Review Article

Hormonal Contraception: New Insights on the Risk of Venous Thromboembolism

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Abstract

Introduction: Women using oral hormonal contraceptives are exposed to an increased risk of venous thromboembolism. The incidence of venous thromboembolism in women is difficult to quantify but figures suggest it is in the range of 2 per 10,000 women in 1 year. However, it causes significant cause of morbidity and mortality.
Aim: This study aims to provide a comprehensive overview of the risk of venous thrombosis in women using oral hormonal contraceptives.
Methods: Extensive literature search in the electronic database "Pubmed", "Google Scholar", the website of the center for Disease Control and Prevention (CDC) and in scientific journals via search engine. There was a time restriction, the last fifteen years. Exclusion criteria of articles were articles related to the other side effects of hormonal contraception. Finally, 47 articles were included in the study.
Results: Use of hormonal contraceptives increases the risk of venous thrombosis, especially in women with a similar predisposition. Epidemiological studies have shown that combined oral contraceptives increase the risk of venous thromboembolism significantly. The progestogen-only pills are not associated with an increased risk of venous thromboembolism. Thus, the risk of venous thrombosis of oral contraceptives is dependent on the dose of ethinylestradiol and the type of progestin. The risk is increased during the first year of their use or when restarting after a break of at least one month. Risk factors for venous thrombosis can be genetic or acquired, permanent or transient, such as current or previous venous thrombosis, family history, known thrombogenic mutations, post-pregnancy use, obesity, smoking, surgery and other conditions leading to immobilization.
Conclusions: The management of women taking hormonal contraceptives should include disclosure of risk factors to prevent events related to thrombosis and with other harmful situations generally.

Key Words: Contraception, oral contraceptives, estrogens, progestogens, venous thromboembolism, risk factors.

Introduction

Since their introduction in the 1960s, epidemiological studies have shown that women using combined oral contraceptives are exposed to an increased risk of venous thromboembolism (VTE) (Lidegaard et al, 2009). VTE is defined as a condition in which a blood clot forms in a vein, usually in the deep veins of the legs or pelvis [deep vein thrombosis (DVT)] and pulmonary embolism (PE) occurs when the clot is displaceable in the pulmonary arteries, causing death in 1-2% of patients. The VTE is significant risk to the health of women and is a significant cause of morbidity and mortality and one of the main causes of maternal mortality in the western world (Reprod, 2013). The survival after VTE is worse than anticipated, especially after PE as ¼ of patients with PE exhibits sudden death. Of the patients who survive with VTE, approximately 30% will develop recurrence of VTE in 10 years with a mortality rate of 4-12% and 30% will develop an inactivated post thrombotic syndrome (Heit et al, 2005*)*.The background incidence of VTE in women of reproductive age is hard to quantify, however, recently published figures suggest it is in the range of 2 per 10,000 women in 1 year (European Medicines Agency, 2014).

Hormonal contraceptives contain either a combination of estrogen and progestogen [combined hormonal contraceptives (CHC)], or progestogen-only contraceptives (POC). Epidemiological data suggest that subsequent changes in the composition of combined oral contraceptives by altering the progestin content can exacerbate thrombotic risk. Moreover, the estrogen dosages in contraceptive products have diminished dramatically over the last fifty years and the lower doses of ethinylestradiol (EE) have lead to a significant decrease in VTE (Tricotel et al, 2014). Progestin-only pills (POPs) are believed to have similar effectiveness to COCs (Hall et al, 2012) and do not increase the risk of VTE (Mantha et al, 2012). Progestin-only contraceptive methods are recommended for women at increased risk of VTE such as current or previous VTE, family history, known thrombogenic mutations, post-pregnancy use, obesity, smoking, surgery and other conditions leading to immobilization (CDC, 2010).

Mechanisms of Venous Thrombosis

Virchow's triad refers to three mechanisms that increase thrombotic risk: endothelial disruption; venous stasis; and procoagulant changes in blood proteins. Endothelial disruption occurs frequently with catheter insertion and also with trauma, surgery, burns, and toxins. Venous stasis may be associated with immobilization (orthopedic casting, prolonged travel), external compression (tumor, pregnancy), or cardiac conditions (heart failure, atrial fibrillation, or other arrhythmias). Progesterone has mild procoagulant effect while estrogen helps reduce the activity of the fibrinolytic enzyme system. Also, various alterations of blood proteins promote venous thrombosis and can be categorized as 1 of 3 categories: decreased anticoagulants, increased procoagulants and decreased fibrinolytics (Cameron et al, 2011).

History of Oral Hormonal Contraceptives

The first steroidal oral contraceptive pill (OCP) was approved in the 1960s

and the popularity of the pill consistently expanded all through the 1960s. Nonetheless, concerns arose over the adverse effects, particularly cardiovascular and neoplastic impacts, in spite of the fact that were uncommon in the youthful populace of OCP users, yet these were widely published leading to a decrease in their utilization. After its introduction, extensive changes have occurred in the composition of OCPs in terms of type and dose of both the estrogen and the progestin (Sitruk-Ware et al, 2013).

The first generation OCPs contained mestranol which was then replaced by EE initially in doses as high as 150 mcg per pill, which decreased to 100, 80, and 50 µg. The initial EE dose of 50 mcg was then decreased to 30 and 20 µg. The lower doses of EE in currently marketed OCPs lead to a significant decrease in VTE (Sitruk-Ware et al, 2013).

Progestogens are often grouped according to the time they were first marketed as constituents of COCs and may be referred to by "generation". (Table 1) Most progestins used in OCPs of the first and second generation were chemically related to testosterone (19-nortestosterone

derivatives; estrane and gonane groups). These progestins were responsible for undesirable androgenic side effects. New progestins derived from the progesterone structure or from spironolactone have been developed to avoid the androgenic effects and to improve the safety profile (Sitruk-Ware et al, 2006). Nevertheless, their combination with EE did not result in a better safety profile in terms of VTE and may have increased this risk (Lidegaard et al, 2009).

More recently, COC products have been introduced onto the market with a change in the type of estrogen. A naturally occurring human hormone, estradiol (E2) and estradiol valerate (E2V) are being used with the objective of overcoming metabolic effects and decrease the thrombotic risk of formulations with EE. A recently approved four-phasic pill containing estradiol valerate (E2V) and dienogest has shown favourable results in haemostasis and metabolism studies (Parke et al, 2008), and similar favourable metabolic profile has been reported with a combination of E2 and nomegestrol acetate recently approved in Europe. Traditional forms of OCP included the 21 days of hormone-containing pills and 7 days of placebo during the hormone-free interval (Egren et al, 2011).

Epidemiological studies have shown that both the estrogen dose as well as the progestogen type of oral contraceptives contributes to the increased risk of VTE in oral contraceptive users (Vandenbroucke et al, 2001). “High-dose” oral contraceptives containing 50 mg EE are associated with a higher risk of thrombosis than “low-dose” oral contraceptives containing 20–30 mg EE (Rosendaal et al, 2003). Furthermore, COC containing the third-generation progestogens, such as gestodene and desogestrel are more prothrombotic than earlier formulations containing the second-generation progestogen levonorgestrel (Kemmeren et al, 2001; Vasilakis-Scaramozza & Jick, 2001). When combined with an oestrogen, the newer progestins increase activated protein C resistance more than older progestins, which may account for the observed increased incidence of VTE. Progestins can modulate oestrogen induced activated protein C resistance and have been shown to influence the cellular expression of tissue factor as well as circulating tissue factor pathway inhibitor (Van Vliet et al, 2008).

Fourth-generation OCPs were introduced onto the market in 2000 and are characterized by the addition of the progestin drospirenone, which was believed to be associated with a lower risk of thrombosis (Orti et al, 2007). Drospirenone containing OCPs is currently the only available oral contraceptive with three indications: the contraception, the treatment of premenstrual dysphoric disorder and the treatment of moderate acne (Mishell, 2008). However, recent observational studies have provided conflicting results regarding the effects of drospirenone-containing OCPs on the risk of VTE (Dingeret et al, 2010; Wu et al, 2013).

Methods

The search of the resources of this literature review was primarily conducted on the

Internet. There was a time restriction, the last fifteen years. We used the following scientific databases: Pubmed, Google Scholar and the site of the Center for Disease Control and Prevention (CDC). The content of the articles was related to hormonal contraceptive pills and more specifically to the risk of venous thromboembolism, which is associated with their use. These articles were scientific reviews and epidemiological studies. Another basic criterion in the selection of articles was the English language. The key-phrases that were used were as follows: oral contraceptive pills, combined oral contraceptives, progestogen-only pills, estrogens, progestogens, venous thromboembolism, risk factors. Exclusion criteria of articles were languages other than English and articles that do not allow access to the full text. Totally, 127 articles were found, 44 of them were excluded on the basis of the title or abstract due to the content, as they related to other risks of hormonal contraception. Moreover, 32 articles were excluded because they were not available as full texts and other 4 because were in different language than English. Finally, depending on the purpose of the study 47 articles were used.

Table 1. Classification of combined oral contraceptives according to the type of progestogen.

GENERATION OF PROGESTOGEN	EXAMPLES OF PROGESTOGEN
First generation	Norethisterone, norethisterone acetate
Second generation	Levonorgestrel
Third generation	Desogestrel, gestodene, norgestimate
Fourth generation	Drospirenone, dienogest, nomegestrol acetate

Sourse: Faculty of Sexual and Reproductive Healthcare, 2014

Table 2. Risk Factors of Venous Thromboembolism

Previous VTE	Inflammatory bowel disease	Cancer-related therapy (chemotherapy)	Respiratory failure
Advanced age	Trauma	Heart failure	Surgery
Pregnancy/puerperium	Malignancy	Thrombophilia abnormalities	Immobility
Hormone use (CHC and HRT)	Myeloproliferative neoplasms	Varicose veins	Obesity
Infection	Long-haul travel	Smoking	Nephrotic syndrome

Sourse: Jaffer, 2008

Purpose

The purpose of this study is to describe the risk of venous thrombosis in women using oral hormonal contraceptive pills. Moreover, risk factors for venous thrombosis and a brief over view of the historical background regarding the development of contraceptives are referred.

Combined Oral Contraceptives

Use of COCs increases the risk of VTE compared with non-use (relative risk 3.5, 95% confidence interval 2.9 to 4.3). One study conducted in women taking COCs recorded VTE included deep vein leg thrombosis (61.8%), PE (26.2%), femoral vein thrombosis (4.7%), portal thrombosis (1.2%), caval or renal thrombosis (0.8%) and unspecified deep vein thrombosis (5.4%). Furthermore, the same study conducted to investigate the risk of VTE in women using different COCs showed that the relative risk of VTE of COCs with 30-35 µg EE and gestodene, desogestrel, cyproterone acetate or drospirenone was similar and about 50-80% higher than for COCs with levonorgestrel. A dose related effect

of EE was observed for gestodene, desogestrel and levonorgestrel, with higher doses being associated with higher thrombosis risk (Hedenmalm & Samuelsson, 2005).

Moreover, are retrospective study conducted in Sweden and included women aged 15-44 years suggested a higher incidence of fatal VTE use contraceptives containing desogestrel and norethisterone compared with contraceptives containing levonorgestrel (Hedenmalm & Samuelsson, 2005). Users of COCs with third generation progestogens have a higher risk of VTE than those using second-generation progestogens *(*Hylckama et al, 2009). Other progestins have been developed after the introduction of the third generation progestogens, such as drospirenone (introduced in 2001). The risk of thrombosis for contraceptives drospirenone was found to be higher than for the COCs second-generation progestogens (Jick & Hernandez 2011; Parkin et al, 2011).

Oral contraceptives increase the risk of VTE, with the extent depending on the dose of EE and the type of progestin: the risk is about 20 cases per 100,000 woman-years with norethisterone or levonorgestrel and less than 50 mg of EE and 30 to 40 cases per 100,000 woman-years with gestodene or desogestrel. Since the beginning of this decade, some oral contraceptives have combined EE with drospirenone, a spironolactone-derived progestin with antimineralocorticoid activity, which carries a risk of hyperkalemia. A Danish cohort study was based on a registry containing 3.3 million woman-years of data on oral contraceptives, including more than 130,000 woman-years of drospirenone exposure. Compared with levonorgestrel, a statistically significant increase in the risk of VTE was observed in women using drospirenone (relative risk 1.64, 95% confidence interval 1.27-2.10).

COCs have a 2- to 6-fold greater relative risk of VTE compared to non-users (Hatcher et al, 2011). A case-control study conducted in the Netherlands that included 1524 patients and 1760 controls showed a statistically significant 6-fold increase in the risk of thrombosis among women using combinations containing drospirenone compared to women who did not use oral contraception and a non-significant 1.7-fold increase compared to women using combinations based on levonorgestrel (Raps et al, 2012).

Progestogen Only Pills

Usually, POPs are used in the postpartum period. During this period it is wise to avoid estrogen, given women's higher risk of VTE in postpartum and because of the potential effects of estrogen on breast milk supply and infant development (CDC, 2011). POPs have been considered as generally safe with respect to the risk of VTE. Studies of coagulation factors and other metabolic indices during use of POPs have not discovered clinically significant changes for pills (Vieria et al, 2007). Normal, or even increased, sensitivity to activated protein C was reported 3 months after the insertion of a levonorgestrel-releasing intrauterine system indicates that this contraceptive method does not have a prothrombotic effect (Vliet et al, 2009; ESHRE, 2013).

Although a small number of women are using progestogen-only contraceptives, data from a study suggested that there was little or no increased risk of VTE associated with use of progestogen-only methods. The odds ratio for POPs users was 1.74 (relative risk 95% confidence interval 0.76-3.9947). A case–control study, conducted in Denmark and included women 15-49 years with no history of cardiovascular disease, found no increased risk of thrombosis with progestogen-only methods. POPs containing levonorgestrel 30 μg or norethisterone 350 μg and desogestrel 75 μg did not confer any increased risk of VTE when compared with non-users of oral contraceptives (Lidegaard et al, 2009). Norethisterone and norethisterone acetate have been indicated to be partly metabolised to EE. At an oral dose of 5mg a conversion ratio of about 0.4+/-0.4 was found (Chu et al, 2007).

Therapeutic doses of norethisterone for gynaecological treatment should be prescribed with consideration in women with risk factors or contraindications to estrogen. Epidemiologic evidence regarding the cardiovascular safety of progestogen-only methods of contraception is limited. In most countries POC amounts for only a very small proportion of contraceptive methods and in those countries where POC use is common

(Depo Proveraw in South Africa), routine epidemiological data collection at a national levels uncommon or incomplete and so record linkage studies are not possible. In addition, since POC are the obvious alternative for women with contraindications to estrogen-containing contraceptives, it is probable that cohorts of POC users will contain a proportion of women with known risk factors for VTE such as obesity or a family history of thrombosis and so the data need to be regarded with caution (ESHRE, 2013). Finally, there are few data on VTE risk with progestogen-only contraception and, although a lack of evidence does not necessarily suggest an absence of effect, it is generally accepted (FSRH, 2014).

Risk Factors of VTE

Risk factors for VTE can be genetic or acquired, permanent or transient and are listed in Table 2.

Current or Previous VTE

For women with a current VTE on anticoagulants or previous VTE the use of CHC is not advised (FRSH, 2009). The benefits of using POCs outweigh any risk for women with a current VTE or previous VTE. Although there is a small risk of haematoma with use of progestogen-only methods, the risk is small. There is no evidence of haematoma formation or haemorrhage at the time of insertion of intrauterine contraception or subdermal implants in women using anticoagulants which causes harm. The levonorgestrel intrauterine system can be used to manage menorrhagia associated with anticoagulant use (RCOG, 2010).

Family History

A family history of VTE may alert clinicians to women who may have an increased risk of VTE themselves (Cosmi et al, 2013).However, a family history alone cannot identify with certainty an underlying thrombophilia. For women with a family history of VTE, the risks of using a CHC may outweigh the benefits. Progestogen-only methods may be used regardless of family history (RCOG, 2010).

Known Thrombogenic Mutations

For women with a known thrombogenic mutation the use of CHC poses an unacceptable health risk. Women with reduced levels of naturally occurring anticoagulant (anti-thrombin III, protein C or protein S) or factor V Leiden who use COC have up to a 5-fold increase in the risk of VTE compared with non-users without this deficiency (Vandenbroucke et al, 2001). Women with factor V Leiden can have up to a 35-fold increase in the risk of VTE with COC use. Not all women with a thrombogenic mutation will develop a VTE and most VTEs occur in women without the defect. However, if a woman has an identified thrombogenic mutation the risks of VTE will be high enough to advise that the use of combined hormonal methods poses an unacceptable health risk (FRSH, 2009). Progestogen-only methods do not increase the risk of VTE above that associated with the thrombogenic mutation itself and these methods can be used without further increasing the risk of VTE (RCOG, 2010).

Post- Pregnancy Use

For women who are postpartum and not breastfeeding, COCs should not be initiated before day 21 postpartum. All hormonal contraception can be safely initiated immediately following a first- or second-trimester termination of pregnancy. In the first 3 weeks postpartum, coagulation and fibrinolytic factors have not returned to their pregnancy state and therefore the risk of VTE is still higher than in non pregnant women. However, the risks of using COC before day 21 postpartum usually outweigh the benefits (FRSH, 2009). In terms of considering VTE risk, progestogen-only methods can be started any time postpartum as they do not pose an increased risk (RCOG, 2010).

Smoking

For women aged over 35 years who have stopped smoking less than 1 year ago or who are current smokers, the use of CHC is not recommended. Most data on smoking and thrombosis are related to arterial rather than venous thrombosis. Compared with non-smokers, light smokers (fewer than15 cigarettes/day) have almost a 2-fold increased risk of myocardial infarction and heavy smokers (more than 15 cigarettes/day) have a 4-fold increased risk. The use of CHC in heavy smokers appears to increase the risk 20-fold. Other studies support increasing risk of

VTE with increasing amount smoked. The risks of stroke, myocardial infarction and VTE increase with increasing age and mortality from cigarette smoking increases from age 35 years. Smokers who are aged over 35 years should be advised against the use of CHC. The use of progestogen-only methods in women who smoke is unrestricted (FRSH, 2009).

Obesity

For women with a body mass index (BMI) of 35 kg/m or greater, the risks of CHC may outweigh the benefits. Obesity is an independent risk factor for VTE. Case–control studies suggest that COC users who are obese are more likely to experience VTE than users who are not obese (Abdollahi et al, 2003). COC users who are obese have a 5-8 fold increased risk of VTE compared with non-users and up to a 10-fold increase in risk compared with that of non-users who are not obese. The absolute risk of VTE in women with increased BMI is still low. The National Institute for Health and Clinical Excellence (NICE) classification of obesity I, II and III depends on the BMI (NICE, 2006). For women with obesity I (BMI 30.0–34.9 kg/m²), the benefits of using CHC in most cases outweigh the risk. For women with obesity II (BMI 35.0–39.9 kg/m²) and obesity III (BMI 40 kg/m² or more) the risks of CHC may outweigh the benefits. However, use may be considered with expert clinical judgment and/or referral if other methods are unavailable or unacceptable. Progestogen-only contraception may be used safely regardless of weight (FRSH, 2009).

Surgery and Other Conditions Leading to Immobilisation

CHC should be discontinued and an alternative estrogen-free method used at least 4 weeks before major elective surgery where immobilisation is expected but does not need to be discontinued before minor surgery without immobilisation. The benefits of using CHC outweigh risks for women having minor surgery where immobilisation is not expected or for major surgery without prolonged immobilisation. For women undergoing major elective surgery with prolonged immobilisation, the use of CHC poses an unacceptable health risk (FRSH, 2009). A woman should be encouraged to use a method of contraception (such as progestogen-only methods) which does not increase the risk of VTE and does not need to be discontinued before surgery (RCOG, 2010).

Literature Review of Studies

Guidelines for the use of CHC in specific clinical situations have been conducted by multiple groups (WHO, 2009). The Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians and Gynaecologists in the United Kingdom has developed the United Kingdom Medical Eligibility Criteria for Contraceptive Use (FSRH, 2010). In the United States of America (USA), the American College of Obstetricians and Gynecologists has published recommendations for various non contraceptive uses of hormonal contraceptives and for use of hormonal contraception in women with coexisting medical conditions as practice notifications (ACOG, 2010). The CDC released the U.S. Medical Eligibility Criteria for Contraceptive Use in 2010 (CDC, 2010). All of these groups recognize that, in general, most of the medical risks of hormonal contraceptives are heightened in older patient groups with risk factors (Trenor et al, 2011).

The extent of an overall risk estimate of VTE in current users of oral contraceptives depends on several factors. The estimate would also be increased by the inclusion of relatively more new users or short term users of oral contraceptives, or if many women were using oral contraceptives that contain desogestrel, gestodene, or drospirenone compared with those containing levonorgestrel (Lidegaard et al, 2009). All COCs are associated with an increased risk of VTE. The effect size depended both on the progestogen used and the dose of ethinylestradiol. The risk of VTE in current users of COC decreases with duration of use and decreasing oestrogen dose. For the same dose of oestrogen and the same length of use, oral contraceptives containing desogestrel, gestodene, or drospirenone were associated with a higher risk of VTE than oral contraceptives containing levonorgestrel (Bastos et al, 2014).

On the other side, many clinicians remain concerned that POPs are less tolerated and as a result less effective than estrogen-containing

contraceptives. Nevertheless, studies have reported similar satisfaction and continuation rates for women who used POPs or COCs (Grimes et al, 2009).Recommendations for specific use of POPs, such as stringent daily timing (POPs should be taken at the same time daily) and missed or late pills rules (back-up contraception is recommended for pills taken more than 3h late), may also play an important role in clinicians perceptions of POPs and ultimately hinder their provision (Fritz & Speroff, 2011). In Northern Europe and other regions, availability of POP formulations which are more consistently suppress ovulation and contribute to less irregular bleeding (such as 0.075mg desogestrel) than other formulations available in the USA may help explain their more widespread use (De Melo, 2010; Wilson et al, 2012).

As long as, it concerns the duration of use, the risk of VTE is highest in the four months following initiation of COPs or when restarting after a break of at least one month. The risk then is reduced over the next year and remains stable thereafter. Although the risk is high in the first few months of COPs use and then falls, it remains higher than in non-users (RCOG, 2010). At a case-control conducted in the Netherlands, for 1005 patients with venous thrombosis and 533 control subjects, the risk of VTE was clearly highest during the first three months of use (odds ratio 12.6, 95% CI 7.1 to 22.4). After one year, the risk of VTE for oral contraceptive users compared with non-users decreased to the overall estimate of a 5-fold increased risk. In all time intervals, including those of prolonged use, both second and third generation oral contraceptives were used (Hylckama et al, 2009).

Conclusions

VTE is a serious health problem and is a particular risk to the health of women. The management of women taking hormonal contraceptives should include the disclosure of VTE increased risk and the need to take a detailed history to identify coexisting risk that there is prevention. Furthermore, should advise women use hormonal contraceptives, using appropriate language. Written materials and providing a comparison of risks and benefits can help women to judge the level of risk that is acceptable.

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