

Oral contraceptives

Pathology of hormonal contraceptive exposure

- Hormonal formulations and mechanisms
- Cancer associations, thrombotic risk, and cardiovascular effects
- Hepatocellular adenoma as a drug-associated pathology entity

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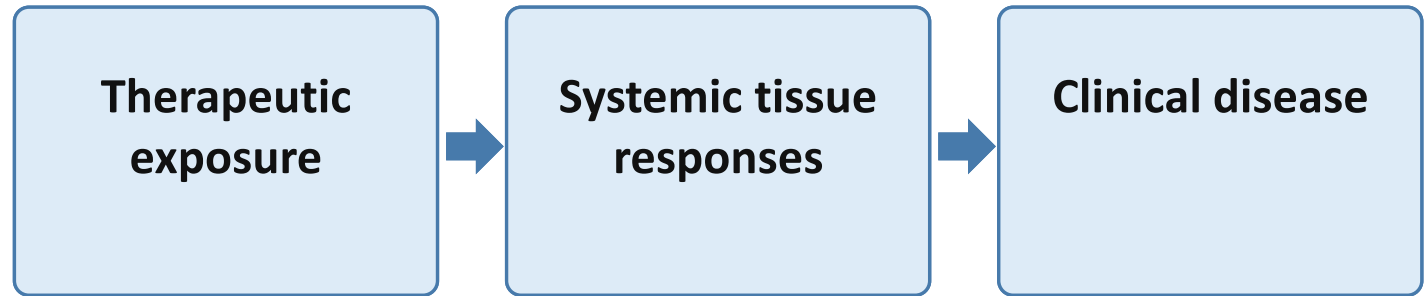
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Learning objectives

- Distinguish combined and progestin-only oral contraceptives and recognize formulation heterogeneity.
- Interpret site-specific cancer associations without inferring a universal cancer effect.
- Connect estrogen-associated hypercoagulability to deep vein thrombosis and pulmonary embolism.
- Recognize the morphology and key molecular subtypes of hepatocellular adenoma.

Why oral contraceptives appear in a pathology chapter

- Therapeutic agents can produce clinically significant adverse reactions.
- Oral contraceptives are highly prevalent exposures, making even uncommon complications relevant.
- The key pathology questions concern cancer, thrombosis, vascular disease, and liver neoplasia.



Conceptual framework

Adverse drug reactions: Mechanistic perspective

- Adverse drug reactions may reflect a drug's pharmacologic action or an unintended systemic effect.
- The affected organ and individual susceptibility influence clinical expression.
- Hormonal contraceptives exemplify exposure-dependent risks rather than a single toxicity syndrome.

Oral contraceptives are not one exposure

Formulation

Combination estrogen + progestin

Progestin-only option

Exposure dimensions

Hormone dose

Type of progestin

Delivery route

- The term covers differing estrogen–progestin compositions and progestin-only preparations.
- Hormone dose and formulation have changed over time.
- Associations must be interpreted for the actual formulation studied.

Combined hormonal preparations

- A combined oral contraceptive includes an estrogen component plus a progestin.
- The combination alters reproductive endocrine physiology to prevent pregnancy.
- Cancer and thrombotic associations should not automatically be assigned to every formulation.



Components and outcome

Progestin-only oral contraception

Combined

Estrogen component

Progestin component

Progestin-only

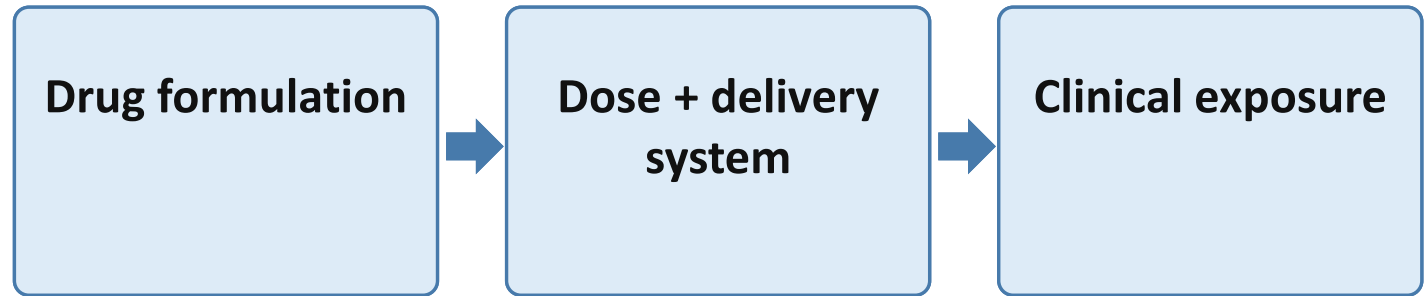
No estrogen component

Specific progestin formulation

- Some oral formulations contain no estrogen component.
- Norgestrel (Opill) as a U.S. Over-the-counter progestin-only oral product.
- Evidence from combined preparations cannot simply be transferred to progestin-only tablets.

Oral versus other hormonal delivery systems

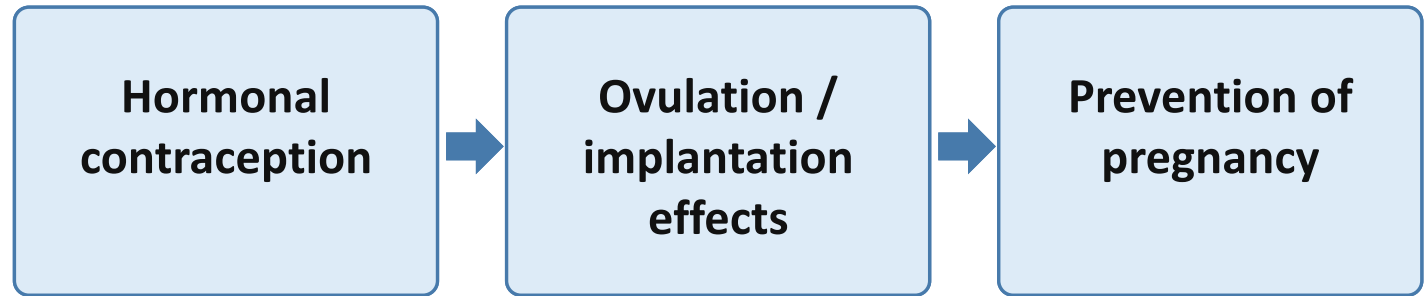
- Robbins also notes transdermal and implantable hormonal contraception.
- Delivery routes differ in pharmacokinetic exposure; They should not be conflated with oral therapy.
- The actual question is which formulation, dosage, and delivery system an outcome study assessed.



Interpretation chain

Primary contraceptive actions

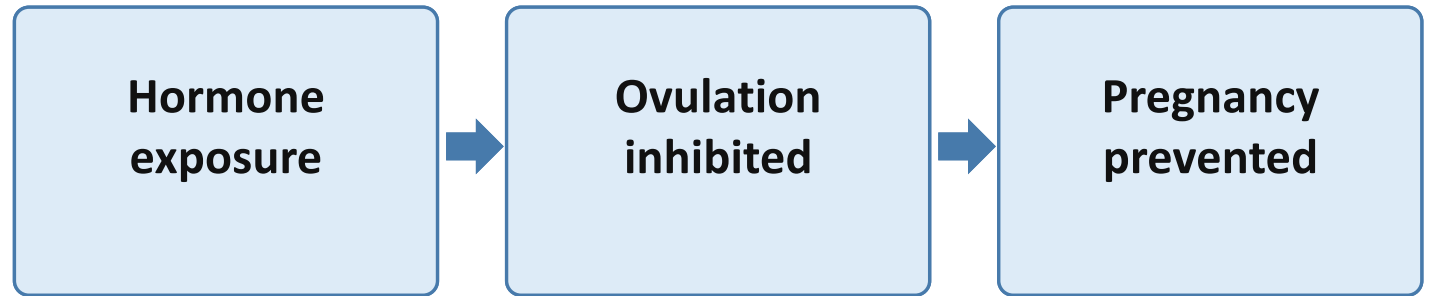
- Contraceptive action to suppression of ovulation or prevention of implantation.
- The underlying hormone manipulation is a systemic intervention, not merely a local reproductive-tract exposure.
- Systemic actions help explain why nonreproductive organs appear in the adverse-effect profile.



Mechanism: Textbook description

The ovarian component of contraception

- Ovulation suppression removes a necessary step in natural conception.
- A pharmacologic reproductive effect can coexist with adverse responses in other tissues.
- Clinical safety therefore cannot be inferred solely from contraceptive effectiveness.



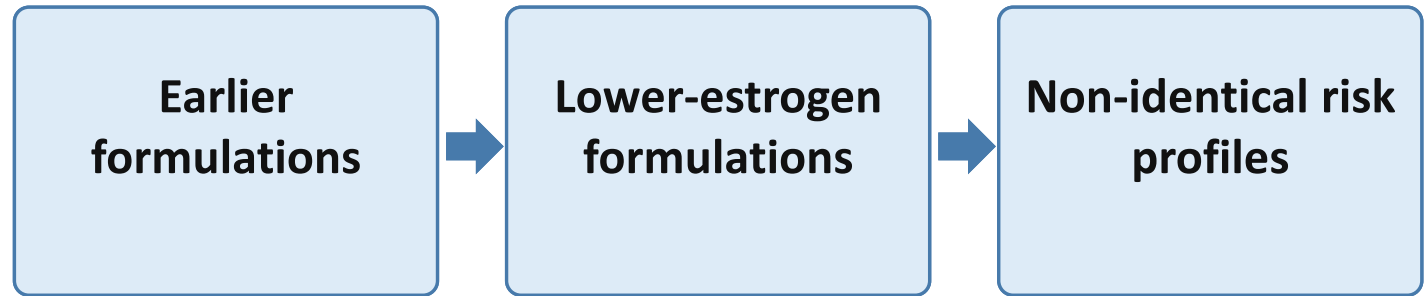
Simplified physiology

Implantation-related action in the source

- Robbins also identifies prevention of implantation as a contraceptive mechanism.
- This broad statement is not a formulation-specific mechanistic ranking.
- Avoid claiming the same predominant mode of action for all oral contraceptives.

How newer formulations change interpretation

- Currently prescribed products typically contain less estrogen than earlier products.
- It associates lower estrogen exposure with fewer side effects.
- Historical risk estimates need formulation and dose context.



Historical comparison

Dose-dependent interpretation

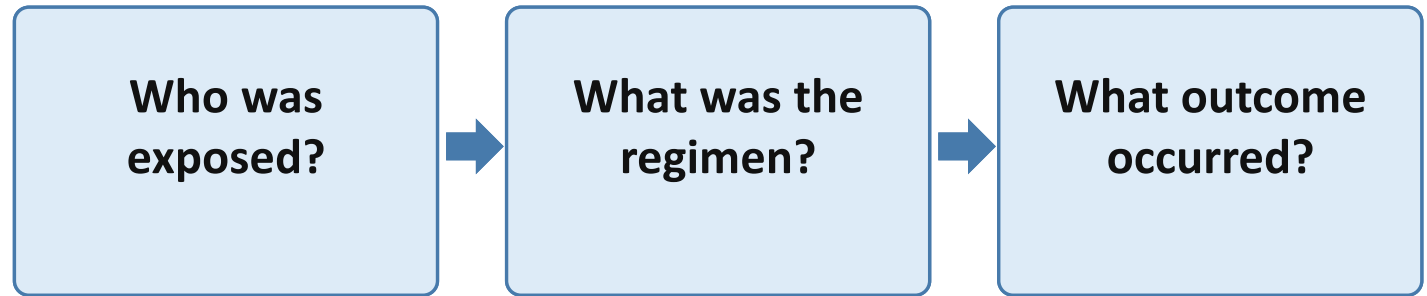
- The same name “oral contraceptive” can refer to materially different estrogen exposures.
- A relative risk from one formulation may not generalize to a different formulation.
- Formulation stratification is central when interpreting older and newer epidemiologic studies.

Time since contraceptive exposure matters

- Endometrial and ovarian cancer protection may remain long after contraception is discontinued.
- Hepatocellular adenoma is associated particularly with prolonged exposure.
- Current use and remote prior use should not be treated as biologically identical histories.

Epidemiology needs exposure specification

- Specify combination versus progestin-only exposure where data permit.
- Distinguish dose, duration, and route; Age and smoking status can also modify risk.
- Treat observed associations separately from demonstrated causal mechanisms.



Study appraisal

Outcomes differ by organ system

Potential protection	Endometrium; Ovary
Potential association	Cervix in HPV infection; Hepatic adenoma
Vascular risk	Venous thromboembolism; Context-specific arterial risk

- Potential cancer protection at some sites and potential increased risk at others.
- Thromboembolism is mechanistically linked to a hormone-induced procoagulant state.
- Hepatocellular adenoma is a specific, recognizable benign neoplasm associated with exposure.

Breast carcinoma: Wording matters

Robbins: Oral contraception

“Prevailing view” of no increase

Formulation-dependent evidence

Separate intervention

Menopausal hormone therapy

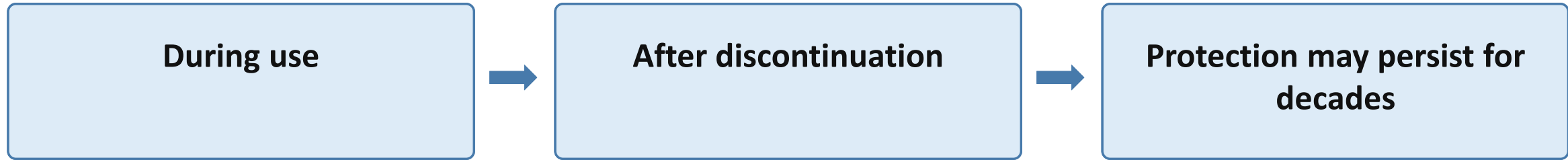
Different population and regimens

- The Robbins oral-contraceptive passage states that the prevailing view is no increase in breast-cancer risk.
- This is a source-specific summary, not an independently updated meta-analysis.
- Do not extrapolate this statement to menopausal hormone therapy, which is discussed separately.

Endometrial cancer: Protective association

- An association between oral-contraceptive use and lower endometrial cancer risk.
- The protective effect may remain after treatment is stopped.
- This is an epidemiologic disease-endpoint statement, not a claim that individual endometrial lesions regress.

The long duration of endometrial protection

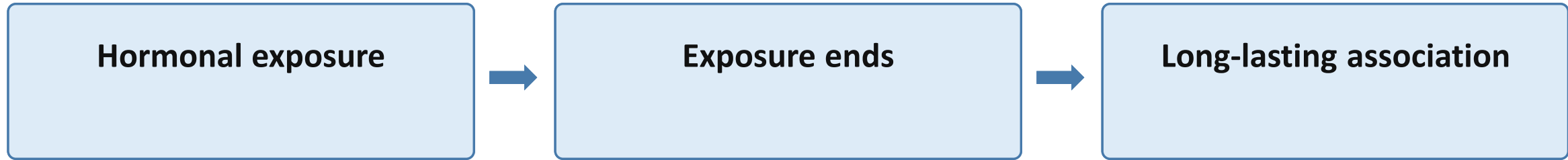


- Protection is described as lasting for decades after cessation.
- Past exposure may therefore matter even when a patient is no longer taking contraception.
- A durable association should not be confused with proof of a single permanent molecular mechanism.

Ovarian cancer: Protective association

- Robbins also reports a protective association for ovarian cancers.
- The favorable association is separate from contraceptive efficacy.
- The text does not provide a magnitude stratified by tumor subtype or progestin formulation.

Ovarian protection may outlast exposure



- The reported protection can persist for decades after stopping use.
- Risk histories should distinguish current use from ever-use and previous duration of use.
- Do not assign a precise absolute risk reduction without an appropriate primary study.

Cancer sites cannot be pooled conceptually

Breast	No increase: Prevailing textbook view
Endometrium	Protective association
Ovary	Protective association
Cervix	Possible increase in HPV-infected females

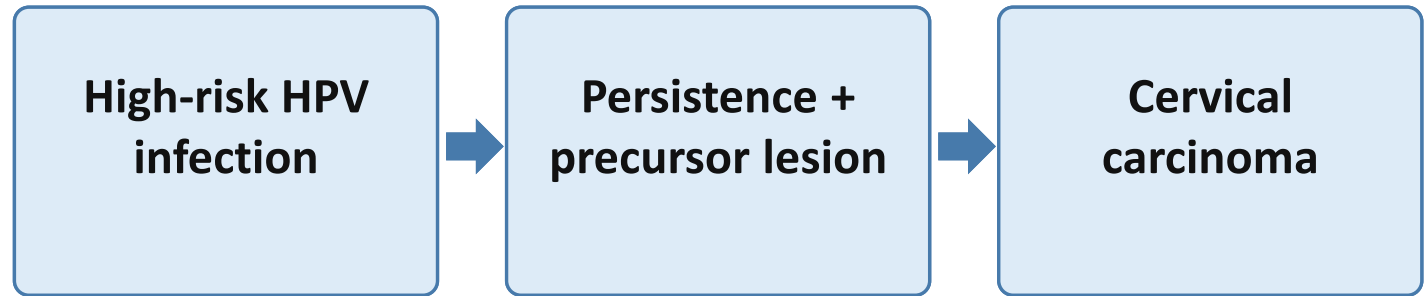
- Breast, endometrium, ovary, and cervix show different site-specific associations.
- “Cancer risk” is not a single biological endpoint.
- Interpret each organ within its relevant etiologic context.

Cervical carcinoma requires HPV context

- The oral-contraceptive section describes possible increased cervical cancer risk in women infected with HPV.
- HPV infection is the relevant cofactor named.
- Do not describe oral contraceptives as sufficient to cause cervical cancer.

High-risk HPV: The main cervical carcinogen

- High-risk HPV infection is the dominant etiologic factor in cervical cancer.
- Persistent infection increases the likelihood of precursor lesions and invasive carcinoma.
- The contraceptive association must be interpreted in this causal setting.



Primary etiologic pathway

HPV E6 and E7 establish biologic plausibility

HPV E6

Impaired p53 activity

Reduced damage checkpoint

HPV E7

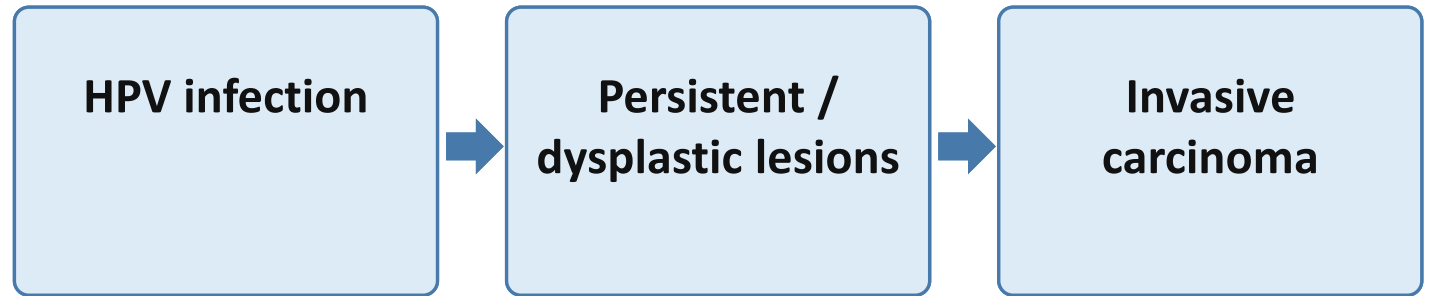
Impaired RB activity

Increased cell-cycle entry

- High-risk HPV E6 promotes degradation of p53; E7 disrupts RB-mediated cell-cycle control.
- Loss of tumor-suppressor function favors cell-cycle progression and mutation accumulation.
- The source does not establish that contraceptives directly activate E6 or E7.

HPV infection versus invasive cervical cancer

- HPV infection is common; Only a subset becomes persistent and progresses.
- An exposure associated with cancer in HPV-infected women should not be treated as synonymous with causing HPV infection.
- Precancer and invasive carcinoma are distinct pathologic endpoints.



Disease progression

Cervical risk: What the source does not establish

- The passage uses “may increase” rather than asserting an unqualified causal effect.
- No absolute probability, dose threshold, or additional molecular pathway is provided.
- Cervical screening and HPV-centered prevention remain conceptually distinct from contraception.

Separating etiologic factor from risk modifier

Etiologic driver

High-risk HPV

E6/E7 tumor-suppressor disruption

Possible modifier

Hormonal contraceptive exposure

Association conditional on HPV

- An etiologic agent participates directly in carcinogenesis: High-risk HPV.
- A risk modifier changes the probability of an outcome in an exposed subgroup: Oral-contraceptive association in HPV-infected females.
- The two should not be merged into a single causal label.

Venous thromboembolism is a central adverse outcome

- Oral contraception with venous thrombosis and pulmonary thromboembolism.
- The proposed mechanism is a hormone-induced hypercoagulable state.
- The risk is clinically important even with lower-estrogen preparations.

Magnitude: Relative venous thrombotic risk

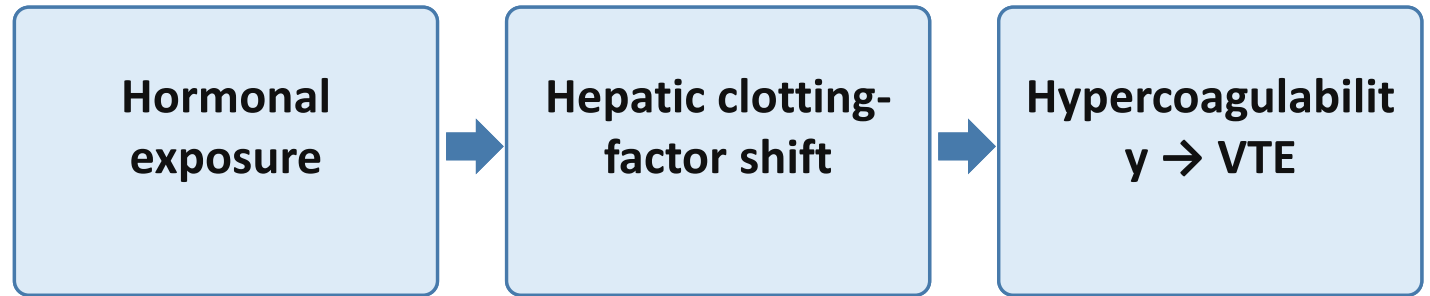
Users versus reference

2–4× relative risk

- Most cited studies report a 2- to 4-fold relative increase in venous thrombosis and pulmonary thromboembolism.
- This range includes lower-dose products defined in the source as less than 50 µg of estrogen.
- A relative increase is not an absolute event rate.

Hepatic coagulation-factor synthesis

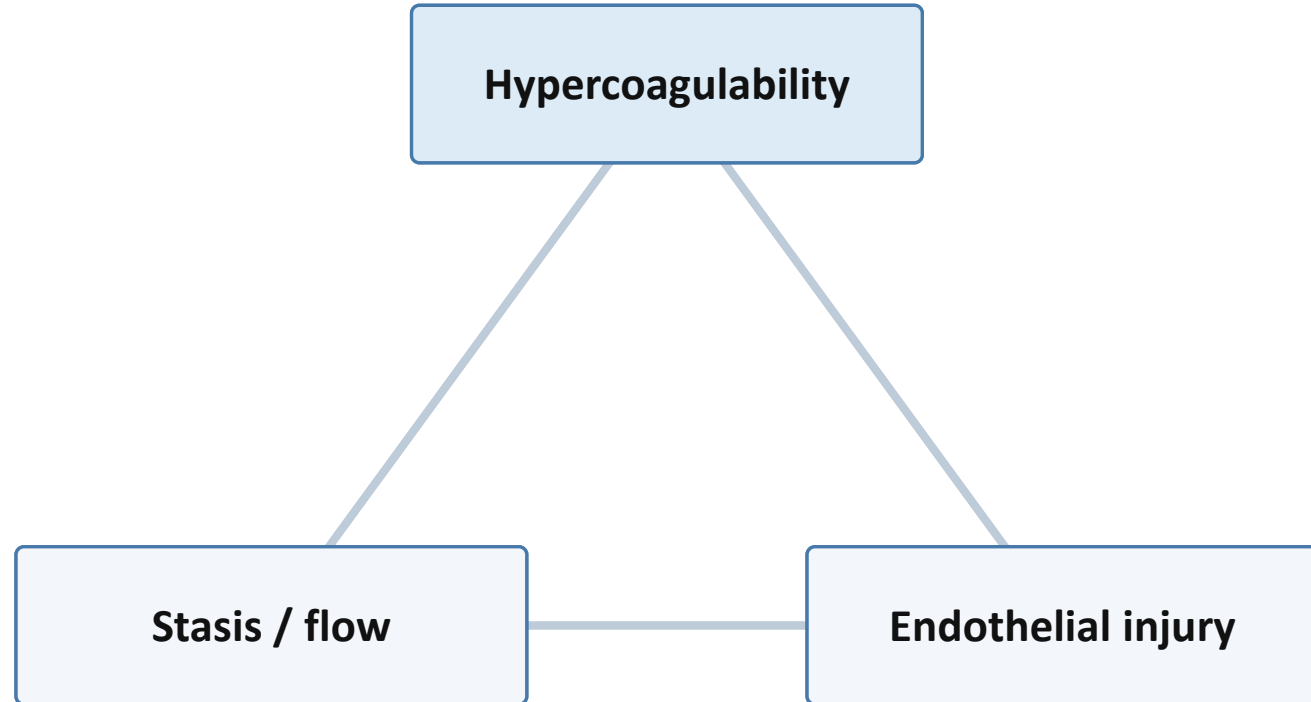
- The acquired hypercoagulable state to increased hepatic production of coagulation factors.
- The thrombosis chapter also notes decreased anticoagulant synthesis as a potential contributor.
- The resulting prothrombotic balance favors venous clot formation.



Procoagulant sequence

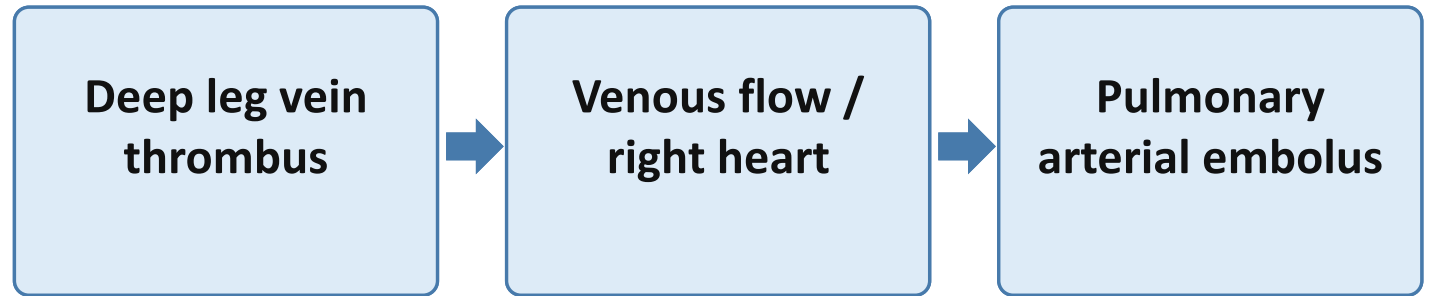
Hypercoagulability in Virchow's triad

- Virchow's triad comprises hypercoagulability, altered blood flow, and endothelial injury.
- Oral contraceptive use primarily enters the framework through acquired hypercoagulability.
- Other coincident risks can affect different arms of the triad.



Deep vein thrombosis: Likely source of emboli

- Venous thrombi frequently develop in deep veins of the leg.
- Portions may detach and traverse the venous circulation and right heart.
- An embolus may obstruct pulmonary arterial branches.



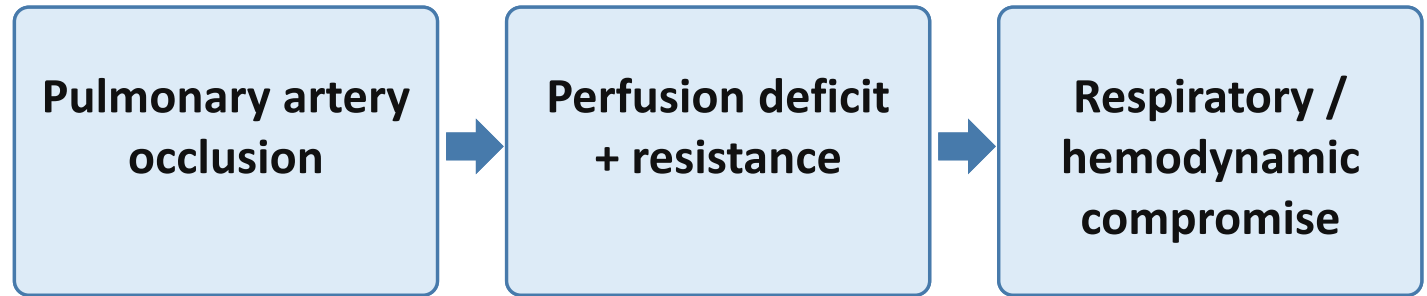
Embolic route

Deep venous thrombosis: Pathologic substrate

- Stasis favors venous thrombus formation; Hypercoagulability amplifies the tendency to clot.
- A DVT can be symptomatic or clinically silent before embolization.
- The contraceptive exposure is a risk factor, not a morphologically unique thrombus subtype.

Pulmonary thromboembolism: Immediate consequences

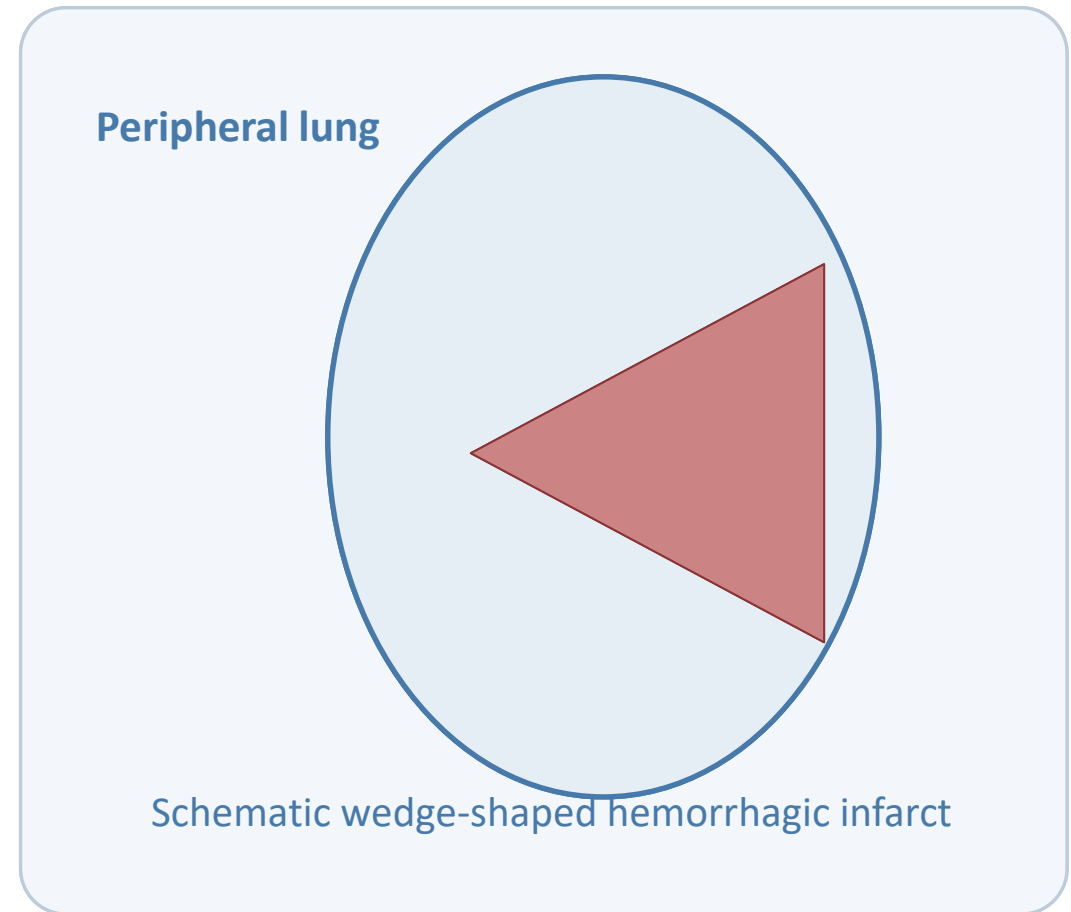
- Pulmonary arterial obstruction creates ventilated but nonperfused lung regions.
- Major obstruction also increases pulmonary vascular resistance and can cause acute right heart strain.
- Severity depends on thrombus burden and cardiopulmonary reserve.



Consequences of embolization

Pulmonary emboli: Recognizable morphology

- Large emboli may lodge in the main pulmonary arteries or at their bifurcation as a saddle embolus.
- Peripheral occlusions may produce hemorrhage or hemorrhagic infarction.
- Classical pulmonary infarcts are peripheral wedge-shaped lesions.

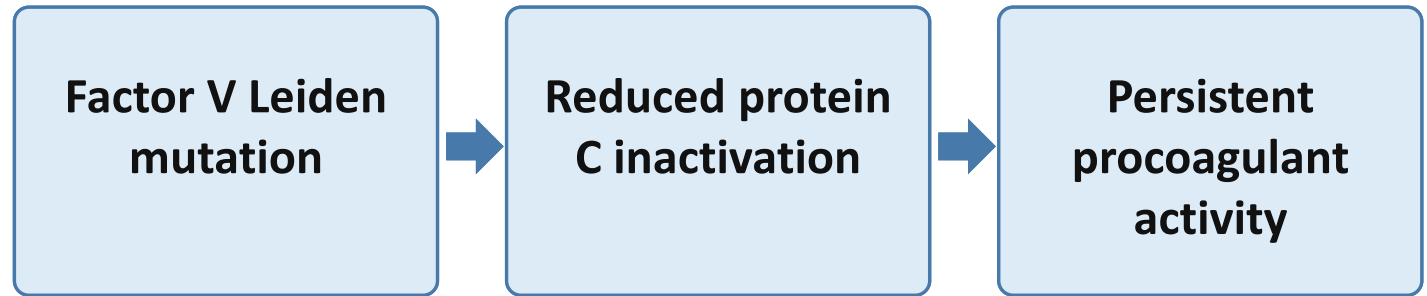


Pulmonary embolism: Clinical expression

- Large emboli may cause sudden collapse and hemodynamic shock.
- Symptomatic cases may present with dyspnea, pleuritic pain, and cough.
- Hemoptysis and fever can accompany pulmonary infarction.

Factor V Leiden: Inherited thrombophilia

- Factor V Leiden is a factor V variant resistant to inactivation by activated protein C.
- This weakens an important physiological anticoagulant pathway.
- Higher thrombotic risk when this mutation and certain contraceptive exposures coexist.



Inherited mechanism

Combined inherited and acquired risk

Inherited factor

Factor V Leiden

Protein C resistance

Acquired factor

Hormonal exposure

Coagulation-factor shift

- An inherited propensity to thrombosis may be clinically silent until another prothrombotic exposure occurs.
- Oral contraception adds an acquired component to an existing susceptibility.
- The relevant question is cumulative risk, not whether one exposure is the sole cause.

Third-generation formulations: Careful interpretation

- A potentially greater thrombosis risk with some third-generation synthetic-progestin OCs.
- The text emphasizes especially susceptible women carrying factor V Leiden.
- The observation should not be generalized to all progestins or progestin-only contraception.

Risk comparison: Contraception versus pregnancy

OC-associated versus pregnancy-associated VTE

2–6× lower

- VTE risk associated with contraceptive use is two to six times lower than that associated with pregnancy.
- This is a contextual comparison of thromboembolic hazards.
- Risk assessment should consider both the exposure and the alternative state of pregnancy.

Relative risk is not absolute incidence

Relative measure

Ratio of event probabilities

Robbins gives 2–4×

Absolute measure

Events per population/time

Not supplied in passage

- A 2–4-fold relative risk does not specify how many patients have an event.
- Absolute risk depends on the baseline population and additional risk factors.
- Avoid drawing incidence curves or counts when no denominators are supplied.

How to read a thrombotic risk statement

- Identify the outcome: DVT, PE, or combined VTE.
- Identify comparator, duration of exposure, and hormonal formulation.
- Account for smoking, inherited susceptibility, pregnancy, and other co-exposures where data allow.

Arterial and venous events are distinct

Venous

DVT / pulmonary embolism

Hypercoagulability prominent

Arterial

Atherosclerosis / MI

Different causal context

- Venous thrombosis is strongly linked to acquired hypercoagulability.
- Coronary artery disease and myocardial infarction involve different vascular pathophysiology.
- The strength and certainty of the associations are not interchangeable.

Coronary disease: Uncertainty in the source

- Considerable uncertainty regarding atherosclerosis and myocardial infarction among OC users.
- Avoid presenting a uniform dose-independent increase or decrease in coronary risk.
- Age and smoking status are explicitly relevant modifiers.

Younger OC users: Coronary risk statement

- The textbook finds no apparent increase in coronary artery disease in females younger than 30 years.
- This is an age-group summary, not a guarantee of individual safety.
- VTE and hepatic adenoma risks are separate endpoints.

Older nonsmokers: Coronary risk statement

- No apparent increased coronary disease risk in older women who do not smoke.
- The group distinction reflects effect modification by other vascular risks.
- Do not treat the statement as evidence about all formulations and all vascular outcomes.

Women older than 35 who smoke

Smokers older than 35 years

≈2× coronary risk

- That coronary risk approximately doubles among female OC users older than 35 years who smoke.
- Both age and smoking are relevant to interpretation.
- This passage is an association and does not quantify absolute myocardial infarction incidence.

Why smoking status changes interpretation

- A comparison that ignores smoking may combine biologically different vascular-risk groups.
- A treatment effect estimated in nonsmokers should not be assumed to apply in smokers.
- This is an example of risk-stratified interpretation rather than a universal contraceptive contraindication rule.

Avoid conflating VTE and myocardial infarction

VTE	2–4× relative increase: Reported in the source
Coronary disease	Uncertain overall; Smoking/age interaction
Risk explanation	Different vascular endpoints

- The source offers a stronger and more explicit quantitative VTE association.
- The coronary disease assessment is qualified by uncertainty and subgroup differences.
- Risk communication should retain both the outcome and its evidentiary confidence.

Hepatocellular adenoma: An exposure-associated tumor

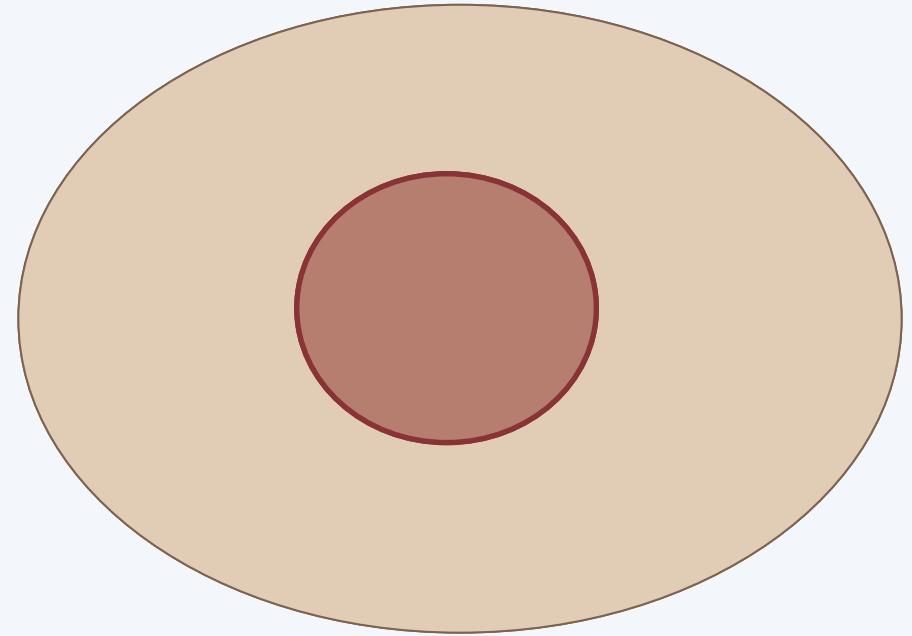
- Hepatocellular adenoma is a benign hepatocytic neoplasm.
- A strong association with oral contraceptives, especially prolonged exposure.
- The liver chapter also describes associations with anabolic steroids and metabolic factors.

Clinical context of the association

- Prolonged OC exposure, particularly in older female users, in its adverse-effect section.
- The liver chapter describes many tumors in young women and the roles of obesity and metabolic syndrome.
- These statements describe overlapping but not identical risk strata.

Hepatocellular adenoma: Gross morphology

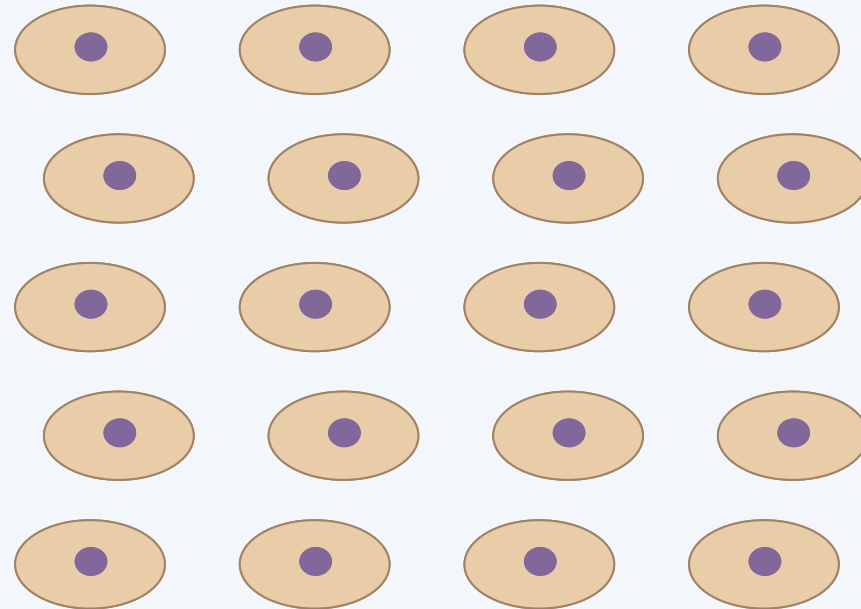
- A discrete hepatic mass is characteristic.
- Hemorrhage may occur within or around the lesion.
- Tumors can present incidentally or with pain or hemorrhagic necrosis.



Schematic hepatic mass — not a specimen

Hepatocellular adenoma: Basic histology

- Neoplastic hepatocytes are arranged in plates approximately one to two cells thick.
- Large arteries can be present within scant fibrous stroma.
- Normal portal tracts and interlobular bile ducts are absent within the lesion.



Schematic hepatocyte plates; No portal tract

Why absent portal tracts matter

Normal liver architecture

Portal tracts present

Interlobular bile ducts present

Hepatocellular adenoma

Absent normal portal tracts

No interlobular ducts

- Portal tracts normally contain a portal venous branch, hepatic arterial branch, and bile duct.
- Their absence in hepatocellular adenoma is a useful architectural discriminator.
- It must be assessed in tissue context rather than inferred from a single missing structure.

Adenoma is heterogeneous at the molecular level

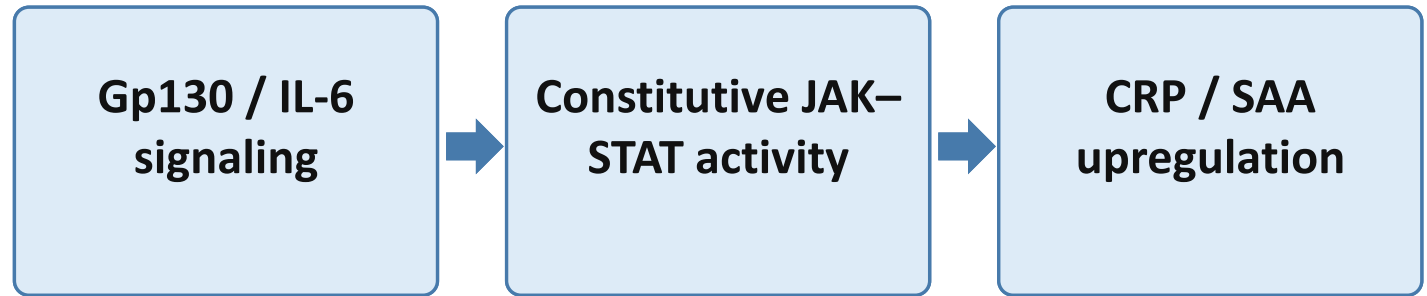
HNF1A-inactivated	Fat-rich; LFABP loss
Inflammatory	JAK–STAT; CRP/SAA expression
β-catenin–activated	Wnt activation; Subtype-specific malignancy risk
Sonic hedgehog	GLI1 fusion; Hemorrhage propensity

HNF1A-inactivated adenoma

- HNF1A loss-of-function can lead to conspicuous lesional steatosis.
- Loss of liver fatty acid-binding protein expression is a characteristic immunophenotypic feature.
- Comparatively little risk of malignant transformation in this subtype.

Inflammatory hepatocellular adenoma

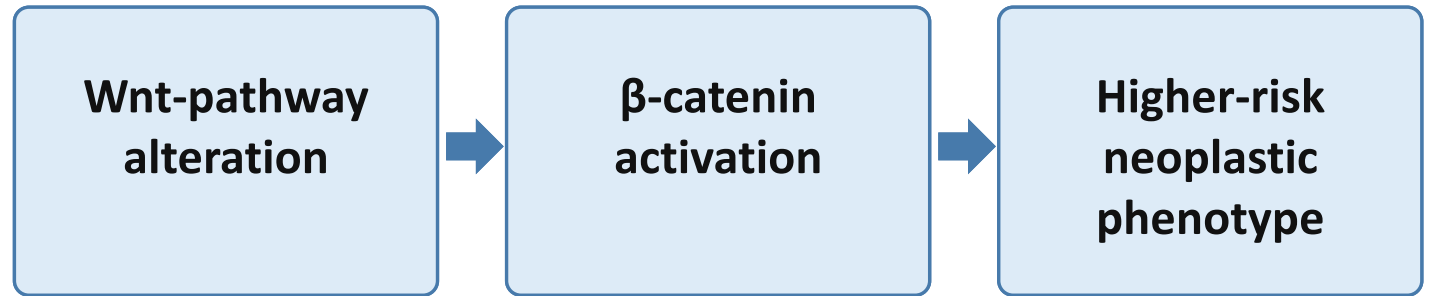
- Activating gp130/IL-6–pathway alterations stimulate JAK–STAT signaling.
- Inflammatory adenomas may show sinusoidal dilation and mimic focal nodular hyperplasia.
- CRP and serum amyloid A are upregulated in neoplastic hepatocytes.



Inflammatory subtype

β-catenin–activated adenoma

- CTNNB1 or related Wnt-pathway alterations activate β-catenin signaling.
- High-level activation, notably some CTNNB1 exon 3 alterations, is linked to malignant transformation risk.
- Nuclear β-catenin immunoreactivity may support pathway activation.



Wnt-related subtype

Sonic hedgehog adenoma

- The source describes GLI1 fusion-driven activation of hedgehog signaling.
- This subtype has an important propensity to hemorrhage.
- A benign label does not exclude potentially life-threatening bleeding.



Molecular-to-clinical link

Hemorrhage and rupture

- Hemorrhagic necrosis may produce abdominal pain.
- Rupture of a hepatocellular adenoma can cause massive intra-abdominal hemorrhage.
- This is a clinically serious complication of a histologically benign neoplasm.

Malignant transformation is subtype-dependent

Lower-risk pattern

HNF1A-inactivated subtype

Minimal malignant transformation risk

Higher-risk pattern

Certain β -catenin–activated lesions

Transformation concern

- β -catenin pathway activation is a key determinant of increased malignant potential.
- Risk is not identical across all hepatocellular adenomas.
- Morphology, molecular classification, and clinical context jointly inform assessment.

Textbook management implications of adenoma

- Robbins recommends resection for male patients, β -catenin–activated tumors, and lesions measuring at least 5 cm.
- Smaller lesions without β -catenin activation may be followed, with cessation of relevant hormone or steroid exposure.
- These are textbook statements, not independently validated contemporary management guidelines.

Hepatocellular adenoma versus FNH

Hepatocellular adenoma

Neoplastic hepatocytes

Portal tracts absent

Hormone association

Focal nodular hyperplasia

Non-neoplastic response

Central scar / ductular reaction

Altered perfusion

- Focal nodular hyperplasia is a non-neoplastic hyperplastic lesion related to altered vascular flow.
- FNH typically has a central scar and ductular reaction; Adenoma lacks normal portal tracts and ducts.
- Inflammatory adenoma may mimic FNH, so pattern recognition alone has limits.

Other hepatic adverse reaction: Cholestasis

Cholestasis

Drug-associated bile-flow disturbance

Non-neoplastic injury

Hepatocellular adenoma

Benign hepatocyte neoplasm

Mass lesion / hemorrhage

- The general adverse-drug-reaction table lists estrogens and contraceptive agents among causes of cholestasis.
- This drug-associated liver injury should not be confused with hepatocellular adenoma.
- Cholestasis and neoplasia represent different pathologic response types.

Balance favorable and unfavorable outcomes

Favorable	Endometrial and ovarian cancer associations
Potentially harmful	VTE; Hepatic adenoma; Possible cervical risk
Dependent on subgroup	Coronary outcomes by age/smoking

- Endometrial and ovarian cancer protection coexist with potential venous thrombotic harm.
- HPV-associated cervical risk and liver adenoma are distinct concerns requiring their own contexts.
- Cancer, vascular, and liver endpoints should not be compressed into a single “safe/unsafe” category.

Case: Thrombosis with inherited susceptibility

A person taking combined oral contraception develops a deep vein thrombosis and is found to carry factor V Leiden.

Interpretation question

Which elements are inherited and which are acquired?

Answer: Protein C-resistant factor V is inherited; Hormone-associated coagulation shift is acquired.

Case: A smoking-related coronary concern

A 38-year-old current smoker asks whether OC-associated vascular risk is identical to that in a 25-year-old nonsmoker.

Interpretation question

How does the Robbins passage stratify coronary risk?

Answer: Its higher coronary-risk statement applies specifically to smokers older than 35, not all users.

Case: Benign mass with serious consequences

A long-term OC user has a discrete hepatocytic liver mass with hemorrhage and no portal tracts.

Interpretation question

Which lesion is most consistent with the described architecture?

Answer: Hepatocellular adenoma; Rupture and molecular subtype are important next considerations.

Case: A cervical-cancer association

An epidemiologic study reports cervical carcinoma among HPV-infected OC users.

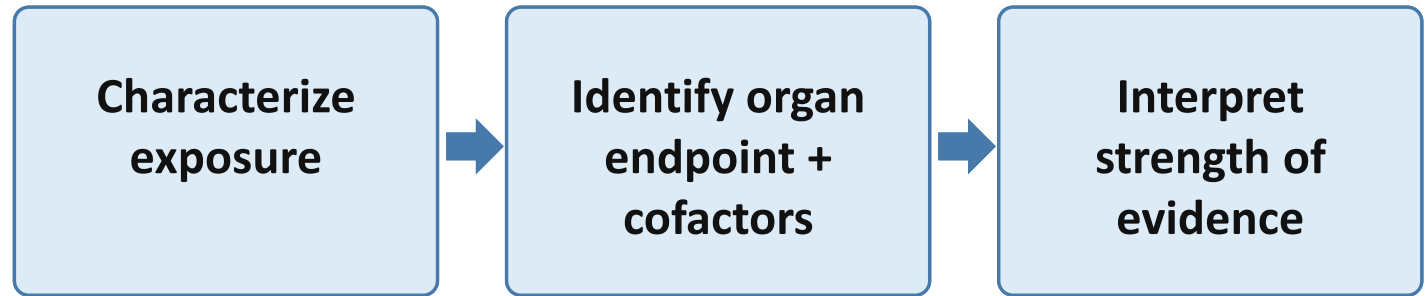
Interpretation question

Can the OC exposure replace high-risk HPV as the principal etiologic explanation?

Answer: No. High-risk HPV drives cervical carcinogenesis; OCs are described as a possible risk modifier.

A structured clinicopathologic interpretation

- First specify formulation, dose, duration, and route when known.
- Next identify the exact pathology endpoint and major host cofactors.
- Then separate a mechanistic explanation from an observational association and state uncertainty.



Reasoning workflow

Core pathology conclusions

- Cancer associations are organ-specific: Protective at endometrium/ovary, possible conditional cervical risk, source-qualified breast statement.
- Acquired hypercoagulability links hormonal exposure with DVT and pulmonary embolism.
- Hepatocellular adenoma is a hormone-associated benign tumor with hemorrhagic and subtype-dependent malignant risks.

Primary textbook references

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026). Chapter 9, “Oral Contraceptives,” pp. 384–385.
- Chapter 4: thrombosis, hypercoagulability, and factor V Leiden; Chapter 15: pulmonary embolism.
- Chapter 18, pp. 788–790: hepatocellular adenoma; Chapter 22, pp. 905–909: HPV-mediated cervical carcinogenesis.