

Preeclampsia

- Vascular disorder in pregnancy.
- Named common maternal association with SGA.

Chronic hypertension

- Pre-existing or chronic vascular burden.
- Also implicated in impaired placental blood flow.

Both are linked through uteroplacental perfusion in the source.

Maternal exposures: Preventable factors named by Robbins

- Maternal opiate abuse is associated with fetal growth restriction.
- Alcohol intake is another listed factor.
- Heavy cigarette smoking is specifically emphasized.

Clinicopathologic perspective

Clinical counseling should distinguish association from proof in one fetus.

Medications and maternal nutritional influences

Potential contributor	Textbook example
Chemotherapeutic agents	Classic teratogenic drug exposure
Phenytoin (Dilantin)	Commonly administered therapeutic agent listed
Maternal malnutrition	Reduced substrate availability for fetal growth
Prolonged hypoglycemia	Nutritional/metabolic influence specifically emphasized

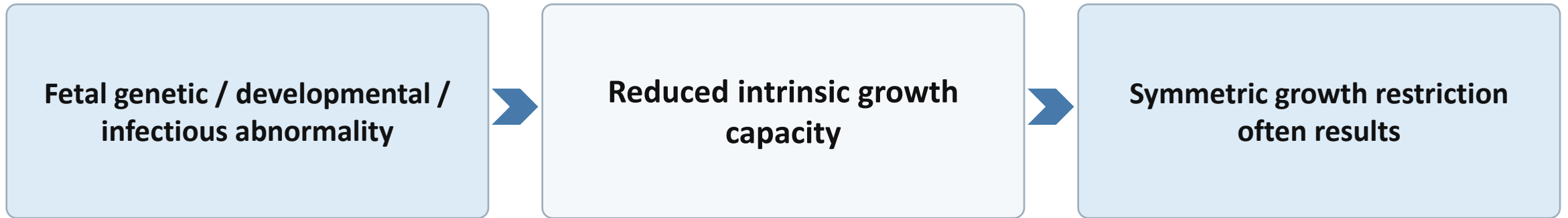
The source provides examples, not an exhaustive medication-risk list.

Maternal compromise: Interpret the pathway



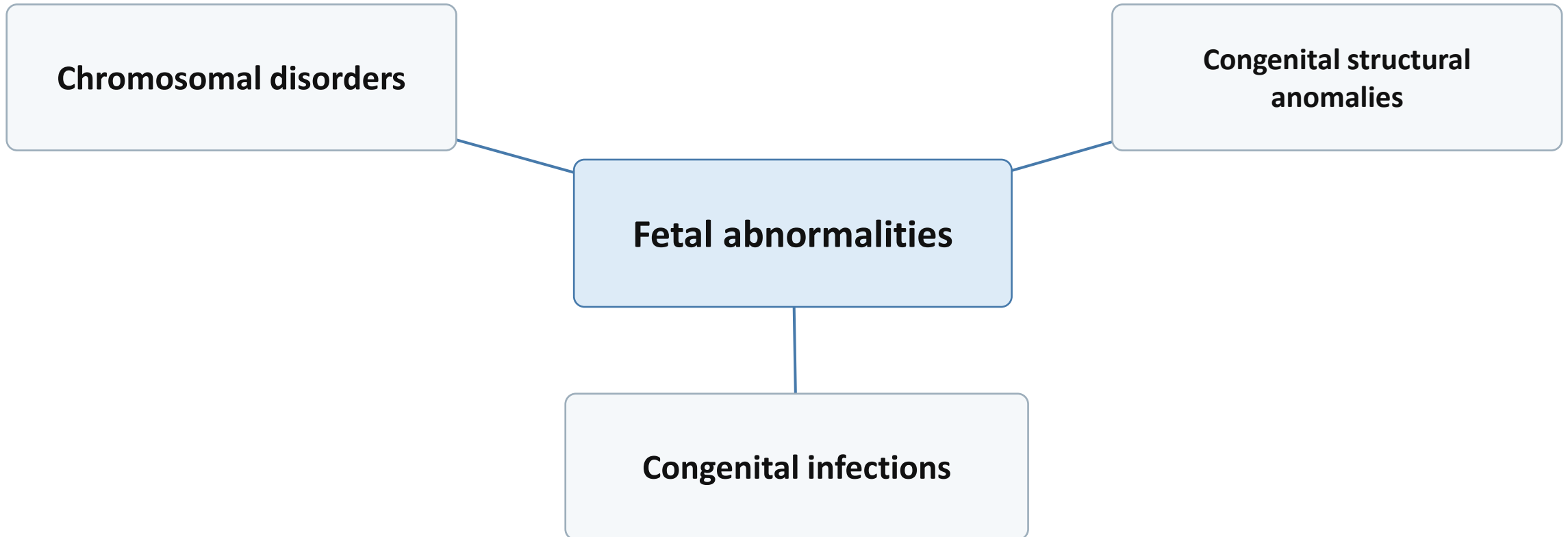
- Decreased placental blood flow is the main pathway for maternal vascular disease.
- Other listed maternal exposures may act through distinct mechanisms not specified in the excerpt.

Intrinsic fetal factors: A different causal logic



- Fetal causes may impair growth despite sufficient maternal nutrient supply.
- Fetal pathology therefore differs conceptually from reduced uteroplacental delivery.

Intrinsic fetal etiologies



These are the prominent fetal categories in the chapter.

Chromosomal findings in selected FGR evaluations

Up to 17%

Of fetuses sampled for FGR

- The source separately reports up to 66% in fetuses with ultrasonographically documented malformations.
- These percentages describe selected samples, not universal population prevalence.
- Sampling context is essential to interpretation.

Chromosomal abnormalities in the selected FGR group

Abnormality	Proportion reported in source
Triploidy	7%
Trisomy 18	6%
Trisomy 21	1%
Trisomy 13	1%
Deletions and translocations	2%

These within the sampled FGR group; Do not generalize uncritically.

Malformations change the cytogenetic context

FGR detected



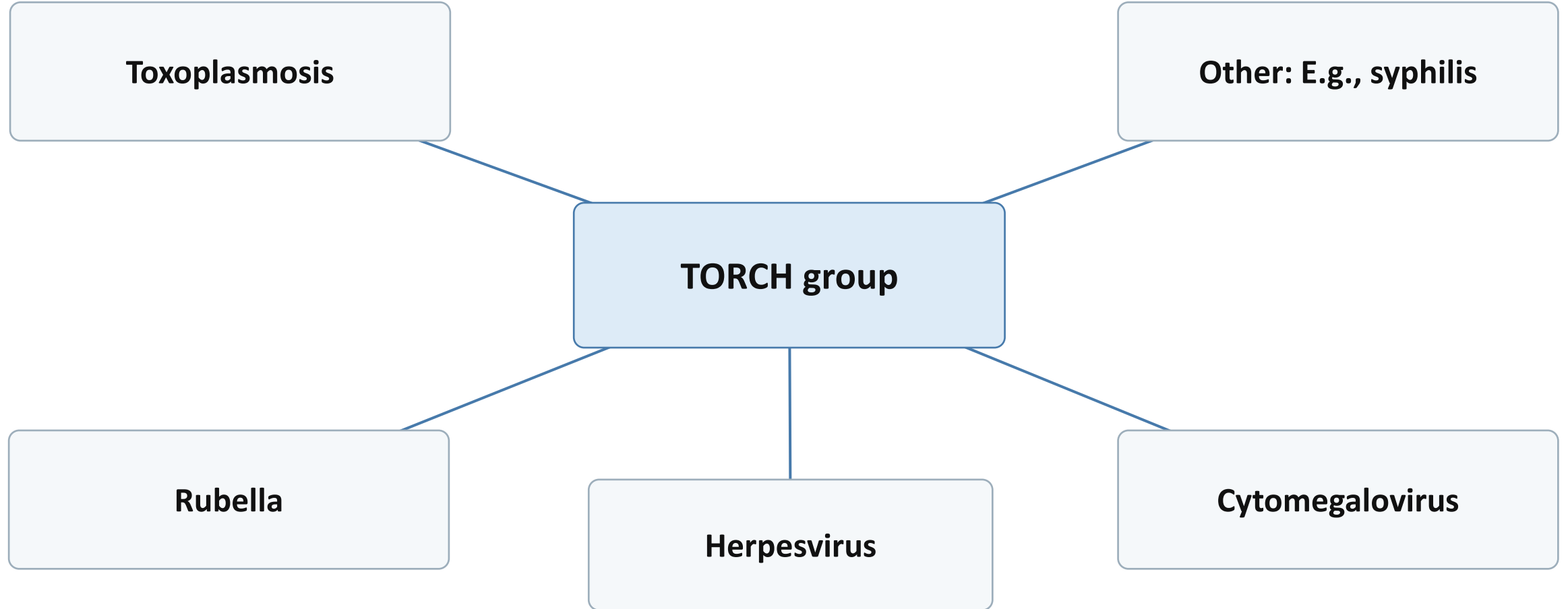
**Ultrasonographic malformation
present**



**Chromosomal abnormalities
more common in selected sample**

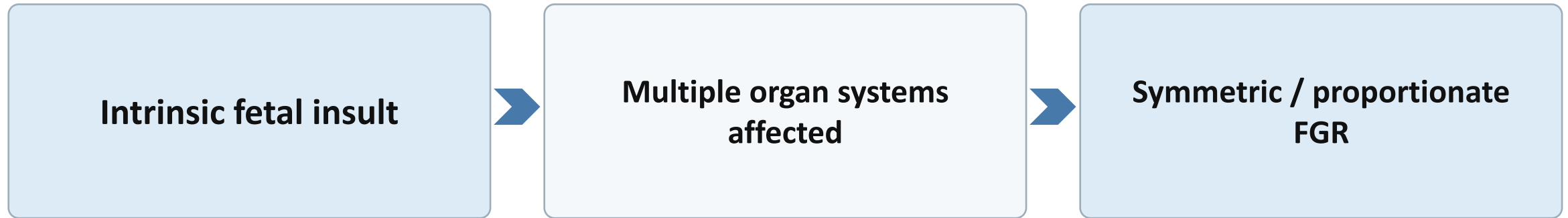
- Up to 66% in the malformation-enriched sampled group.
- Interpretation depends on selection for testing rather than growth measurements alone.

Congenital infections included in the TORCH framework



Congenital infection should be considered in infants with growth restriction.

Fetal pathology often yields proportionate small size



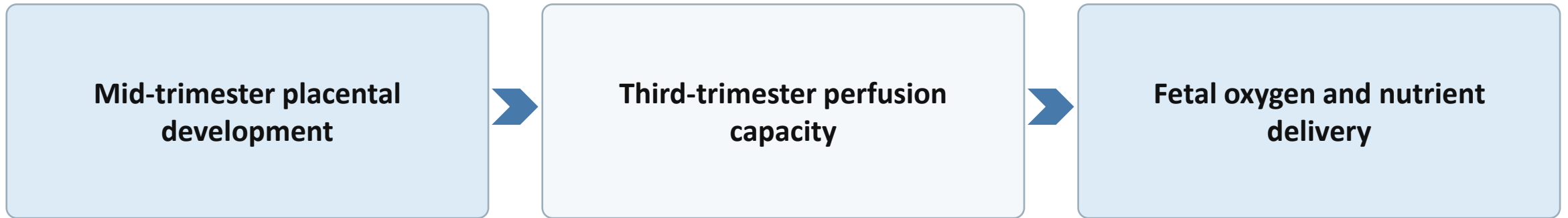
- Fetal etiologies with relatively uniform growth effects.
- Pattern helps reason about cause but does not establish it on its own.

Late gestation increases placental supply requirements



- Placental function becomes especially important during rapid late fetal growth.
- Mid-gestation placental development underpins later reserve.

Placental growth in mid-trimester supports later growth



- Insufficient development or disease may become functionally important later.
- This explains why placental growth and fetal growth can become uncoupled.

Umbilical–placental vascular abnormalities

Vascular/anatomic factor	How Robbins categorizes it
Single umbilical artery	Umbilical-placental vascular anomaly
Abnormal cord insertion	Umbilical-placental vascular anomaly
Placental thrombosis	Thrombotic placental abnormality
Placental infarction	Vascular injury to placenta

These entities may impair effective uteroplacental support.

Additional placental lesions linked to FGR

Placental condition	Source grouping
Placental abruption	Placental abnormality
Placenta previa	Placental abnormality
Chronic villitis of unknown etiology	Inflammatory placental lesion
Placental infection	Infectious placental lesion
Multiple gestations	Placental context / demand

The chapter also allows unexplained small placenta and infant.

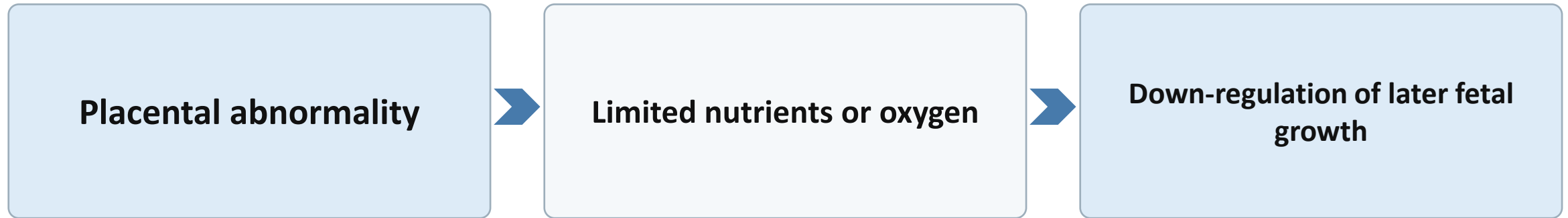
An unexplained small placenta can accompany FGR

- The placenta and infant may both be small with no discernible underlying cause.
- Absence of a detectable lesion does not rule out clinically meaningful growth restriction.
- Placental examination should be interpreted together with maternal and fetal findings.

Clinicopathologic perspective

Causal classification can
remain unresolved.

Placental insufficiency produces a supply constraint



- This as a physiologic adaptation to inadequate supply.
- The pattern typically develops during the latter half of gestation.

Relative brain sparing in placental FGR



- This is an asymmetric (disproportionate) growth pattern.
- Brain sparing is relative, not proof that neurologic development is unharmed.

Symmetric versus asymmetric restriction

Symmetric / proportionate

- All organ systems similarly affected.
- More typical of intrinsic fetal causes.
- Examples: Chromosomal conditions, congenital infection.

Asymmetric / disproportionate

- Relative brain sparing.
- More typical of placental insufficiency.
- Limited late fetal oxygen or nutrient supply.

Typical patterns are etiologic clues, not absolute diagnostic rules.

How growth pattern informs the differential

Observed pattern	Etiologic emphasis	What remains unresolved
Proportionately small body and head	Intrinsic fetal abnormalities	Which genetic, developmental, or infectious cause?
Disproportionately reduced somatic growth	Placental nutrient/oxygen limitation	Which placental or maternal vascular lesion?

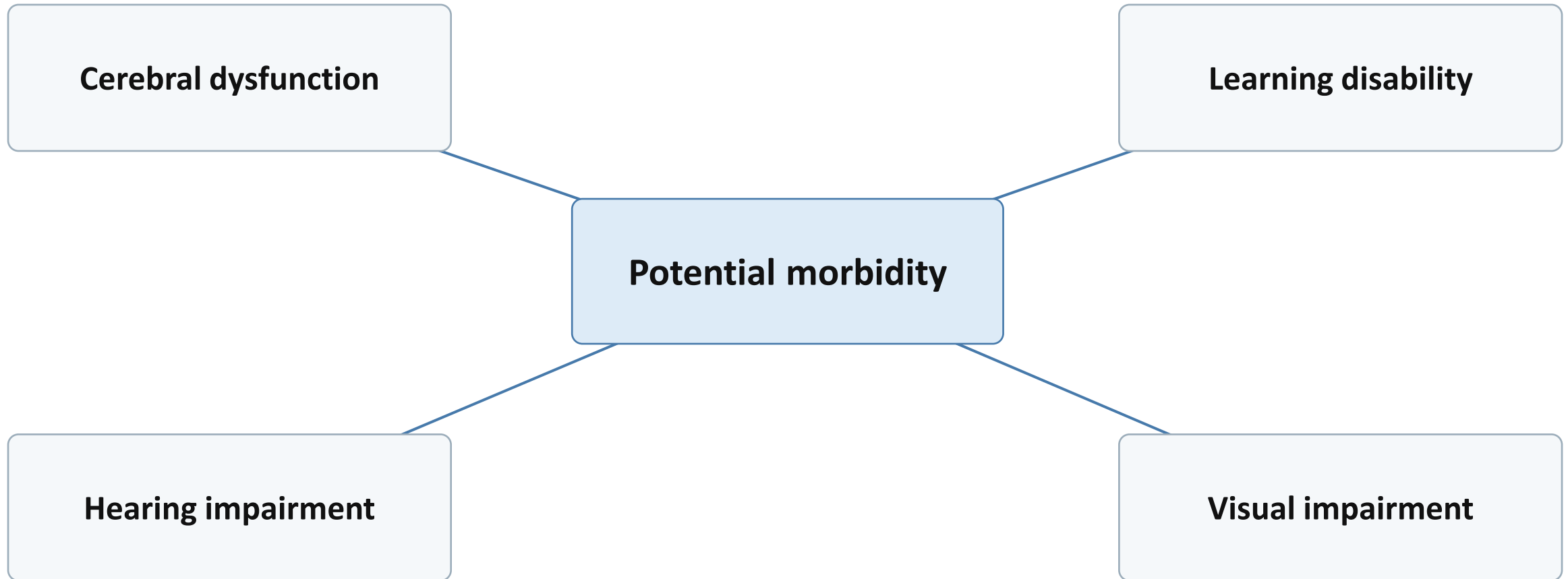
History and placental/fetal evaluation are still necessary.

Consequences persist beyond delivery



- Consequences beyond the neonatal period.
- Outcome depends on underlying cause and, to a lesser degree, prematurity.

Major disabilities associated with FGR



The chapter identifies these possible outcomes without assigning individual prognostic probabilities.

Application: Membrane rupture before term

A pregnancy develops spontaneous membrane rupture before labor at 32 weeks. Which category is correct?

A. PPROM

B. PROM after term

C. FGR by definition

Interpretation: Rupture is prelabor and precedes 37 completed weeks.

Application: Growth restriction with maternal hypertension

An undergrown infant is delivered at term. The mother has chronic hypertension. Which etiologic compartment deserves particular attention?

A. Intrinsic fetal abnormality exclusively

B. Maternal–placental perfusion

C. Prematurity as sole explanation

Interpretation: Chronic hypertension is a maternal vascular factor associated with reduced placental blood flow.

Application: Proportionately small fetus

A fetus has uniformly reduced growth and a congenital infection is suspected. Which growth pattern is more consistent with the textbook discussion?

A. Asymmetric FGR with relative brain sparing

B. Prematurity is demonstrated by size

C. Symmetric FGR

Interpretation: Intrinsic fetal causes, including congenital infections, often affect all organ systems.

Application: Placental vascular insufficiency

A fetus shows disproportionate somatic growth reduction. The placenta has vascular abnormalities. What mechanistic link is most consistent?

A. Uniform intrinsic growth-potential loss in every organ

B. Restricted oxygen and nutrient supply

C. An isolated demonstration of neonatal infection

Interpretation: Placental FGR commonly produces relative brain sparing under later gestational supply constraint.

Integrated differential: Prematurity versus FGR

Prematurity

- Diagnosed by gestational age <37 weeks.
- Think PPRM, infection, structural factors, twins.
- Anticipate lung, bowel, infection, and cerebral hemorrhage hazards.

Fetal growth restriction

- Inadequate growth relative to gestation.
- Think maternal, fetal, and placental factors.
- Differentiate symmetric from asymmetric patterns.

A neonate may satisfy both clinical descriptions.

Final synthesis: An etiologic approach

- Assess gestational maturity independently from attained fetal size.
- For prematurity, trace potential triggers: Membranes, inflammation, anatomy, and multiplicity.
- For FGR, classify maternal supply, intrinsic fetal factors, and placental pathology.
- Interpret neonatal and long-term consequences in light of both processes.

Clinicopathologic perspective

Mechanism →
morphologic correlate →
clinical vulnerability.

Further reading and source context

Primary teaching source

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Elsevier.

Teaching emphasis: prematurity is defined by gestational age, whereas fetal growth restriction demands analysis of maternal, fetal, and placental determinants.