Blood Reviews 28 (2014) 123–133

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Sex, thrombosis and inherited thrombophilia

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ARTICLE INFO

Keywords:
Venous thromboembolism
Hormonal contraceptives
Pregnancy
Hereditary thrombophilia
Gender

ABSTRACT

The incidence of venous thromboembolism (VTE) is two-fold higher in women than in men during reproductive age, which is likely explained by the use of hormonal contraceptives and by pregnancy in this phase of life. After adjustment for these factors, men have a two-fold higher risk of developing a first VTE compared with women, which is in line with earlier observations that men have a two-fold higher risk of recurrent VTE. These findings indicate that the intrinsic risk of VTE is higher in men than in women. Hormonal contraceptives increase the risk of VTE and the risk varies per type, dose, and administration route. In women with a high baseline risk of VTE, avoidance of some hormonal contraceptives should be considered, as well as thrombosis prophylaxis during pregnancy. Presence of hereditary thrombophilia increases the risk of a first VTE episode. This review focuses on the differences in risk of VTE between men and women, hormonal risk factors for women, and how these interact with common types of hereditary thrombophilia.

1. Sex and the epidemiology of VTE

Venous thromboembolism (VTE) is a frequently occurring disease with an incidence of a first episode of 1–2 per 1000 person-years (p.y.). The risk of developing VTE is relatively low for younger people (incidence 0.3 per 1000 p.y. for individuals aged 20–44 years) but increases exponentially with age to 6.4 per 1000 p.y. in individuals 80 years or older [1]. In about half of all cases, VTE is associated with a clinical risk factor such as surgery, trauma, immobility, active cancer, use of hormonal contraceptives, pregnancy and the puerperium. In the remaining 50% of patients no such clinical risk factor is present and these episodes are referred to as unprovoked. In individuals between 20 and 44 years of age the incidence of VTE in women is about twice as high as the incidence rate in men, which is likely explained by the use of hormonal contraceptives and by pregnancy during this phase of life [1]. Oral hormonal contraceptive use as a risk factor for VTE is present in about 1 in 2–4 women in cohorts that also included postmenopausal women [2,3]. In a recent case–control study it was elegantly shown that after adjustment of reproductive risk factors, the risk of a first VTE is in fact twice as high in men as in women (odds ratio 2.1; 95% CI 1.9–2.4). This indicates that the intrinsic risk of VTE is higher in men than in women [4]. It also reemphasizes the potential to reduce VTE on a population level, by prudent prescribing of hormonal contraception and targeted thrombosis prophylaxis in pregnant women at an increased risk of developing VTE.

After a first episode of VTE the risk of recurrence is highly dependent on the circumstances at the time of first VTE. The risk is lowest for postoperative VTE (0.7% per 100 p.y. during the first two years) and higher after VTE provoked by a non-surgical temporary risk factor including pregnancy and use of hormonal contraceptives (HC) (4.2% per 100 p.y. for the first two years) [5]. After unprovoked VTE the risk of recurrence is estimated to be as high as 20% in the first two years, thereafter declining to an annual risk of recurrence of 5% [5–10]. Interestingly, the risk of recurrent VTE is about twice as high for men compared with women. This was first described in 2004 and later confirmed by several studies [11–13]. The exact mechanism explaining this phenomenon has not yet been elucidated. It may reflect a higher intrinsic risk of VTE in men compared with women as also seems the case for first episodes of VTE [4]. Alternatively, it has often been suggested that the lower recurrence risk in women could be explained by further avoidance of hormonal risk factors. Many first VTE events in women are associated with oral HC, pregnancy or the puerperium and the risk of recurrence in women is likely lowered by discouraging further oral HC use and by the use of thrombosis prophylaxis during and after subsequent pregnancies. Inclusion of these women in comparisons between recurrence risk of women and men will therefore introduce bias. However, even population based studies that compared men with women who had their first VTE unrelated to oral HC, pregnancy or the puerperium, showed a 2-fold higher risk of recurrence in men [2,8,12].

Besides exogenous risk factors there is a clear familial predisposition for VTE, which is in part explained by hereditary abnormalities in the coagulation cascade, commonly referred to as thrombophilia. The implications of having a type of hereditary thrombophilia, and indications for testing for the presence of these defects, remain subject of debate.

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http://dx.doi.org/10.1016/j.blre.2014.03.005
0268-960X/

In this review we will focus on VTE risk factors for women, and how these interact with common types of hereditary thrombophilia.

2. Hormonal contraception and venous thromboembolism

In the 1960s combined oral HC, containing both an estrogen and a progestogen, was introduced as a promising new way to prevent unplanned pregnancy. Since then oral HC, also referred to as "the pill", has been a remarkable and lasting success. It is estimated that over 100 million women worldwide currently use oral HC [14]. Apart from birth control, modern contraceptives afford various non-contraceptive benefits, ranging from regulation of menstrual disorders (such as menorrhagia and dysmenorrhea) to improvement of acne and hirsutism. In addition, in lower doses it can be used as hormone replacement therapy for women with perimenopausal complaints. Combined oral HC are the most frequently prescribed contraceptives, but several alternatives are available such as progestogen-only pills and non-oral HC including hormone releasing intrauterine devices (IUDs), injectables, subcutaneous implants, vaginal rings and skin patches.

The possibility that the use of oral HC may cause VTE was raised shortly after its introduction by a case report of a 40-year old woman who developed pulmonary embolism (PE) a few weeks after having started a combination of norethynodrel and mestranol for treatment of endometriosis [15]. In the following years many hundreds of similar case reports were published. Nowadays, a body of evidence underlines the association between HC and VTE.

Most currently available oral HC are preparations containing both an estrogen (i.e. ethinylestradiol) as well as a progestogen. There are numerous types of oral HC available, containing different doses of estrogen and different types of progestogens. The earliest preparations contained 150 μg of estrogen. As the reported increased VTE-risk associated with combined oral HC was attributed to the amount of estrogen, the dose has been reduced gradually over the past 50 years. It was lowered to 50 μg in the 1960s and to 30 μg and 20 μg in the 1970s. The lowering from 50 μg and higher dosages to 30 μg indeed reduced the VTE-risk by 30 to 50% [16–18]. A further reduction of the estrogen dose to 20 μg was shown to be associated with an additional 18–20% reduction in VTE risk [17,19].

Although the estrogens in combined oral HC seem to be most responsible for the VTE risk, the progestogens in combined oral HC modulate the prothrombotic effect of estrogens. Based on the type of progestogen that a combined oral HC contains, a classification can be made into first, second and third generation contraceptives. The classification does not cover preparations containing drospirenone or cyproterone acetate and therefore these are referred to as 'other combined oral HC'. Progestogen-only preparations are also available and, in higher doses, these carry an increased risk of VTE as well [20,21].

2.1. Pathophysiology of increased VTE risk with hormonal contraceptive use

The use of HC increases the levels of coagulation factors II, VII, VIII and X [22]. Furthermore, its use leads to decreased levels of the natural anticoagulants protein S and antithrombin [23], and increased resistance to activated protein C (APC) which is in part explained by the decrease of free protein S and free tissue factor pathway inhibitor (TFPI) [24,25]. In addition, a decrease of fibrinolytic activity is present during HC use, mainly through an increase of thrombin-activatable fibrinolysis inhibitor (TAFI) [26]. Therefore, use of HC leads to a procoagulant risk profile through various mechanisms. In line with the observed differences in the risk of VTE with different progestogens (which will be addressed in the 'Oral hormonal contraceptives' section) a more pronounced APC resistance was found in users of third generation contraceptives [27,28] as well as in users of drospirenone and cyproterone acetate [29] compared with users of second generation contraceptives. This implies that coagulation markers may be a valid surrogate endpoint if studies with clinical endpoints are not available.

2.2. Oral hormonal contraceptives

Several large studies have shown that currently used combined oral HC increase the risk of VTE 2- to 6-fold [17,19,30–32]. The risk is highest in the first three months of use, with an estimated odds ratio (OR) of 12.6, and this risk remains 5-fold increased after one year [17]. Despite the low baseline incidence of VTE in women of reproductive age, the effect of oral HC on VTE in the population is large, considering that many women worldwide use oral HC. In the following paragraphs we provide an overview of the risk increase associated with all types of oral HC. The overview is mainly based on results from large case–control studies [17,33], a large cohort study [34] and a recent systematic review and network meta-analysis [35]. The latter provides somewhat lower risk estimates compared with the other studies, in particular for third generation oral HC and oral HC containing cyproterone acetate and drospirenone. Interestingly, in the sensitivity analysis sources of bias were explored, showing lower risk estimates in industry-sponsored studies, case–control studies and studies without objectively confirmed VTE. Thus, the presented risk estimates in this meta-analysis may be an underestimation and should be interpreted with caution. The associated estimated relative and absolute risks are also shown in Table 1.

2.2.1. Combined oral hormonal contraceptives

The first available types of progestogens were lynestrenol and norethisterone. These so-called first generation progestogens are not used very often nowadays. Compared with non-users, the relative risk of VTE in users of oral HC with a first generation progestogen was found to be increased 2- to 5-fold [35]. Second generation progestogens include levonorgestrel and norgestrel. Combined oral HC containing these types of progestogen are the ones most prescribed worldwide. They carry the lowest, 2- to 4-fold risk increase of VTE compared with non-users [17,34,35]. Gestodene, desogestrel and norgestimate comprise the third-generation progestogens, although sometimes norgestimate is categorized as a second generation progestogen. Use of third generation combined oral HC carries a 3- to 8-fold increased risk of VTE as compared with non-use, which is consistently higher than during the use of a second generation oral HC [17,34–36].

Cyproterone acetate is a progestogen that has been on the market since 1988. Besides its contraceptive effects it has an antiandrogenic effect, and therefore preparations containing this progestogen are often prescribed for treatment of acne vulgaris, seborrhea, or mild idiopathic hirsutism. Preparations containing drospirenone, an anti-mineralocorticoid, were heavily marketed, arguing that these pills would have less side effects compared with the older contraceptives such as bloating and mood swings. They have been available since 2000. Cyproterone acetate and drospirenone containing oral HC are associated with a 6- to 7-fold increased risk of VTE compared with non-users [17,34,35].

In April 2013 the French health regulator Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) decided to withdraw the combined oral HC Diane-35, containing 2 mg cyproterone acetate and 35 μg ethinylestradiol after several reports of women who had experienced VTE or an ischemic stroke while using this oral HC [37]. Although the increased VTE risk associated with the use of cyproterone acetate was already well established, civic law suits by women with thrombosis have led to increased media attention emphasizing the thrombosis risk of oral HC, in particular third generation combined oral HC, cyproterone acetate and drospirenone.

According to a recent report of the European Medicines Agency (EMA), the benefits of Diane-35 may outweigh the risks of VTE in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism in women of reproductive age, if other therapies have failed [38]. In all other cases, a second generation oral HC with the lowest possible dose of ethinylestradiol should be prescribed, and prescription of third generation oral HC, cyproterone acetate or drospirenone should be discouraged.