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Review

Progestogens and venous thromboembolism among postmenopausal women using hormone therapy

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ABSTRACT

Hormone therapy (HT) is the most effective treatment for correcting menopausal symptoms after menopause. HT initially consisted of estrogens alone and progestogens were secondly added to estrogens for preventing the risk of endometrial cancer associated to estrogens use. Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is a major harmful effect of HT. It is now well known that oral and transdermal estrogens are differentially associated with VTE risk but progestogens may be another important determinant of the thrombotic risk among HT users. Both randomized controlled trials and meta-analysis of observational studies suggested that the VTE risk was higher among users of estrogens plus progestogens than among users of estrogens alone. With respect to the different pharmacological classes of progestogens, there is evidence for a deleterious effect of medroxyprogesterone acetate on VTE risk. In addition, observational studies showed that norpregnane derivatives were significantly associated with an increased VTE risk whereas micronized progesterone could be safe with respect to thrombotic risk. The effect of tibolone on VTE risk remains uncertain. In conclusion, progestogens may have differential effects on VTE risk according to the molecules and therefore represent an important potential determinant of the thrombotic risk among postmenopausal women using estrogens.

Contents

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Table 1
Hormonal effect of the different progestogens used among postmenopausal women.

Pharmacological class	Molecules	Progestogenic activity	Estrogenic activity	Androgenic activity	Anti-androgenic activity	Gluco-corticoid activity	Anti mineralo-corticoid
Micronised progesterone	Micronised progesterone	+	–	–	±	±	+
Pregnanes	Dydrogesterone	+	–	–	–	–	–
	Medrogestone	+	–	–	–	–	–
	Chlormadinone acetate	++	–	–	+	+	–
	Cyproterone acetate	++	–	–	+++	+	–
	Medroxyprogesterone acetate	+	–	+	–	+	–
Norpregnanes	Nomegestrol acetate	+	–	–	+	–	–
	Promegestone	+	–	–	–	+	–
	Trimegestone	+	–	–	±	–	–
	Nestorone	+	–	–	–	–	–
19 Nortestosterone ethinylated							
Estranes	Norethisterone acetate	++	+	+	–	–	–
Gonanes	Levonorgestrel	++	–	+	–	±	–
	Gestodene	++	–	+	–	±	–
19 Nortestosterone non ethinylated	Dienogest	++	–	–	+	–	–
Spironolactone derivatives	Drospirenone	+	–	–	+	–	++
Tibolone	Tibolone	+	+	++	–	–	–

1. Introduction

After menopause, many women suffer from postmenopausal symptoms associated with the decline of endogenous estrogens levels due to the cessation of ovary activity. Postmenopausal hormone therapy (HT) has been introduced in the 50′ for correcting climacteric symptoms, vaginal dryness and depression. Initially, HT exclusively consisted of an estrogenic compound and in 70′, progestogens were added to estrogens to reduce the increased risk of endometrial hyperplasia and cancer associated with estrogens therapy (ET) [1]. Currently, women may be prescribed several molecules including natural progesterone and synthetic compounds which have very different pharmacological effects.

Venous thromboembolism (VTE), either deep vein thrombosis or pulmonary embolism, is a main harmful effect of HT among postmenopausal women [2–4]. For about 10 years, epidemiological data have shown a differential association of oral and transdermal estrogens with the VTE risk among postmenopausal women [5–8]. Indeed, oral estrogens increase the VTE risk while transdermal estrogens appear to be safe with respect to thrombotic risk [4,9]. More recently, the type of progestogens has also emerged as another important determinant of the thrombotic risk among HT users [6,7,9–11].

This review focuses on the different progestogens pharmacological classes in relation to VTE risk among postmenopausal women, including the current knowledge regarding the effect of progestogens on relevant haemostatic variables (prothrombin fragment 1+2 (F1+2) and Ddimers) as well as on activated protein C resistance (APCr), a validated surrogate marker of VTE.

2. Different pharmacological classes of progestogens

Progestogens include both progesterone, the physiological molecule synthesized and secreted by ovary, and synthetic compounds named progestins which derived from either progesterone (pregnanes and 19-norpregnanes) or testosterone (19-nortestosterone) [1]. Pregnanes derivatives consist of several molecules including dydrogesterone, medrogestone, chlormadinone acetate, cyproterone acetate and medroxyprogesterone acetate (MPA). Norpregnane derivatives include nomegestrol acetate, promegestone, trimegestone and nestorone. Finally, nortestosterone derivatives consist of ethinylated derivatives, non ethinylated derivatives, spironolactone derivatives and tibolone. Nortestosterone ethinylated derivatives are composed of estranes, including especially norethisterone acetate (NETA) and of gonanes which are preferentially used in contraceptive pills [1]. Nortestosterone non ethinylated derivative is dienogest and the spironolactone derivative is drospirenone. In European countries and especially in France, women are prescribed a wide variety of progestogens while MPA and some specific testosterone derivatives are the almost exclusive progestogens used in Anglo-Saxon countries [12].

Progestins have different pharmacological properties depending upon the parent molecules which they are derived and the metabolites they product (especially for nortestosterone derivatives). In addition, changes in progestogen effect occur according to the administered daily dose. Very small structural changes may induce considerable differences in the progestin activity (Table 1). The effects of progestins are related to interactions with the progesterone receptors but also with other steroid hormone receptors such as estrogens receptors, androgens receptors, glucocorticoid and mineralocorticoid receptors [13,14]. These interactions may either induce or prevent the transactivation of steroid receptors. Therefore, the balance between the receptor coactivators and corepressors recruited by a progestin determines whether the overall effect of a molecule will be agonistic or antagonistic for each hormonal effect [15]. For example, some of progestins have a high antiandronegic activity and others possess progestogenic effect with antiestrogenic actions.

3. Progestogens and venous thromboembolism: clinical data

3.1. Estrogens alone versus estrogens plus progestogens

Since 1996, several observational studies have separately assessed the impact of unopposed estrogens and estrogen–progestogen therapy (EPT) on VTE risk among postmenopausal women. In these analyses, women used oral estrogens and no distinction was made between the different types of progestogens [5,8,16–19]. Using a random-effect model meta-analysis as previously described [4,9], the overall VTE risk was 1.7 (95% confidence interval (CI): 1.3–2.2) for ET use and 2.3 (95%CI: 1.7–3.2) for EPT use (Fig. 1). Despites a non significant difference between these two overall risk ratios ($p = 0.15$), this result showed that the VTE risk would be more elevated among EPT users as compared