Venous and Arterial Risks Associated with Combined Hormonal Contraception

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9.1 Introduction

The oral contraceptive pill is used by 9% of women worldwide [1] and is one of the most commonly used birth control methods in the United States, Canada, and Europe. Pills are used by approximately 25% of contraceptive users in the United States [2], 33% of contraceptive users in Canada [3], and the majority of women in Europe—reaching as high as 84% of contraceptive users in Germany [3].

Since combined oral contraceptives (COCs) first became commercially available in the 1960s, we have seen significant changes related to their hormonal formulations and dosing to balance contraceptive efficacy against common side effects and potential risks. Higher dose pills contribute to more side effects, like nausea and breast tenderness, which limit patient tolerability and continuation. Additionally, venous thromboembolism (VTE) was discovered early on as one of the most important risks associated with combined hormonal contraceptive pills [4]. This drove drug development to produce pills with reduced VTE risk and side effects, while maintaining contraceptive efficacy. Compared to the first pill formulations, contemporary oral contraceptive pills contain significantly lower hormone doses.

Today, all combined hormonal pills contain an estrogen component, most commonly ethinyl estradiol, and a synthetic progestogen (progestin), with specific formulations often marketed for their non-contraceptive benefits. Women and their providers now have a large number of combined hormonal contraceptive (CHC) methods to choose from. In addition to pills, transdermal patches and vaginal rings offer alternative routes of administration and dosing schedules—and will be discussed briefly in

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this chapter in relation to their VTE risk. Contraceptive counseling should be guided by evidence about risks and benefits of the method, which are individualized to the patient with consideration of her preferences and comorbidities.

Thrombosis represents the most serious side effects of combined hormonal contraceptives. This side effect occurs in direct relationship to the degree of hepatic stimulation by the estrogen component of combined products. Whether the progestin component modifies the effect of estrogens on thrombosis risk, or acts independent to affect coagulation, remains highly controversial.

9.2 Hormones Used in Contraception

It is important to understand the different types of estrogens and progestogens used in hormonal contraception and the chemistry behind their varying effects in the body [5].

9.2.1 Estrogens

The term estrogen refers to both natural and synthetic hormones which act on the estrogen receptor. Activity and potency vary widely among the family of estrogen hormones.

9.2.1.1 Natural Estrogens

There are four natural estrogens in humans; all contain a 19-carbon steroid backbone and are distinguished by the number of hydroxyl (-OH) groups on the cyclopentanophenanthrene ring as well as their site of primary production. These account for differences in activity in the body and also over a woman's lifetime.

Estrone (E1), the first human estrogen discovered, is the dominant estrogen during menopause. Estrone is produced primary through conversion of adrenal androstenedione by aromatase made by peripheral adipose. Estrone is approximately 12 times less potent than estradiol [6], but can be converted into estradiol by isomerization with 17b-hydroxy-steroid dehydrogenase. In obese women, aromatase in peripheral fat leads to higher levels of estradiol.

Estradiol (E2), the most potent and biologically active natural estrogen, is produced in the ovaries from menarche to menopause. Theca cells in the ovary produce androgens—androstenedione and testosterone—which are then aromatized to estradiol (E2) and estrone (E1) by granulosa cells. E2 undergoes isomerization to the less potent E1, a principle means of metabolism. Ovarian estradiol production is regulated by the hypothalamus-pituitary-ovary axis.

Estriol (E3) is produced by the placenta and is present during pregnancy. It is 80 times less potent than estradiol (E2) [6] and is rapidly metabolized. During pregnancy, the placenta also produces E1 and E2, though in lower quantities.

Estetrol (E4) is produced by the fetal liver and present during fetal life until approximately 1 week after birth. Estetrol is 30–35 times less potent than E2 [7].

It is important to note that E1, E2, and E3 all undergo rapid metabolism when given orally where they are conjugated by the liver, marking the hormone for excretion. These metabolites are inactive. This is known as **first-pass metabolism.** The short half-life of E2 (14–16 h), E1, and E3 limits the utility of these natural estrogens for oral contraception. In contrast, estetrol is minimally metabolized by the liver, resulting in a longer half-life of about 28 h.

9.2.1.2 Synthetic Estrogens

The primary synthetic estrogen used in oral contraceptive pills today is ethinyl estradiol (EE). In the development of the first oral contraceptive—a synthetic progestin-only pill—scientists discovered that norethynodrel synthesis was contaminated with about 1% mestranol, a synthetic estrogen. Mestranol, which is demethylated in the liver, is a pro-drug for ethinyl estradiol. Further studies using purified norethynodrel only found that women experienced breakthrough bleeding (as seen with today's progestin-only pill). Thus, an estrogen was added back in for improved cycle control. EE is used in the majority of oral contraceptive pills today and is also the primary estrogen component in currently available transdermal and transvaginal combined hormonal contraceptives.

Like estradiol, oral ethinyl estradiol undergoes hepatic conjugation and the two actually have similar half-lives. However, ethinyl estradiol is about 100-fold more potent than estradiol [8]. This is due to enhanced estrogen receptor binding and different metabolism. Since EE passes through the liver on first pass without extensive conjugation, the liver effects of EE remain potent on recirculation. While the stimulation effects of estradiol on the liver following oral administration occur primarily as a result of first pass, EE provides potent stimulation regardless of route of administration. Thus, hormonal contraception with transdermal or transvaginal administration of EE is associated with a risk of VTE similar to that observed with oral preparations [9]. While hepatic conjugation of natural estrogens results in decreased potency, conjugates of EE remain highly potent. In contrast, transdermal administration of estradiol in physiologic doses for postmenopausal hormone therapy does not increase the risk of thrombosis [10].

To summarize these points, the enhanced effects of ethinyl estradiol (EE) over estradiol (E2) on induction of hepatic globulins occur due to greater potency, lack of significant first-pass conjugation, and potent induction on recirculation.

9.2.1.3 Other Estrogen Preparations Used in Hormonal Contraception

Estradiol valerate and estradiol cypionate, both esterified forms of estradiol, are rapidly hydrolyzed to estradiol and act as pro-drugs of estradiol. Estradiol valerate is currently marketed in pill form in the United States (Natazia®) and Europe (Qlaira®). Estradiol cypionate is currently combined with medroxyprogesterone acetate as a monthly injectable contraceptive (Cyclofem®, Lunelle®). Pills containing estradiol (Zoely®) have been developed and are available in Europe. Vaginal rings containing estradiol are currently under investigation.

9.2.2 Progestogens

The term progestogen refers to both natural and synthetic hormones which act on the progesterone receptor. It is incorrect to refer to the family of progesterone receptor binding compounds as progesterones.

9.2.2.1 Natural Progestogens

As opposed to the four natural estrogens, progesterone is the only natural progestogen in humans. Progesterone is an early precursor in the steroidal hormone pathway involving androgens, estrogens, glucocorticoids, and mineralocorticoids. The primary source of circulating progesterone is the ovary, predominantly in the luteal phase of the menstrual cycle. Progesterone is produced by the placenta during pregnancy.

9.2.2.2 Synthetic Progestogens

Several synthetic progestogens, or progestins, have been developed for therapeutic use. In some texts, these are classified based on the chronological order of discovery: as first-, second-, third-, and fourth-generation progestins. This classification system provides little information about the biological activity, and thus it is clinically more informative to understand progestins as derivatives of their parent molecule—testosterone, progesterone, or spironolactone.

19-Nortestosterone Compounds (Progestins Derived from Testosterone)

The first progestin synthesized from testosterone was norethindrone. Norethindrone was created in a two-step process, first by the addition of an ethinyl group at the 17-carbon of testosterone, making the androgen ethisterine, followed by removal of the 19-carbon. This modification changes the molecular activity from that of an androgen to that of a progestogen. Thus, all progestogen derivatives of testosterone as the parent compound are called 19-nortestosterones.

The 19-nortestosterone progestins are further subcategorized based on modifications at the 13-carbon position: estranes refer to compounds with a methyl group and gonanes refer to compounds with an ethyl group. Estranes include norethindrone, norethindrone acetate, ethynodiol diacetate, norethynodrel, and lynestrenol, which are all rapidly converted to the parent compound, norethindrone. Gonanes include norgestrel, norgestimate, desogestrel, and gestodene. The ethyl group modification in gonanes makes these compounds somewhat more progestational and less androgenic. Unlike estranes, which are essentially all norethindrone products, individual gonanes do exhibit some differences in activity. Levonorgestrel, the active isomer of norgestrel is commonly used in oral contraceptive pills as well as contraceptive implants, intrauterine devices, and as an oral emergency contraceptive. Etonogestrel (or 3-ketodesogestrel), the active metabolite of desogestrel, is not orally available, but is used in contraceptive vaginal rings and implants.

It is important to note that the androgenic properties are not completely eliminated in these progestins, though androgenic activity is typically considered

minimal with current doses of modern oral contraceptives. In addition, norethindrone can be aromatized to ethinyl estradiol, and some estranes bind weakly to the estrogen receptor, but clinical effects on the estrogen receptor are thought to be minimal in the low doses used in contemporary pills [11]. Finally, while 19-nortestosterones have the potential to exhibit glucocorticoid effects (decrease glucose tolerability or increase insulin resistance), the impact in clinical practice appears to be insignificant.

17-Alpha-Hydroxy-Progesterone Compounds (Progestins Derived from Progesterone)

Chemists developed progestins structurally related to progesterone, by acetylation of the 17-hydroxygroup of 17-alpha-hydroxy-progesterone. These are subclassified as pregnanes or norpregnanes based on whether they contain a methyl group at the 10-carbon position. Pregnanes include medroxyprogesterone acetate (Provera), megestrol acetate, chlormadinone acetate, cyproterone acetate, dydrogesterone, and medrogesterone. Norpregnanes (also called 19-nonprogesterones) include nomegestrol acetate, segesterone acetate, and trimegestone. The norpregnanes have strong progestational activity with no androgenic, estrogenic, or glucocorticoid activity.

Dienogest is a hybrid estrane-pregnane combining the properties of a 19-nortestosterone derivative with a progesterone derivative [12].

17-Alpha-Spironolactone Compounds (Progestins Derived from Spironolactone)

Spironolactone has anti-mineralocorticoid activity and is a potassium-sparing diuretic used to treat hypertension. It also has anti-androgenic and progestogenic activity and has been used for the treatment of androgenic symptoms like acne and hirsutism. Drospirenone is an analogue of spironolactone, which has more progestogenic and less anti-mineralocorticoid activity than spironolactone and is used in modern oral contraceptive pills.

9.2.2.3 Progestin Generations

While the above classification of progestins based on their parent molecule is more valuable scientifically regarding pharmacologic activity, the generation terminology is used frequently in the medical literature. Understanding this classification aids evaluation of the evidence from studies classifying pills this way. The generation classifications of progestins primarily involve testosterone-derived compounds. First-generation progestins are estranes (i.e., norethindrone). Second- and third-generation progestins are gonones, based on when they were introduced. Levonorgestrel (LNG) is a second-generation progestin, used in oral contraceptive pills since the 1980s. Given its long-standing and widespread use, LNG is often used as the reference group in epidemiologic studies regarding oral contraceptive pills. Later progestins with less androgenicity were introduced to reduce androgen-related side effects. Third-generation progestins

include desogestrel, norgestimate, gestodene, and etonogestrel. Fourth-generation progestins include drospinenone and dienogest, introduced most recently, but differ in their androgenicity. Thus, the classification by generation lacks a chemical or biological basis and contributes to the confusion regarding differential effects of formulations.

9.3 Venous and Arterial Thrombosis

Venous thromboembolism (VTE) refers to a spectrum of pathologic conditions where a blood clot (thrombus) forms within the venous system, most commonly within the deep veins of the extremities, known as a deep vein thrombosis (DVT). Approximately two-thirds of VTEs present as DVTs [13]. An embolic event occurs when the thrombus travels through the bloodstream to a distant organ—approximately one-third of VTEs present as pulmonary embolism, where a blood clot travels to the lungs. The most significant mortality associated with venous thromboembolism is pulmonary embolism, which causes sudden death in 20–25% of cases [14]. Other morbidities related to venous thromboembolism include pulmonary hypertension, chronic venous insufficiency, and recurrent thromboembolism.

Arterial thromboembolism (ATE) refers to similar events within the arterial system—most notably myocardial infarction in the heart and ischemic stroke in the brain.

9.3.1 Coagulation and Thrombosis

There are three main categories that influence thrombus formation, described in Virchow's triad. These include hypercoagulability, changes in hemodynamic flow, and response to endothelial injury. Increased tendency to thrombosis can be caused by numerous factors as they interact with the coagulation cascade—including physiologic and exogenous hormones, inherited and acquired thrombophilias, age, smoking, obesity, prolonged immobilization or long-haul travel, surgery, and cancer. VTEs are often the result of several acquired and/or inherited risk factors; however approximately 25–50% of first-time VTE patients present without readily identifiable risk factors [15].

9.3.2 Physiologic Effects of Hormones on the Coagulation Cascade

The risk of VTE in response to combined hormonal contraception is attributable to effects of estrogens on the coagulation cascade, shown in Fig. 9.1. Estrogen stimulates an increase in clot-promoting, or thrombogenic, clotting factors—factor I, II, VII, VIII, and X—as well as a decrease in clot inhibitors—tissue plasminogen activator, antiplasmin, and protein S (Box 9.1).

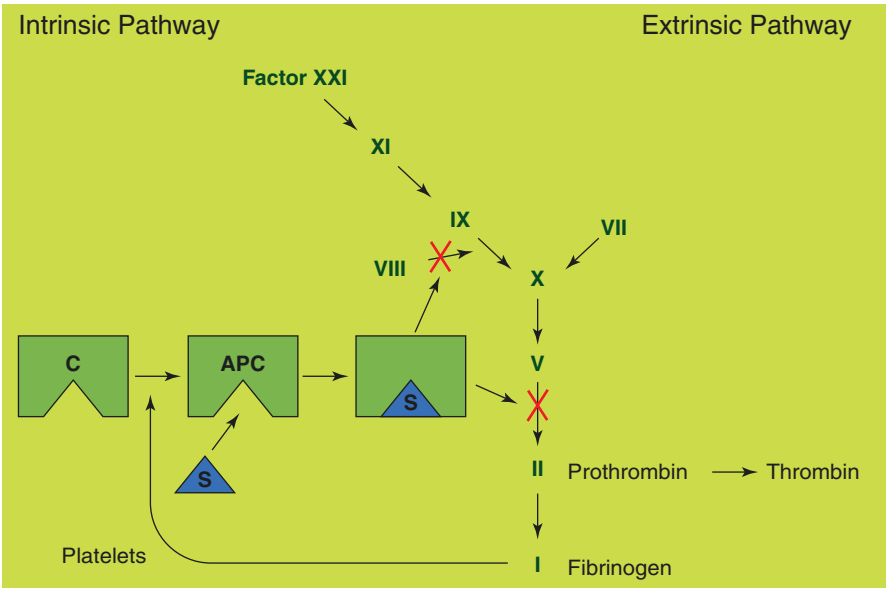

Fig. 9.1 The coagulation cascade. The simplified coagulation cascade. Activated protein C (APC) exerts an anticoagulant effect primarily through inhibition of factor V. Protein S is required for this interaction. C = protein [63]. (From Jensen JT, Burke AE, Barnhart KT, et al. *Effects of switching from oral to transdermal or transvaginal contraception on markers of thrombosis*. Contraception 2008;78(6):456)

Box 9.1 Manipulation of the Coagulation Cascade to Favor Clotting in Response to Estrogen

Favor clotting when increased	Favor clotting when decreased
Coagulation factors	
Factor VII, VIII, IX	Antithrombin III
Fibrinogen	Protein C
	Protein S
Fibrinolytic factors	
Plasminogen activator inhibitor-1	Antiplasmin

Estrogen stimulates an increase in clot-promoting, or thrombogenic, factors, as well as a decrease in clot inhibitors

The effect of estrogen on the coagulation cascade is a physiologic and evolutionarily protective mechanism, to prepare women for the risks of hemorrhage with childbirth. The physiologic effects of estrogens on the liver in the pregnant and nonpregnant state are shown in Fig. 9.2. A prospective cohort study by Sultan et al. demonstrates the increased risk of DVT with pregnancy. Compared to nonpregnant

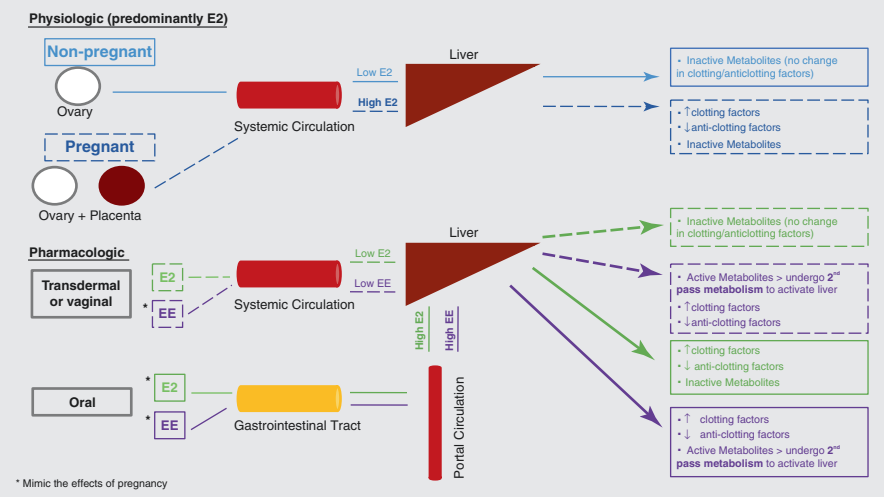

Fig. 9.2 Hormonal effects on the liver and clotting factors. The effects of estradiol (E2) and ethinyl estradiol (EE) on the liver and clotting factors by physiologic and pharmacologic doses, as well as different routes of delivery

women, the incidence risk ratio increases slightly in the first and second trimesters, with a marked increase in the third trimester and early postpartum period. The highest risk is seen within the first 6 weeks postpartum, with a incidence rate ratio 22.1 times that seen in nonpregnant women [16] (Fig. 9.3).

9.3.3 Pharmacologic Effects of Hormones on the Coagulation Cascade

Exogenous estrogens mimic the effects of endogenous estrogens to stimulate hepatic production of clotting factors. The underlying risk of VTE in healthy, nonpregnant women, not using exogenous hormonal birth control, is 5–10 per 10,000 woman-years. This risk increases approximately twofold in women using modern COCs to 10–20 per 10,000 woman-years [17] (Table 9.1).

As early as 1968, the association between oral contraceptives and thromboembolic disease was noted. Vessey and Doll reported that the risk of hospital admission for VTE was approximately nine times higher in women using oral contraceptives compared to those who were not [4]. This finding was confirmed in several other studies [18–22]. Additionally, researchers found this association to be dependent on estrogen dose—higher dose formulations demonstrated increased risk of VTE [23]. Pharmaceutical companies responded. Compared to the first oral contraceptive pill, which contained a daily dose of 150 μg of mestranol, pills today contain 10–35 μg ethinyl estradiol (EE). In fact, all pills today contain less than 50 μg ethinyl estradiol.

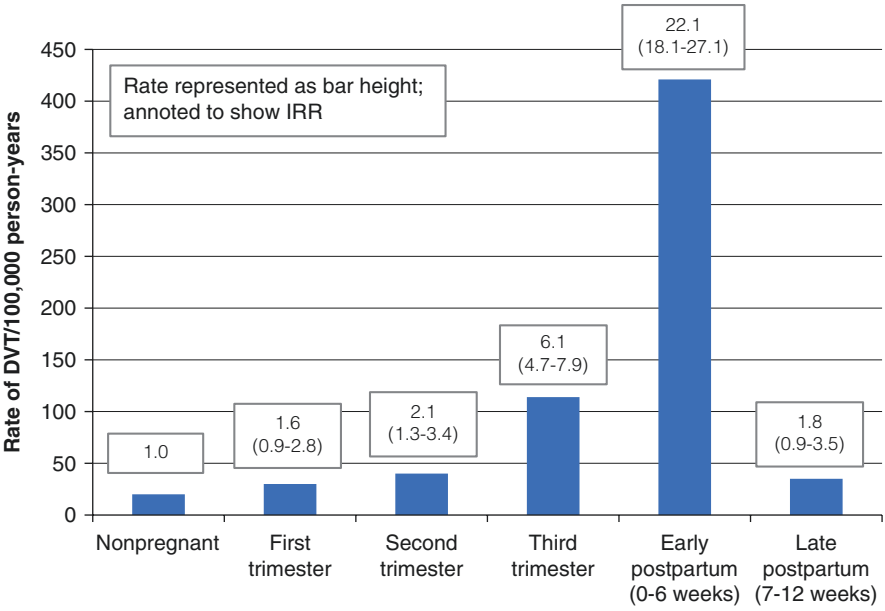

Fig. 9.3 Risk of DVT in pregnancy and postpartum. Rate of VTE per 100,000 person-years during different periods of pregnancy and postpartum compared to time outside pregnancy (nonpregnant = reference). Numerical notations showing Adjusted Incidence Rate Ratio (95% CI) [16]. (Adapted from Sultan, A.A., et al., *Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study.* Br J Haematol, 2012. **156**(3): p. 366–73)

Table 9.1 Relative risk and actual incidence of venous thromboembolism in different patient populations

Population	Relative risk	Incidence (per 10,000 women/year)
Healthy young women (general population)	1	5–10
Pregnant women	12	60–120
Low-dose oral contraceptive users (<50 μg ethinyl estradiol)	2	10–20
High-dose oral contraceptive Users (≥50 μg ethinyl estradiol)	6–10	30–100
Leiden mutation carrier	6–8	30–80
Leiden mutation carrier + oral contraceptive use	10–15	50–100
Leiden mutation homozygous	80	400–800

Taken from Fritz, M., & Speroff, Leon. (2011). *Clinical gynecologic endocrinology and infertility* (eighth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins [17, 52, 70, 71]

Combined hormonal contraceptive pills have systemic effects, with the primary contraceptive mechanism of action on the hypothalamic-pituitary-ovarian axis to inhibit ovulation. However, pharmacologic doses of hormones also influence other systems in the body—notably the liver and production of hepatic globulins which influence the coagulation cascade.

Estrogens administered orally, both estradiol (E2) and ethinyl estradiol (EE), undergo first-pass hepatic metabolism and mimic the effects of pregnancy: decreased anti-clotting factors, increased clotting factors, increased C-reactive protein, and increased HDL (Fig. 9.2). When given in transdermal or transvaginal preparations, estradiol is diluted systemically, low levels reach the liver, and inactive metabolites are formed. Conversely, despite dilution of EE in systemic circulation when given transdermal or transvaginal, EE produces active metabolites, which stimulate hepatic production of clotting factors when recirculated, known as second-pass metabolism. This explains the increased VTE risk with EE given in transdermal or transvaginal routes [9, 24, 25].

To date, existing studies examining the risk of VTE based on different progestins are limited to observational data. These have given mixed results, discussed in more detail below (see **Controversy Regarding Third- and Fourth-Generation Progestins**). The biologic plausibility of progestin-induced hypercoagulability is challenged by the fact that there are no known progesterone receptors in the liver and that progestin-only methods do not appear to increase risk of thrombosis [26]. If a true biologic difference exists between different progestins, the mechanism is not yet understood, but may be related to a modification of the estrogen response, rather than a direct effect. A modified estrogen effect between the so-called second- and third-generation progestins has been hypothesized to be mediated by the androgenic properties of the progestin. Studies have shown differential effects on hemostatic biomarkers [27, 28] with use of third-generation (desogestrel, gestodene, norgestimate) compared to second-generation (levonorgestrel) progestin-containing pills, but changes were within the normal range and were not associated with increased risk of VTE. Differences in specific surrogate markers, including activated protein C (APC) and sex hormone binding globulin (SHBG), have been identified. Higher APC resistance and higher SHBG levels are measured in response to less-androgenic, newer progestins [28, 29]—leading some to speculate this as a mechanism for differences in estrogenicity and thus VTE risk. However, neither has been prospectively validated and at this time, no surrogate marker for VTE risk has been identified [30].

9.3.4 Pharmacologic Risk of Hormones on Arterial Thromboembolic Events

The risk of arterial thromboembolic events (ATEs) like cerebrovascular stoke and myocardial infarction is much lower than VTE events in young women; however, the sequelae can lead to greater morbidity and mortality. Combined hormonal contraceptives also increase the risk of arterial thromboembolism [31, 32], and certain risk factors modify this risk including age, smoking, hypertension, and migraine headache

with aura [33]. Estrogen-containing methods are contraindicated in these high-risk women [34, 35]. A retrospective cohort of healthy, reproductive-aged women using hormonal contraception found that the absolute risk of ATE events was low, the risk increased by a factor of 0.9–1.7 with oral contraceptives containing a 20 μg dose of ethinyl estradiol and by a factor of 1.3–2.3 with those containing a 30–40 μg dose and with small differences according to the progestin type [31]. Since ATE events are exceptionally rare in healthy young women, the risks with contemporarily dosed COCs do not appear to be significant for most women [33, 36].

9.4 Important Risk Factors for VTE

Overall the risk of VTE with COCs is low and should be balanced against the much higher increased risk of VTE in pregnancy in women desiring contraception. The prescription of combined hormonal contraception should also be considered within the context of patient-specific risk factors. Despite the low overall risk of VTE in both COC and non-COC users, the sequelae can be significant and should be minimized when additional known risk factors are present. A combination of patient factors put certain women at higher risk of VTE both in pregnancy and with exogenous hormones, as summarized in the guidance provided by the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use [34, 35].

In addition to VTE risk during pregnancy/postpartum and with the therapeutic use of estrogen, non-hormonal risk factors for VTE include age, obesity, inherited thrombophilias, personal or family history of VTE, malignancy, surgery, and immobilization or long-haul travel.

VTE increases with age—from incidence estimates of 0.7 per 10,000 women-years in teens aged 15–19 years old to 5.8 per 10,000 women-years in 45–49-year-olds [37]. Obesity also increases VTE risk two- to threefold compared to normal weight women [38, 39]. Inherited thrombophilias contribute significant risk [40] and hormonal contraception magnifies the risk of inherited thrombophilias [18] (Table 9.1). Factor V Leiden mutations are prevalent in 15–20% of patients with VTE [41]. Women using COCs with factor V Leiden mutations have a nearly 30-fold increased risk of DVT compared to nonusers without the mutation [42]. Other important inherited thrombophilias which increase VTE risk include antithrombin deficiency, protein C deficiency, protein S deficiency, and prothrombin mutations [41].

9.5 Controversy Regarding Third- and Fourth-Generation Progestins

In regard to examining VTE risk associated with the progestin component of COCs, studies have contributed conflicting and sometimes biologically confusing data [21, 22, 43–48]. This has led to scientific debate about how the progestin in particular

CHCs modifies VTE risk. The majority of studies finding a differential effect by progestin are database studies, based on retrospective review of medical records and insurance claims or case-control studies. A consistent twofold increase in the risk of VTE with third-generation and fourth-generation progestins compared to levonorgestrel or LNG (a second-generation progestin) has been reported in these studies; however, this effect has not been observed in larger, prospective studies.

Combined hormonal contraceptives containing third-generation progestins were introduced in the 1980s, and by the 1990s epidemiologic studies were published warning of increased VTE risk compared to second-generation pills [21, 22, 43, 45]. A case-control study by the WHO found increased risk with desogestrel (OR 2.4 [1.4–4.9]) and gestodene (OR 3.1 [1.6–5.9]) compared to LNG [21]. A case-control study by the Transnational Research Group also found an increased risk with third-generation pills compared to LNG pills (OR 1.5 [1.1–2.1]) [45]. Additionally, a retrospective study using the UK General Practitioner's Research Database found increased risk with desogestrel and gestodene compared to LNG, with similar risk estimates to the prior studies [22]. In response to these findings, in 1995, the UK Committee on the Safety of Medicine issued a "Dear Doctor" letter and an emergency media announcement, which created the first "pill-scare." Finally, the MediPlus study was published in 1998, analyzed a separate database from the UK, and failed to demonstrate this effect after age was identified as a major confounder [49].

About a decade later, a second "pill-scare" emerged. In 2009, a study using the Danish National Database by Lideegaard and colleagues found increased risk with desogestrel and gestodene, as well as increased risks with drospirenone and cyproterone acetate compared to LNG—with similar risk estimates to the prior studies [46]. The MEGA study, a Dutch case-control study, found even higher risk estimates [48]. Further observational studies in the United States and UK supported these findings, with an approximate twofold increase in risk of VTE in drospirenone-containing pills [50, 51]. Criticisms of these studies included limitations in the collection of baseline characteristics, notably missing data of key confounders. Despite these limitations and an acknowledgment that causality could not be determined, this prompted the US Food and Drug Administration (FDA) to publish a Drug Safety Communication in 2012, warning of potential higher risk with drospirenone. Similar fears in Europe led to Diane® (EE/cyproterone acetate) being pulled from the market in France, despite a near unanimous recommendation for continued approval from the Pharmacovigilance Risk Assessment Committee (PRAC), the French National Agency for the Safety of Medicine and Health Products.

While the epidemiologic data has received significant attention in the popular media, by lawyers, and by regulatory agencies in the United States and Europe, caution should be used in interpreting such studies. There are inherent methodological limitations to these studies including missing data on baseline confounders (age, smoking, BMI, personal/family thrombosis history), unconfirmed VTE diagnosis, misclassification of duration of use, and other sources of information and detection bias [38]. Prospective studies provide better risk estimates by accounting for these limitations, and the data from these studies do not show a differential effect based on progestin.

The European Active Surveillance (EURAS) study, which included over 58,000 new contraceptive pill users and provided over 140,000 woman-years of follow-up, found no difference in risk estimates of VTE between drospirenone and LNG or other oral contraceptives; the adjusted hazard ratio for drospirenone versus levonorgestrel was 1.0 (0.6–1.8) [52]. The International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC) study, followed over 85,000 American and European women and again failed to find a difference in VTE risk based on progestin type—the adjusted hazard ratio for drospirenone versus levonorgestrel was 0.8 (0.4–1.5) [53]. Both of these studies have low loss-to-follow up (2.4% and 3.3%, respectively), account for baseline differences, and reflect real-world prescribing habits. A US study found similar results—the adjusted hazard ratio for drospirenone was 0.9 (0.5–1.6) [54]. Furthermore, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) study demonstrated no difference in VTE risk between users of the etonogestrel/ethinyl estradiol vaginal ring and combined oral contraceptive pills [9].

Even with this prospective data, the debate continues among experts. More prospective studies are needed to clarify this debate. Furthermore, the available evidence should be critically evaluated for confounding and bias.

9.6 Critically Evaluating the Evidence

In any scientific investigation, several factors related to study design influence the validity of conclusions reached. No randomized trials have been conducted to evaluate different effects of progestogens on VTE risk. Retrospective database and case-control studies can be informative in examining rare outcomes when RCTs are not feasible; however, they are limited in their collection of confounding variables (to identify differences in baseline characteristics), use of appropriate comparison groups, and ability to draw conclusions of causality. Additional concerns with these epidemiologic studies include problems with clinical care trends over time, exposure measurements (duration of use), and outcome measurements including under-ascertainment of VTE incidence, inability to confirm VTE diagnosis, and diagnostic bias [55, 56]. Moreover, VTE is a rare event and studies are typically not powered to detect differences in these outcomes. Again, prospective studies therefore provide the best data for risk estimates.

Many baseline characteristics are known risk factors for VTE and must be accounted for when comparing groups. Obesity is a known risk factor for VTE [38–40] and must be adjusted for. Given the rise in population obesity in recent decades, cohorts used today are difficult to compare to historical cohorts. Additionally, polycystic ovarian syndrome (PCOS), associated with obesity and hyperandrogenic symptoms, may be an independent risk factor for VTE [57, 58]. Furthermore, these patient characteristics may lead to preferential prescribing of newer, anti-androgenic formulations for non-contraceptive benefits to women with baseline higher VTE risk. Heritable thrombophilia conditions are another important independent risk factor for VTE and can differ between populations studied. Factor

V Leiden mutations are most commonly found in white people, present in up to 5% of the Caucasian population [13, 59]. This population effect must be considered in evaluating large database studies performed in European populations. Significant VTE risk factors also include age, smoking, malignancy, and genetic factors, which are not always accounted for in baseline characteristics of epidemiologic studies.

We have also seen a new-user effect, whereby higher risk of VTE is observed in new users of combined hormonal contraception [52, 60]. Among new users, the risk of VTE is highest in the first several months with the adjusted rate ratio peaking in the first year of use and subsequently decreasing thereafter. This observation is seen for both second- and third-generation pills [60]. This creates an effect referred to as a "cohort of survivors," where healthy patients or those who are inherently at lower risk are selected for over time. New users therefore are untested in regard to their baseline risk, and we would expect those with higher risk for an event to experience that event when they initiate therapy [38, 61]. Studies that compare new users to existing users allow this type of selection bias to occur. In addition to new users being untested for potentially unknown or undiagnosed risk factors, we also observe an increased risk of VTE in women who have used COCs, stop using, and then resume use—even with the same pill [62]. This may be explained by the physiologic changes that occur in response to a changing hormonal environment and an equilibrating period required for any new exposure. Interestingly, we also observe higher risk of VTE in women switching between pills or from the pill to the transdermal patch or vaginal ring [62, 63], which may also represent subtle changes in the hormonal environment and its effect on the coagulation system. Moreover, given the increased risk of VTE with age and the accumulation of other medical comorbidities with time, it can be challenging to compare different episodes of use even in the same woman.

We also must consider how changes in the field of medicine over time have influenced prescribing patterns, particularly in higher risk populations. The range of contraceptive options available during the 1980s and 1990s, the time frame of many of these epidemiologic studies, was more limited than today. More women used pills overall, including higher risk women who today may be counseled to consider other methods. We have observed an evolving understanding of VTE and cardiovascular risk during this time as well. Newer pills were developed containing lower estrogen doses and with later-generation progestins, with decreased androgenicity. These were meant to mitigate androgen-related side effects and to treat hyperandrogenic symptoms in women with conditions like PCOS. This creates a cohort of higher risk women who may have preferentially been prescribed newer pills, and thus, comparisons between pill formulations without accounting for confounders can lead to faulty conclusions.

One example of preferential prescription bias is seen in the study by Farmer and Lawrenson [64], examining the World Health Organization, Transnational, and UK General Practitioner's Database studies, which found an inverse dose-response for estrogen and VTE risk (Table 9.2). Women using 20 μg EE pills (which were newer pill formulations including newer progestins) had higher VTE risk compared to women taking 30 μg EE pills—opposite of the expected estrogen dose-dependent

Table 9.2 Paradoxical decrease in risk with higher E2, an example of prescribing bias [64]

Study	Reference	Case patients	OR	95% CI	Case patients	OR	95% CI
			Desogestrel + 20 µg EE			*Desogestrel + 30 µg EE*	
WHO	Nonusers	8	38.2	4.5–325	27	7.6	3.9–14.7
Transnational	LNG	13	2.8	1.3–6.5	32	1.5	0.9–2.5
BCDSP	LNG	4	2.7	NA	26	1.9	NA
MediPlus UK	LNG	13	2.9	0.9–10.0	19	0.6	0.3–1.5
			Cyproterone + 35 µg EE			*Cyproterone + 50 µg EE*	
WHO	LNG	9	5.1	1.3–20.3	9	1.3	0.5–3.8

OR odds ratio, *CI* confidence interval, *EE* ethinyl estradiol, *LNG* levonorgestrel, *NA* not available in the publication

Inverse dose-response relationships with dose of estrogen with desogestrel and cyproterone from UK and German MediPlus Database Study

Taken from Farmer, R.D. and R.A. Lawrenson, *Oral contraceptives and venous thromboembolic disease: the findings from database studies in the United Kingdom and Germany.* Am J Obstet Gynecol, 1998. **179**(3 Pt 2): p. S78–86

effect. This suggests preferential prescription of newer pills to higher risk women. At the same time, it was discovered that low-androgen progestogens can increase high-density lipoprotein cholesterol (HDL), a cardioprotective factor, which may have led to preferential prescribing in higher risk women with underlying cardiovascular risk or disease. This has been demonstrated in several studies. In a Dutch study, women being treated with cardiovascular medications were more likely to be prescribed third-generation pills compared to second-generation pills [65]. Likewise, the European Active Surveillance (EURAS) study demonstrated that drospirenone pills were more commonly prescribed to obese women and those with preexisting arrhythmias, indicating a higher baseline risk in this group compared to those using levonorgestrel or other progestin-containing pills [52].

Also important is the effect of detection bias regarding VTE diagnosis in older vs. newer studies. Advances in imaging like Doppler ultrasound and computed tomography have improved diagnosis of smaller thrombi, which may or may not be clinically important. Diagnostic bias might also be introduced when women with perceived higher risk are more likely to have tests performed. In a German survey, physicians were more likely to prescribe third-generation pills to higher risk patients and also to refer these women for DVT workup even for nonspecific symptoms [66].

Funding for a study is also a potential form of bias that should be considered, as many contraceptive studies are funded by pharmaceutical companies. However, it should also be noted when these investigations have been mandated by regulatory agencies who review their protocols and are approved independently by review boards.

9.7 Patient-Centered Contraceptive Counseling

What does this mean for our patients? Contraceptive counseling should be guided by evidence about risks and benefits of the method, which are individualized to the patient's preferences and with consideration of her comorbidities. The Medical Eligibility Criteria for Contraceptive Use published by the CDC and the WHO provide useful guidelines regarding safety of birth control methods in women with medical conditions [34, 35]. To date, besides screening for the known risk factors in a woman's history, there are no cost-effective universal screening tests for VTE risk in women initiating combined hormonal contraceptives [67].

In deciding on a birth control method, women consider efficacy, side effects including bleeding pattern, ease of use (which may be lifestyle and patient specific), confidentiality, perceived self-control, and cost. Women consider both positive and negative side effects, and it is important to understand how these considerations influence tolerability and continuation of a method. Side effects are commonly cited as the reason for discontinuation of a method. The many non-contraceptive benefits of birth control will be discussed in the next chapter.

Another important counseling point regarding efficacy relates to cyclic versus extended or continuous dosing and the hormone-free interval. As lower dose pills have been developed, the suppression of the HPO axis is decreased, particularly in the hormone-free interval or with missed doses. As such, lower estrogen dose pills and longer hormone-free intervals are associated with increased follicular development and potential higher risk of ovulation and unintended pregnancy [68, 69]. Pill formulations with shorter hormone-free intervals and the ability for continuous cycling should be offered.

9.8 Conclusions

Patients expect their physician to prioritize their safety and preferences and to provide them with accurate information regarding risks and benefits of therapeutic interventions. In counseling patients regarding birth control, this means not only discussing the efficacy of each method and factors specific to her compliance (given the risks of an unintended pregnancy) but evaluating a patient's baseline risk factors and sharing our knowledge of the body of literature.

We should always evaluate available data with a critical eye for bias and confounders, as well as what is lacking in the evidence. Since DVTs are a rare outcome, randomized clinical trials (the gold standard in examining the relationship) are not feasible. Therefore, we must use the next best data available, while being aware of its limitations.

Despite the heterogeneity in study results regarding the safety of different progestins [13], we must emphasize that the risks of VTE are substantially higher in pregnancy than in women using COCs, both those with and without additional risk factors for VTE, so finding a method which a patient continues is essential in preventing an unintended pregnancy.

Finally, in the development of new hormonal methods of birth control, our focus should be on preparations that reduce the impact of estrogens on the liver. This includes using estradiol (E2) or estradiol valerate (EV2), estetrol (E4), and possibly even estriol (E3) which do not produce the active metabolites seen with EE. We should also take advantage of alternative routes of administration to avoid first-pass metabolism. For example, E2-containing contraceptive vaginal rings are currently being studied. Development of these alternatives will enhance safety for all patients.

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