Hormonal Contraceptives: Progestogen and Thrombotic Risk

8

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8.1 Introduction

The various types of hormonal contraceptives have proven to be very effective modes of contraception [1]. However, the additional effects of hormonal contraceptives vary, and this is also true for thrombotic events that occur with the use of hormone replacement therapy (HRT).

As progestogens are to be considered with regard to thrombotic events, it has to be taken into account that the progestogenic steroids have the progestogenic effect in common, including the conversion of the endometrium into a secretory state, which prevents abnormal estrogen stimulation of the endometrium and in this way prevents abnormal endometrial hyperplastic changes, and last but not least, endometrial cancer [2]. Progestogenic action is also mandatory for proper secretory changes of the endometrium for implantation. If this occurs, further changes of the endometrium into decidualization take place and the blood flow to the uterus increases with trophoblastic invasion and proper development of the spinal arteries.

In addition, various progestogens have other different partial biological effects that are of clinical relevance. This is also true with regard to thrombosis incidence. Therefore, the partial biological effect pattern is different for the different progestogens and this is of utmost clinical relevance, if thrombotic events are taken into consideration [3].

Therefore, one can conclude that progestogens are not the same, based upon differences in structure, differences in the partial effect pattern (action profile) and differences in organ effects.

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Unfortunately, there is still a lot of confusion, even in well-known international journals such as *Climacteric*, where the title of an article talks about progesterone, but in the text only studies on medroxyprogesterone acetate (MPA) were reported. Indeed, MPA does have a vasoconstrictive effect on the arterial vessels – in this case the ophthalmic artery and retinal artery – while progesterone, in contrast, widens the arterial vessels and lowers the blood pressure, which was particularly well demonstrated in pregnant women with preeclampsia [4]. Nowadays, this can be clearly demonstrated and quantified by Doppler ultrasound measurements [5, 6]. Indeed, with the rise of the circulating progesterone in the corpus luteum phase, the blood flow to the uterus and the ovaries increases and if pregnancy occurs, the blood flow, which is common for all progestogens, increases. If no conception and implantation occur, the blood flow decreases.

The following partial effects – besides the progestogenic effect – are present for each progestogen in a particular way, which was alluded to more than 10 years ago [3]. Thus, each progestogen is associated with a particular partial effect pattern. The following partial effects should be considered: androgenic, antiandrogenic, estrogenic, antiestrogenic, glucocorticoid and antimineralocorticoid.

How do these partial effect patterns of the progestogens determine the different thrombotic risks of estrogen/progestogen combinations (COCs), oral, vaginal and transdermal, as well as in HRT? Answering this question will be the aim of this chapter.

8.2 Hemostasis and Thrombotic Events

The hemostatic system comprises coagulation and fibrinolysis

Normally, this system is in balance [7]. It consists of procoagulation, anticoagulation as well as profibrinolysis and antifibrinolysis. There can be venous and arterial thrombotic events. Afterwards, we focus on venous thrombosis. This is an essential risk factor for using a premenopause estrogen/progestogen combination, but also in postmenopausal HRT (oral, vaginal, transdermal). Risk factors for thrombosis are listed in Table 8.1.

8.3 The Risk of Venous Thrombosis, When Taking COCs

It has been known since the 1960s that oral estrogen/progestogen combinations are associated with an elevated risk of venous thrombosis. At first, the thrombotic risk was related to the type and dose of the estrogen component. In the 1990s the debate started that different progestogens are associated with different thrombotic risks. In general, the thrombotic risk is double compared with women of a similar age group who are not taking the pill. The number of events is highest in the first year and levels off over time. Therefore, the so-called pill pause is dangerous, as with each restart of the pill the thrombotic risk shoots up in the first year [8].

The frequency of venous thrombosis is as follows:

1. Non-user of COCs have a risk of 4–5/10,000 women years
2. COC users have a risk of 9–10/10,000 women years

Table 8.1 Risk factors for thrombosis

1. Increasing age
2. Increasing body weight
3. Pregnancy/post partum
4. Hormonal contraceptive pill as estrogen/progestogen combination (a) Type of estrogen (EE, E2, E2V) (b) Estrogen dose (c) Type of progestogen in combination with an estrogen (d) Dose of progestogen (e) Length of use (f) Type of application (oral, vaginal, transdermal)
5. Hormone replacement therapy (HRT) as estrogen/progestogen combination listed as above for a, b, c, d, e, f
6. Genetic predisposition
7. Family/personal history of thrombosis
8. Immobility (operation, accident)
9. Long distance air travel
10. Smoking

3. Pregnant women have a risk of 29/10,000 women years
4. Postpartum women have a risk of 300–400/10,000 women years [9]

Overall, the risk of venous thrombosis in users of a low estrogen dose (<50 μg ethinyl estradiol [EE]) COCs is two- to threefold higher than for non-users of COCs. Thrombotic risk is modified using COCs or HRT by the type and dose of the estrogen (EE, estradiol [E2], estradiol valerate [E2V]) and by the progestogen used, depending on the partial effect pattern of each progestogen. Extensive comparative studies with 35 versus 50 μg EE [7] or 20 versus 30 μg EE have been carried out, demonstrating the changes in the parameters of hemostasis depending on the EE dose [10].

Hormone replacement therapy can increase the thrombotic risk by up to three times depending on the estrogen/progestogen combination used and other risk factors such as changes in body composition (particularly an increase in visceral adipose tissue), pro-atherogenic changes in lipid metabolism, worsening of the imbalance in carbohydrate metabolism and the increasing risk of climacteric women of developing a metabolic syndrome [11].

8.4 Mode of Action of Progestogens in Combination with Estrogens (Pill, HRT)

The extent of the progestogens used on the hemostatic system is dependent on the extent of the modification of the total estrogen effect on the body – mainly the liver. There can be an increase or decrease in liver protein synthesis by the action of progestogen, which is reflected by the levels of sex hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and thyroxine-binding globulin (TBG).

Table 8.2 Comparison of indices of venous thrombosis in drospirenone (DRSP)- or levonorgestrel (LNG)-containing estrogen/progestogen combinations (COCs) per 100,000 years

	Australian study [17]	American study [18]
Drospirenone	23.0; 95 % CI 13.4–36.9	30.8; 95 % CI 26.6–26.8
Levonorgestrel	9.1; 95 % CI 6.6–12.2	12.5; 95 % CI 9.6–15.9
Incidence ratio	2.7; 95 % CI 1.5–4.7	2.8; 95 % CI 2.1–3.8

Table 8.3 Thrombotic risk with COCs with different progestogens compared with COCs containing LNG

Progestogen	Relative risk
Levonorgestrel	1.00
Norethisterone	0.98
Norgestimate	1.19
Desogestrel	1.82
Gestodene	1.86
Drospirenone	1.64
Cyproterone acetate	1.88

Indeed, SHBG levels using different EE/progestogen combinations vary when comparing the various COC preparations. In addition to the overall increase in SHBG there are differences in the extent of SHBG level elevation: ethinyl estradiol/cyproterone acetate (EE/CPA) is associated with a higher SHBG level than estradiol/drospirenone (EE/DRSP) and lower estradiol/desogestrel (EE/DSG) [12].

Progestogens induce through their different partial effect patterns (androgenic, antiandrogenic, estrogenic, antiestrogenic, glucocorticoid and antimineralocorticoid) the estrogen action of the estrogen used (EE, E2, E2V) regarding the production of proteins of the hemostatic system.

In addition, there are other risk factors such as genetically induced changes in the hemostasis inhibitors (antithrombin III, protein C and protein S) or a hereditary resistance of factor V Leiden against activated protein C (APC resistance).

Progestogens with a partial glucocorticoid effect (i.e. MPA, CPA) regulate the thrombin receptor and stimulate the procoagulatory activity at the vessel wall [13]. Stimulatory progestogens are MPA, CPA, gestodene, 3-ketodesogestrel and DRSP. This is not the case with levonorgestrel (LNG). These events only occur when these progestogens are used together with an estrogen (EE, E2, E2Val). COCs containing DSG or gestodene (third-generation progestogens) increase the risk of thrombosis by 70 % compared with COCs with LNG (second-generation progestogen) [14]. The elevated risk of gestodene- and DSG-containing COCs is associated with a higher SHBG concentration (increased liver protein synthesis) than LNG-containing COCs [15]. This was brought up again in 2009 with two articles published in the *BMJ* [8, 16]. These articles reported on the results of two retrospective epidemiological studies that assessed the risk of thrombosis using hormonal contraceptives. These studies suggested that COCs were associated with a differential risk of thrombosis caused by their progestogenic components. The risk of thrombosis was reportedly lower in women with LNG-containing COCs versus the so-called third-generation COCs and COCs containing DRSP [8, 16]. This was further

Table 8.4 Ratio between thrombosis and HRT used over 5 years according to Sweet et al. [26]

Type of treatment	Thrombotic risk
No medication	1:650
Oral estrogen alone	1:475
Estradiol/progestogen combination (norethisterone, norgestrel)	1:390
Estrogen/progestogen combination (MPA)	1:250

MPA medroxyprogesterone acetate

substantiated by the Australian study by Parkin et al. [17] and by the American study by Jick and Hernandez [18], as shown in Table 8.2.

The safest COCs with regard to thrombosis are those with LNG, norethisterone and norgestimate [19, 20]. Out of all this, it was recommended that women start COC use with pills containing 20 µg EE combined with norethisterone or LNG or norgestimate [21].

Data on the thrombotic risk of COCs using EE and various progestogens clearly indicate that progestogens with a more prominent androgenic partial effect pattern are more likely not to be burdened with an elevated thrombotic risk (Table 8.3).

Thrombotic risk is dependent upon the partial androgenic effect of the progestogen, which counteracts the protein synthesis in the liver by EE or E2/E2Val. This is reflected in a more subtle increase in SHBG that means decreased protein synthesis and therefore decreased activation of the hemostatic system. Indeed, treatment with tibolone, with the androgenic action of its metabolites, was found to induce a substantial risk reduction of venous thrombosis of 0.27 [22].

In addition to the reduction in protein synthesis (see SHBG) progestogens with an androgenic partial effect pattern are of importance for this favorable action on the hemostasis of COCs, but also of HRT by reduction of fibrinolytic inhibition by PAI-1 and Lp(a) [23].

Changing not only the dose of the estrogens but also the estrogen component in COCs or HRT reduces the risk of thrombosis. It could be demonstrated that when combining E2Val with dienogest (DNG) or DRSP the risk of thrombosis is similar or even lower than with LNG COCs such as Microgynon® [24]. A recent thorough evaluation concluded that the non-oral route of EE administration seems to be more thrombogenic than the oral route [25]. In contrast, low-dose oral progestogen-only contraceptives (POPs) as well as LNG IUS appear to be safe with regard to risk of thrombosis. Overall, newer progestogen formulations of estrogen/progestogen combination contraceptives in addition to non-oral COCs seem to be more thrombogenic than the second-generation COCs.

A similar risk pattern seems to prevail with HRT. There is a relationship with the progestogen used. The relative risk (RR) of HRT with MPA was 2.67; 95 % CI 2.25–3.17, while HRT with other progestogens had an RR of 1.91; 95 % CI 1.67–2.1. This difference is statistically highly significant ($p < 0.0007$; Table 8.4) [26].

In contrast, progesterone and dydrogesterone appear not to increase the RR in combination with estradiol (E2) in postmenopausal women [27]. As shown by Lideguard et al. [8] progestogen-only contraceptives do not increase the risk of thrombosis: LNG/NET RR 0.59, DSG RR 1.12, LNG-IUS RR 0.90 [25].

Conclusion

Estrogen/progestogen combinations carry a higher risk of venous thrombosis. This depends on the type of estrogen (EE, E2, E2V) and the daily dose. At present EE as low as 20 μg/day or replacement with E2 or E2V appear to be mandatory in significantly reducing the risk of venous thrombosis independently of other venous thrombosis risk factors. It also depends on the type of the progestogen used. COCs with progestogens with a partial androgenic effect carry a lower or no thrombotic risk. The second-generation progestogen LNG, in combination with estrogens, has a potentially lower risk of thrombosis than third-generation progestogens (DSG, gestodene, DRSP) or antiandrogenic progestogens such as CPA. Non-oral routes of COCs with EE seem to be more thrombogenic. Progestogen-only pills and LNG-IUS are not associated with risk of thrombosis. The common denominator appears to be the effect on liver protein synthesis as expression of the partial androgenic effect pattern, as expressed for instance by SHBG and profibrinolytic activity.

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