

Sex hormones and hormonal contraceptives

Oestrogens, progestins and androgens used to prevent pregnancy, replace a hormone lost at menopause or in hypogonadism, or both - a group defined less by one shared mechanism than by one shared safety theme: venous thromboembolism and hormone-sensitive cancer risk that tracks with estrogen dose, route and the presence or absence of a uterus.

Online guide: <https://www.medguideglobal.com/pharmacology/endocrine-and-metabolic/sex-hormones-and-contraceptives>

Content updated: 2026-09-15

Quick revision

One Liner: Combined hormonal contraceptives, progestin-only methods, menopausal hormone therapy and testosterone replacement all deliver a sex steroid, but the safety conversation for each is different: VTE and age-plus-smoking for combined methods, bone density for depot medroxyprogesterone, endometrial cancer for unopposed estrogen, and virilization-by-secondary-exposure for topical testosterone.

1. Combined hormonal contraceptives (estrogen plus progestin) raise venous thromboembolism risk to roughly 3 to 9 cases per 10,000 woman-years, a rate that is still compared against the background risk of VTE in pregnancy when patients weigh the decision. [1]
2. Women over 35 who smoke should not use combined hormonal contraceptives; the boxed warning on these products exists specifically because cigarette smoking sharply increases serious cardiovascular events in that age-and-exposure combination. [1]
3. Migraine with aura, a personal history of VTE or arterial thromboembolic disease, uncontrolled hypertension and current or past breast cancer are all listed contraindications to combined hormonal contraceptives. [1]
4. Progestin-only methods - the levonorgestrel intrauterine system, the etonogestrel implant, and depot medroxyprogesterone acetate injection - avoid the estrogen-driven VTE signal but each carries its own labelled trade-off: irregular bleeding, an insertion/removal procedure, or reversible bone mineral density loss. [3][4][2]
5. Depot medroxyprogesterone acetate's own boxed warning covers bone mineral density loss that is greater with longer use and may not fully reverse, which is why the label advises against using it as a birth control method for longer than two years unless other options are inadequate. [2]
6. Unopposed estrogen therapy in a woman with an intact uterus raises endometrial cancer risk roughly two to twelve-fold; adding a progestin is the labelled way to reduce that risk, which is the whole rationale for combined rather than estrogen-alone menopausal hormone therapy in these patients. [5]
7. The Women's Health Initiative findings behind the menopausal hormone therapy boxed warning include increased stroke, deep vein thrombosis, pulmonary embolism and myocardial infarction with estrogen-plus-progestin, increased invasive breast cancer with longer combined use, and increased probable dementia in women 65 and older. [6]
8. Topical testosterone's boxed warning is about virilization from secondary exposure - children or partners who contact an unwashed application site can develop signs of androgen exposure themselves, which is a transfer risk rather than a risk to the treated patient. [7]

Overview

1. This class covers four uses of the same small family of steroid hormones - estrogens, progestins and androgens - rather than one drug mechanism applied to one disease. Combined hormonal contraceptives and progestin-only contraceptives prevent pregnancy; menopausal hormone therapy replaces the estrogen (and, when the uterus is present, the progestin) that ovarian function stops supplying at menopause; testosterone replacement restores androgen levels in men with confirmed hypogonadism. What ties them together for exam and prescribing purposes is not a shared target but a shared question: how much estrogen, by which route, and is the uterus (or, for testosterone, a

child in the household) part of the risk calculation. [8]

2. In combined hormonal contraception, progestin does most of the contraceptive work by suppressing ovulation, and the added estrogen chiefly stabilises the endometrium so that predictable withdrawal bleeding occurs; the estrogen component is also the one that drives the venous thromboembolism signal. That VTE risk is quoted in the labelling as roughly 3 to 9 cases per 10,000 woman-years of use, and it is why the same class carries a boxed warning restricting use in women over 35 who smoke - smoking sharply compounds the cardiovascular risk that estrogen alone already raises at that age. [8][1]

3. Progestin-only methods were built around avoiding that estrogen-linked VTE signal while keeping contraceptive efficacy high. The levonorgestrel intrauterine system and the etonogestrel subdermal implant work largely locally or through ovulation suppression with minimal systemic estrogen exposure, and depot medroxyprogesterone acetate suppresses gonadotropin release systemically without an estrogen component at all. None of the three shares the combined-method VTE boxed warning, but each has its own labelled cost: unpredictable bleeding patterns for the first two, and a bone-mineral-density warning specific to the depot injection. [3][4][2]

4. Menopausal hormone therapy turns the same estrogen-and-uterus question around. Estrogen alone relieves menopausal symptoms effectively, but in a woman who still has a uterus it also stimulates endometrial proliferation unopposed, and the labelling for conjugated estrogens states the resulting endometrial cancer risk runs roughly two to twelve times that of non-users, tracking with dose and duration. Adding a progestin restores the endometrial protection that a woman's own ovaries would otherwise provide across a natural cycle, which is the entire pharmacological reason estrogen-plus-progestin products such as conjugated estrogens with medroxyprogesterone acetate exist as a distinct combination rather than estrogen simply being dosed alone in every patient. A woman without a uterus, by contrast, has no endometrium to protect and is typically offered estrogen alone. [5][6]

5. Testosterone replacement sits apart from the other three uses mechanistically - it restores androgen signalling in confirmed male hypogonadism rather than manipulating a female reproductive cycle - but it belongs in the same class because it is the same steroid-hormone-replacement logic applied to a different axis, and it carries its own transfer-risk boxed warning: unwashed skin after topical application can virilise a child or partner who makes secondary contact with it. [7]

Classification and drug examples

Intro: Four groups share this class not because they act on one receptor the same way, but because each is a clinical use of estrogen, progestin or androgen replacement with its own dominant safety question.

1. Name: Combined hormonal contraceptives (estrogen plus progestin)

1. Note: Ethinyl estradiol paired with a progestin; VTE risk and the smoking-plus-age-35 boxed warning are the defining safety features of the whole group.

1. Name: Ethinyl estradiol/levonorgestrel

Juleber

1. Route: Oral

1. Note: A second-generation progestin pairing generally regarded as carrying the lower end of the class's VTE risk range. [8]

2. Name: Ethinyl estradiol/drospirenone

1. Yasmin

2. Yasminelle

2. Route: Oral

2. Note: A newer-generation progestin pairing; drospirenone-containing combinations have been studied for a possibly higher VTE risk than levonorgestrel-containing ones, though estimates vary by study design. [1]

3. Name: Ethinyl estradiol/norethindrone acetate (with ferrous fumarate)

Wymzya Fe

3. Route: Oral

3. Note: A first-generation-progestin combined pill formulated with iron supplementation for the placebo interval. [8] [1]

2. Name: Progestin-only contraceptive methods

2. Note: No estrogen component, so the combined-method VTE boxed warning does not apply, but each method carries its own labelled trade-off.

1. Name: Levonorgestrel intrauterine system

Mirena

1. Route: Intrauterine

1. Note: Also FDA-approved for heavy menstrual bleeding, not only contraception; roughly half of the rare pregnancies that occur with it in place are ectopic. [3]

2. Name: Etonogestrel implant

Nexplanon

2. Route: Subdermal

2. Note: Prevents pregnancy for up to 3 years by suppressing ovulation, thickening cervical mucus and altering the endometrium; insertion and removal require certified training under a REMS programme. [4]

3. Name: Levonorgestrel implant

Jadelle

3. Route: Subdermal

3. Note: A multi-rod subdermal implant using the same progestin as the intrauterine system but delivered systemically rather than locally. [8]

4. Name: Medroxyprogesterone acetate depot injection

Depo-Provera

4. Route: Intramuscular or subcutaneous

4. Note: Carries its own boxed warning for bone mineral density loss with prolonged use; not recommended as a birth control method for longer than 2 years unless other options are inadequate. [2] [3][4][2]

3. Name: Menopausal hormone therapy

3. Note: Estrogen alone for a woman without a uterus; estrogen plus a progestin when the uterus is intact, to protect the endometrium from unopposed estrogen stimulation.

1. Name: Estradiol

1. Route: Oral or transdermal

1. Note: The estrogen most often used for symptom relief; requires added progestin coverage in a woman with a uterus. [5]

2. Name: Conjugated estrogens

Premarin

2. Route: Oral

2. Note: The estrogen studied in the Women's Health Initiative; its label states the endometrial cancer risk of unopposed use directly. [5]

3. Name: Micronized progesterone

Utrogestan

3. Route: Oral

3. Note: An option for the progestin component of combined menopausal hormone therapy in a woman with a uterus. [6]

4. Name: Dydrogesterone

4. Route: Oral

4. Note: Another progestin used for endometrial protection alongside estrogen replacement. [6]

5. Name: Conjugated estrogens/medroxyprogesterone acetate

1. Prempro

2. Premphase

5. Route: Oral

5. Note: The fixed combination studied directly in the Women's Health Initiative substudy behind the class's cardiovascular, breast cancer and dementia boxed-warning language. [6] [5][6]

4. Name: Androgens (testosterone replacement therapy)

4. Note: Restores androgen levels in confirmed male hypogonadism; the labelled boxed warning concerns secondary transfer to a child or partner, not a direct risk to the treated patient.

Name: Testosterone

1. topical gel

2. intramuscular injection

3. transdermal patch

Route: Topical, intramuscular or transdermal, formulation-dependent

Note: A Schedule III controlled substance in the U.S. under the Anabolic Steroids Control Act, reflecting recognised abuse potential alongside its replacement-therapy indication. [7] [7]

Mechanism of action

Summary: All four groups act through the same basic pharmacology - a steroid hormone (or a synthetic analogue) binding its intracellular nuclear receptor and altering gene transcription - applied to different physiological targets. In contraception, exogenous progestin (with or without estrogen) suppresses the hypothalamic-pituitary-gonadal axis strongly enough to blunt the LH surge and prevent ovulation, while also thickening cervical mucus and altering the endometrium as backup mechanisms. In menopausal hormone therapy, exogenous estrogen replaces what the postmenopausal ovary no longer supplies, relieving vasomotor and genitourinary symptoms, while an added progestin opposes estrogen's proliferative effect on the endometrium in a woman who still has a uterus. In androgen replacement, exogenous testosterone restores androgen-receptor signalling that is deficient because of primary gonadal failure or hypothalamic-pituitary failure.

Target: Nuclear estrogen, progesterone and androgen receptors, plus estrogen and progestin negative feedback on the hypothalamic-pituitary-gonadal axis

Cidal Static: Not applicable - these are hormone receptor agonists modulating gene transcription and endocrine feedback loops rather than cytotoxic or cytostatic agents acting on a pathogen

Kill Kinetics: Onset and offset are route- and use-dependent: cervical mucus thickening from a progestin can occur within days, ovulation suppression typically needs a full treatment cycle to be reliable, depot medroxyprogesterone's effect persists for months after the last injection because of its slow-release depot, and an implant or intrauterine system's effect reverses only once it is removed

1. Step: 1

1. Title: Exogenous progestin (with or without estrogen) is absorbed by the labelled route

1. Detail: Oral tablets, a subdermal implant, an intrauterine system, or a depot intramuscular or subcutaneous injection each deliver the hormone into the circulation or, for the intrauterine system, largely into the local uterine environment. [3][8]

2. Step: 2

2. Title: Progestin suppresses gonadotropin-releasing hormone pulsatility and blunts the LH surge

2. Detail: Depot medroxyprogesterone's label describes this directly: the progestin primarily inhibits gonadotropin secretion, which prevents follicular maturation and ovulation. [2]

3. Step: 3

3. Title: Cervical mucus thickens and the endometrium becomes less receptive

3. Detail: The etonogestrel implant's label lists cervical mucus viscosity increase and endometrial alteration alongside ovulation suppression as its three contraceptive mechanisms, and the intrauterine system produces the mucus and endometrial effects locally with comparatively little reliance on ovulation suppression. [4][3]

4. Step: 4

4. Title: In menopausal hormone therapy, estrogen instead activates endometrial and other target-tissue estrogen receptors
4. Detail: Without an opposing progestin, that estrogen receptor activation drives endometrial proliferation in a woman with an intact uterus, which is the mechanistic root of the unopposed-estrogen endometrial cancer signal. [5]
5. Step: 5
5. Title: Adding a progestin (menopausal hormone therapy) or testosterone acting on the androgen receptor (male hypogonadism) completes the intended replacement
5. Detail: A co-administered progestin counteracts the proliferative estrogen effect on the endometrium, while exogenous testosterone binds the androgen receptor directly to restore signalling that primary or secondary hypogonadism has removed. [6][7]

Major clinical uses

1. Drug: Ethinyl estradiol/levonorgestrel, drospirenone or norethindrone acetate combinations
1. Organism: Not applicable
1. Indication: Prevention of pregnancy
1. Line: first-line contraceptive option for women without a contraindication to estrogen
1. Note: Also used off-label for menstrual cycle regulation and acne in some formulations, though pregnancy prevention is the labelled indication reviewed here. [1]
2. Drug: Levonorgestrel intrauterine system
2. Organism: Not applicable
2. Indication: Prevention of pregnancy for up to 8 years; treatment of heavy menstrual bleeding for up to 5 years in women choosing intrauterine contraception
2. Line: a long-acting reversible option, often first-line where estrogen is contraindicated
2. Note: One of the few contraceptives with a second FDA-approved indication beyond pregnancy prevention. [3]
3. Drug: Etonogestrel implant
3. Organism: Not applicable
3. Indication: Prevention of pregnancy for up to 3 years
3. Line: long-acting reversible option requiring a certified insertion/removal procedure
3. Note: Efficacy does not depend on daily, weekly or monthly patient action, unlike a pill. [4]
4. Drug: Medroxyprogesterone acetate depot injection
4. Organism: Not applicable
4. Indication: Prevention of pregnancy
4. Line: an option when estrogen is contraindicated and daily or procedural methods are impractical
4. Note: Labelled against use beyond 2 years as a birth control method unless other options are inadequate, because of the bone density warning. [2]
5. Drug: Estradiol, or conjugated estrogens with a progestin when the uterus is intact
5. Organism: Not applicable
5. Indication: Moderate-to-severe menopausal vasomotor symptoms and genitourinary syndrome of menopause
5. Line: lowest effective dose, shortest duration consistent with treatment goals, per labelling
5. Note: Not indicated for the prevention of cardiovascular disease or dementia, which the boxed warning states directly. [5]
6. Drug: Testosterone (gel, injection or patch)
6. Organism: Not applicable
6. Indication: Testosterone replacement in adult men with primary hypogonadism or hypogonadotropic hypogonadism confirmed by clinical features and laboratory testing
6. Line: first-line once hypogonadism is biochemically confirmed
6. Note: Not indicated for age-related low testosterone ("low T") in the absence of an underlying diagnosed

hypogonadal condition. [7]

Pharmacokinetics

1. Drug: Combined oral contraceptives (ethinyl estradiol + progestin)

1. Route: Oral, daily

1. Absorption: Well absorbed orally, subject to hepatic first-pass metabolism

1. Csf Penetration: Not applicable

1. Metabolism: Hepatic, largely via CYP3A4 for both the estrogen and most progestin components

1. Elimination: Hepatic and renal

1. Dose Adjust: Enzyme-inducing drugs (e.g. certain anticonvulsants, rifampin) can lower contraceptive hormone levels and effectiveness; hepatic impairment is a contraindication rather than a dose-adjustment scenario [1]

2. Drug: Levonorgestrel intrauterine system

2. Route: Intrauterine, in place for up to 8 years

2. Absorption: Released locally at a declining rate (about 21 mcg/day initially, falling to about 7 mcg/day by year 8), with only low-level systemic absorption

2. Csf Penetration: Not applicable

2. Metabolism: Hepatic for the small systemically absorbed fraction

2. Elimination: Hepatic and renal for the absorbed fraction

2. Dose Adjust: No oral dose to adjust; clinical decisions concern removal timing rather than dosing [3]

3. Drug: Etonogestrel implant

3. Route: Subdermal, in place for up to 3 years

3. Absorption: Released continuously from the rod at a declining rate over its labelled duration of use

3. Csf Penetration: Not applicable

3. Metabolism: Hepatic

3. Elimination: Hepatic and renal

3. Dose Adjust: Hepatic impairment can slow clearance and is addressed in the prescribing information; no oral dose to titrate [4]

4. Drug: Medroxyprogesterone acetate depot injection

4. Route: Intramuscular or subcutaneous, every 3 months

4. Absorption: Slowly absorbed from the injection depot, producing sustained serum levels between doses

4. Csf Penetration: Not applicable

4. Metabolism: Hepatic

4. Elimination: Hepatic and renal

4. Dose Adjust: No adjustment mechanism once injected; the depot cannot be removed if an adverse effect develops, unlike an implant or intrauterine system [2]

5. Drug: Estradiol / conjugated estrogens

5. Route: Oral or transdermal

5. Absorption: Oral estrogen undergoes substantial hepatic first-pass metabolism; transdermal delivery bypasses first-pass metabolism and is associated with a different clotting-factor and triglyceride profile in the pharmacology literature

5. Csf Penetration: Not applicable

5. Metabolism: Hepatic

5. Elimination: Hepatic and renal

5. Dose Adjust: Hepatic impairment is a contraindication; lowest effective dose for the shortest duration is the labelled principle for all routes [5]

6. Drug: Testosterone gel

6. Route: Topical, once daily

6. Absorption: Absorbed through the skin over several hours; washing or covering the site too soon reduces absorption and unwashed contact risks secondary transfer

6. Csf Penetration: Not applicable

6. Metabolism: Hepatic, including conversion to dihydrotestosterone and estradiol

6. Elimination: Hepatic and renal

6. Dose Adjust: Titrated to serum testosterone levels measured on treatment; application site rotation and hand-washing are part of the labelled administration technique, not optional advice [7]

1. This page gives no dose regimens by design. Specific dosing for any contraceptive method, hormone therapy regimen or testosterone product depends on the individual patient, the product formulation and a current prescribing reference.

2. Route drives risk as much as the hormone itself does in this class: an intrauterine or implanted progestin acts largely locally with limited systemic exposure, while an oral estrogen passes through the liver on every dose in a way that a transdermal patch does not, which is part of why route is discussed alongside dose in shared decision-making for both contraception and menopausal therapy. [5][3]

Adverse effects

1. Effect: Irregular or unpredictable bleeding

1. Detail: Reported across progestin-only methods including the intrauterine system and the implant, and is one of the most common reasons patients discontinue these methods. [3][4]

2. Effect: Headache

2. Detail: A commonly reported effect across combined and progestin-only hormonal contraceptives, and also reported with testosterone replacement and menopausal hormone therapy. [3][4]

3. Effect: Weight change, acne and breast tenderness

3. Detail: Reported with the etonogestrel implant among its most common adverse reactions (each affecting at least one in ten users in trials). [4]

4. Effect: Mood changes

4. Detail: The etonogestrel implant's label specifically advises careful observation of women with a history of depressed mood, with removal considered if significant depression develops. [4]

1. Effect: Venous thromboembolism

1. Detail: The defining risk of the estrogen-containing combined methods, estimated at 3 to 9 cases per 10,000 woman-years; not shared to the same degree by progestin-only methods, which lack the estrogen component driving the effect.

1. Action: New leg swelling, chest pain or breathlessness during use of any estrogen-containing product is an urgent reason to seek care rather than wait. [1]

2. Effect: Cardiovascular events with combined hormonal contraceptives in smokers over 35

2. Detail: The boxed warning specifically restricts use in women over 35 who smoke, because cigarette smoking substantially increases serious cardiovascular events in combined hormonal contraceptive users in this age group.

2. Action: Smoking cessation counselling and switching to a non-estrogen-containing method are the labelled responses rather than continuing combined use unmodified. [1]

3. Effect: Bone mineral density loss with depot medroxyprogesterone acetate

3. Detail: Greater with longer duration of use and may not be completely reversible; adolescent use during a critical bone-accretion period raises uncertainty about later fracture risk that the label states has not been resolved.

3. Action: The label advises against using this method for longer than 2 years unless other contraceptive options are considered inadequate. [2]

4. Effect: Endometrial cancer with unopposed estrogen

4. Detail: Roughly two to twelve times the risk of non-users in a woman with an intact uterus taking estrogen without a progestin, tracking with dose and duration of use.

4. Action: A progestin is added for endometrial protection in any woman with a uterus receiving estrogen therapy for menopausal symptoms. [5]
5. Effect: Stroke, deep vein thrombosis, pulmonary embolism and myocardial infarction with estrogen-plus-progestin menopausal therapy
5. Detail: Identified in the Women's Health Initiative estrogen-plus-progestin substudy over roughly 5.6 years of treatment; the label states menopausal hormone therapy should not be used for cardiovascular disease prevention.
5. Action: Cardiovascular risk factors are assessed and weighed against symptom severity before starting or continuing menopausal hormone therapy. [6]
6. Effect: Invasive breast cancer with estrogen-plus-progestin menopausal therapy
6. Detail: An increased risk was demonstrated in the same Women's Health Initiative substudy with longer-term combined use.
6. Action: Current or past breast cancer is a contraindication, and breast surveillance continues during treatment per routine care. [6]
7. Effect: Probable dementia in women 65 and older on combined menopausal hormone therapy
7. Detail: The Women's Health Initiative Memory Study found an increased risk in this age group; applicability to younger women starting therapy closer to menopause has not been established in the same way.
7. Action: Age at initiation is one factor the treating clinician weighs in the individualised risk-benefit discussion. [6]
8. Effect: Ectopic pregnancy with the levonorgestrel intrauterine system
8. Detail: The label states that roughly half of pregnancies that do occur with the device in place are ectopic, even though overall pregnancy rates with the method are very low.
8. Action: New pelvic pain or other symptoms suggestive of pregnancy with the device in place warrant prompt clinical evaluation. [3]
9. Effect: Virilization from secondary testosterone exposure
9. Detail: Children and, less commonly, female partners who have unwashed skin-to-skin contact with a testosterone gel application site can develop signs of androgen exposure themselves, which is the subject of the product's boxed warning.
9. Action: Covering the application site, hand-washing after application and avoiding skin contact until the product has dried are labelled precautions, not optional advice. [7]
1. Drug: Depot medroxyprogesterone acetate
1. Effect: The only method in this class with a labelled duration cap (2 years) tied specifically to its own boxed warning rather than to general contraceptive counselling. [2]
2. Drug: Levonorgestrel intrauterine system
2. Effect: Carries a distinct insertion-related risk profile (uterine perforation, expulsion, and a reported association with group A streptococcal infection following insertion) that an oral or injectable method does not share. [3]
3. Drug: Testosterone gel
3. Effect: The only agent in this class whose principal boxed-warning risk falls on a third party (a child or partner) rather than the treated patient. [7]

Contraindications, precautions and interactions

1. Combined hormonal contraceptives: personal history of deep vein thrombosis or pulmonary embolism, cerebrovascular or coronary artery disease, migraine with aura, uncontrolled hypertension, current or past breast cancer, thrombogenic heart valve or rhythm conditions, and known or suspected pregnancy. [1]
2. Combined hormonal contraceptives are specifically contraindicated in women over 35 years old who smoke, reflecting the boxed warning on cardiovascular risk in that group. [1]
3. Progestin-only methods (intrauterine system, implant, depot injection): known or suspected pregnancy, current or past breast cancer or other progestin-sensitive cancer, active liver disease or liver tumours, and undiagnosed abnormal genital bleeding. [3][4][2]

4. The levonorgestrel intrauterine system is additionally contraindicated in acute pelvic inflammatory disease or a history of it (unless a subsequent intrauterine pregnancy has occurred), and in known uterine or cervical malignancy. [3]

5. Menopausal hormone therapy: undiagnosed abnormal genital bleeding, current or past breast cancer, active or prior venous or arterial thromboembolic disease, known thrombophilic disorders, hepatic impairment, and known estrogen-dependent neoplasia. [5]

6. Testosterone replacement is contraindicated in men with known or suspected breast or prostate carcinoma, and in pregnant or breastfeeding women because of the potential for fetal harm. [7]

1. Migraine with aura is treated as a strong caution or contraindication across estrogen-containing methods because of the associated stroke risk, and is specifically flagged in combined hormonal contraceptive labelling. [1]

2. A family history of venous thromboembolism or a known thrombophilic mutation (such as factor V Leiden) is weighed carefully before starting any estrogen-containing method. [8]

3. Adolescent or long-duration use of depot medroxyprogesterone acetate warrants specific bone-health counselling given the labelled uncertainty about peak bone mass and later fracture risk. [2]

4. Starting menopausal hormone therapy well after menopause, or continuing it into older age, is part of the individualised discussion of cardiovascular and dementia risk described in the boxed warning. [6]

1. With: Enzyme-inducing drugs (e.g. certain anticonvulsants, rifampin)

1. Effect: Can lower circulating levels of the contraceptive estrogen and progestin, reducing contraceptive reliability; a non-hormonal or alternative method is generally advised during concurrent use. [1]

2. With: Other estrogen- or androgen-containing products

2. Effect: Concurrent use with another product supplying the same hormone class is generally avoided because it compounds dose-related risk rather than adding a therapeutic benefit. [5]

Comparison tables

Title: Estrogen-containing versus progestin-only contraception

Caption: The estrogen component is what separates the VTE boxed warning from the rest of this class; progestin-only methods trade that risk for a different labelled concern instead of eliminating risk altogether.

1. Key: method

1. Label: Method

1. Is Row Header: true

2. Key: estrogen

2. Label: Contains estrogen

3. Key: signature_risk

3. Label: Signature labelled risk

4. Key: duration

4. Label: Typical duration/route

1. Method: Combined oral contraceptive

1. Estrogen: Yes

1. Signature Risk: VTE; boxed warning against use in smokers over 35

1. Duration: Daily oral dosing [1]

2. Method: Levonorgestrel intrauterine system

2. Estrogen: No

2. Signature Risk: Irregular bleeding; roughly half of rare method failures are ectopic

2. Duration: Up to 8 years, intrauterine [3]

3. Method: Etonogestrel implant

3. Estrogen: No

3. Signature Risk: Unpredictable bleeding; mood changes in a subset of users

- 3. Duration: Up to 3 years, subdermal [4]
- 4. Method: Depot medroxyprogesterone acetate
- 4. Estrogen: No
- 4. Signature Risk: Bone mineral density loss, not fully reversible with prolonged use
- 4. Duration: Every 3 months, injected; label advises against use beyond 2 years unless alternatives are inadequate [2]

High-yield exam pearls

- 1. Pearl: In combined hormonal contraceptives, the progestin does most of the ovulation-suppressing work; the estrogen mainly stabilises the endometrium for predictable bleeding, and it is the estrogen that drives the VTE signal.
 - 1. Why: This is the reasoning that explains why progestin-only methods keep contraceptive efficacy while dropping the estrogen-linked boxed warning. [8][1]
- 2. Pearl: The combined hormonal contraceptive boxed warning names women over 35 who smoke specifically, not smokers of any age.
 - 2. Why: Age and smoking status compound each other's cardiovascular risk in this population, which the label addresses as a defined subgroup rather than a general smoking warning. [1]
- 3. Pearl: Depot medroxyprogesterone acetate's boxed warning is about bone, not clotting.
 - 3. Why: It is easy to assume every hormonal contraceptive shares the VTE warning; DMPA's defining labelled risk is bone mineral density loss instead, because it has no estrogen component. [2]
- 4. Pearl: Unopposed estrogen needs a uterus to cause its signature harm.
 - 4. Why: The endometrial cancer risk from estrogen-alone therapy applies to women with an intact uterus; a woman without a uterus is typically offered estrogen alone precisely because that risk does not apply to her. [5]
- 5. Pearl: Testosterone gel's boxed warning protects a third party, not the patient taking it.
 - 5. Why: Virilization from secondary exposure affects a child or partner who contacts the unwashed application site, which is a different kind of boxed warning from the direct-patient-risk warnings seen elsewhere in this class. [7]

Common exam traps

- 1. Trap: Assuming all hormonal contraceptives carry the same VTE boxed warning.
 - 1. Correction: The VTE warning belongs to estrogen-containing combined methods; progestin-only methods such as the intrauterine system, the implant and depot medroxyprogesterone acetate do not share it, though each has its own distinct labelled risk. [1][2]
- 2. Trap: Treating menopausal estrogen-alone and estrogen-plus-progestin therapy as interchangeable.
 - 2. Correction: Estrogen alone is reserved for a woman without a uterus because of the endometrial cancer risk of unopposed estrogen; a woman with an intact uterus needs the added progestin for endometrial protection. [5]
- 3. Trap: Reading the combined hormonal contraceptive smoking warning as applying to any smoker.
 - 3. Correction: The labelled contraindication specifically targets women over 35 who smoke, reflecting the age-dependent compounding of cardiovascular risk rather than a blanket smoking contraindication at any age. [1]
- 4. Trap: Assuming testosterone replacement is indicated for any man with a low testosterone level on a lab report.
 - 4. Correction: The labelled indication is confirmed primary or hypogonadotropic hypogonadism with clinical features plus laboratory testing, not an isolated low result in an otherwise asymptomatic man. [7]

Self-test questions

- 1. Question: Which component of a combined hormonal contraceptive is primarily responsible for suppressing ovulation?
 - 1. Estrogen
 - 2. Progestin
 - 3. Neither hormone affects ovulation

4. Only the placebo-week tablets

1. Explanation: The progestin component is primarily responsible for inhibiting gonadotropin release and preventing ovulation, while the estrogen component mainly stabilises the endometrium for predictable bleeding. [8]

2. Question: The boxed warning restricting combined hormonal contraceptive use specifically applies to which group?

1. Any woman with migraine

2. Women over 35 years old who smoke

3. All women over age 40

4. Women using the method for more than 5 years

2. Explanation: The labelling contraindicates combined hormonal contraceptive use in women over 35 who smoke because of sharply increased serious cardiovascular event risk in that specific combination of age and smoking. [1]

3. Question: What is the signature boxed-warning risk of depot medroxyprogesterone acetate that is not shared with combined oral contraceptives?

1. Venous thromboembolism

2. Loss of bone mineral density with prolonged use

3. Endometrial cancer

4. Virilization of a partner

3. Explanation: Depot medroxyprogesterone acetate's own boxed warning covers bone mineral density loss that increases with duration of use and may not be fully reversible, distinct from the estrogen-driven VTE warning on combined methods. [2]

4. Question: Why is a progestin added to estrogen therapy for a postmenopausal woman with an intact uterus?

1. To reduce hot flashes further

2. To protect the endometrium from unopposed estrogen's proliferative effect and reduce endometrial cancer risk

3. To reduce the estrogen dose needed

4. It has no additional purpose beyond estrogen alone

4. Explanation: Unopposed estrogen in a woman with a uterus raises endometrial cancer risk roughly two to twelve-fold; adding a progestin counteracts that proliferative effect, which is the reason combined menopausal hormone therapy exists as a distinct product from estrogen alone. [5]

5. Question: According to the Women's Health Initiative findings referenced in the Prempro/Premphase label, which outcome was increased with combined estrogen-plus-progestin therapy?

1. Only endometrial cancer

2. Stroke, DVT, pulmonary embolism, myocardial infarction, invasive breast cancer, and probable dementia in women 65 and older

3. Only bone fracture reduction

4. No cardiovascular outcomes were affected

5. Explanation: The Women's Health Initiative estrogen-plus-progestin substudy found increased stroke, venous thromboembolism, myocardial infarction and invasive breast cancer, and the associated Memory Study found increased probable dementia in women 65 and older. [6]

6. Question: What does the boxed warning on topical testosterone gel primarily address?

1. Direct hepatotoxicity in the treated patient

2. Virilization in a child or partner from secondary skin contact with an unwashed application site

3. An increased risk of osteoporosis

4. A drug interaction with hormonal contraceptives

6. Explanation: The boxed warning concerns virilization from secondary exposure - a child or partner who contacts an unwashed application site can absorb enough testosterone to show signs of androgen exposure themselves. [7]

Frequently asked questions

1. Question: Why don't progestin-only contraceptives carry the same VTE boxed warning as combined pills?

1. Answer: The venous thromboembolism signal in this class is driven by the estrogen component. Progestin-only methods - the levonorgestrel intrauterine system, the etonogestrel implant and depot medroxyprogesterone acetate - contain no estrogen, so they do not carry that specific boxed warning. Each still has its own labelled risk instead: irregular bleeding for the first two, and bone mineral density loss for the depot injection. [1][2]
2. Question: Is menopausal hormone therapy ever given as estrogen alone?
2. Answer: Yes, but the labelling ties that choice to whether the patient has a uterus. A woman without a uterus has no endometrium to protect from unopposed estrogen's proliferative effect, so estrogen alone is a standard option for her. A woman with an intact uterus is given estrogen plus a progestin specifically to prevent the endometrial cancer risk that unopposed estrogen carries. [5]
3. Question: Why is depot medroxyprogesterone acetate not recommended for more than two years of continuous use?
3. Answer: Its boxed warning describes bone mineral density loss that increases with duration of use and may not be fully reversible after stopping, with particular uncertainty about the effect in adolescents still building peak bone mass. The label states it should not be used as a long-term birth control method beyond 2 years unless other options are considered inadequate for that patient. [2]
4. Question: Who should not use testosterone replacement therapy?
4. Answer: The labelling contraindicates testosterone replacement in men with known or suspected breast or prostate carcinoma, and it is contraindicated in pregnant or breastfeeding women because of the potential for fetal harm. It is also not indicated simply for an isolated low testosterone level without clinical and laboratory confirmation of hypogonadism. [7]

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