EDITORIAL

Risk of venous thrombosis associated with different types of combined oral contraceptive preparations

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Introduction Anno 2014, an increased risk of venous thrombosis associated with oral contraceptive use has long been established, decades after the publication of several large studies describing a 2- to 4-fold increased risk of venous thrombosis associated with current oral contraceptive use.[1-6] The duration of oral contraceptive use is associated with the risk of venous thrombosis, with the highest risk of disease during the first 3 months of use, i.e., an approximately 12-fold increased risk compared with nonusers.[5-7] After prolonged use, the risk decreases to an approximately 5-fold increased risk but remains elevated.

Ever since the marketing of different compositions of oral contraceptive preparations, i.e., different doses of estrogen, (17α-ethinyloestradiol or the very recently introduced estradiol valerate) and different types of progestogen, there has been an ongoing discussion regarding the difference in the risk of venous thrombosis associated with these different compositions.

Venous thrombosis in young women is rare with an annual incidence of approximately 3 to 5 per 10,000 women.[8] However, it is a serious, sometimes fatal disease because of its potential complications such as pulmonary embolism and the post-thrombotic syndrome. While the absolute risk of venous thrombosis in young women is low, the fact that millions of women worldwide are using oral contraceptives, indicates that these preparations are responsible for a large proportion of cases with venous thrombosis and that even a small difference in the risk of venous thrombosis between oral contraceptive preparations affects many women.

The aim of this article is to provide a short historical overview of the development of oral contraceptives and the associated risks of venous thrombosis. Furthermore, as venous thrombosis is rare and studies with clinical endpoints are time-consuming, we discuss alternative study designs using intermediate endpoints to assess the risk of venous thrombosis.

Risk of venous thrombosis In 1961, Jordan[9] reported an association between the use of oral contraceptives and the occurrence of a pulmonary embolism. The high dose of ethinyloestradiol in combined hormonal contraceptives was thought to be the main cause of the increased risk of venous thrombosis. Subsequently, the dose of ethinyloestradiol was reduced, indeed resulting in a decrease in the risk of venous thrombosis.[10-12] Oral contraceptives may contain different types of progestogens, i.e., lynestrenol (first-generation progestogen), levonorgestrel, or, less often, norgestrel (second-generation progestogens), and desogestrel or gestodene (third-generation progestogens). Three types of progestogens have been more recently introduced and are not included in the classification in generations: cyproterone acetate (available since 1988), drospirenone (since 2001), and dienogest (since 2009).

More recently, it has been shown that not only the dose of estrogen but also the type of progestogen in combined oral contraceptive preparations is associated with the risk of venous thrombosis. In the 1990s, several large studies showed an approximately 2-fold increased risk of venous thrombosis associated with preparations containing desogestrel or gestodene as compared with those containing levonorgestrel; however, this was not confirmed by all studies.[4,11,13-15] An intense debate on the validity of the evidence followed, with several researchers arguing that these findings could be explained by the presence of bias and confounding in these studies. However, after the publication of a meta-analysis addressing the effect of all these methodological problems, this increased risk has now been established.

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Regarding oral contraceptive preparations containing progestogens that are not included in the classification of generations, the discussion has not been completely settled yet. Several studies reported a highly increased risk of venous thrombosis associated with oral contraceptives containing cyproterone acetate.[5,6,13,16,17] However, also here, uncertainty remained as this increased risk of venous thrombosis was not confirmed in all studies.[18,19] After the introduction of oral contraceptives containing progestogen drospirenone in 2001, a series of reported cases of venous thrombosis was published.[20-24] More recently, several larger studies assessed the risk of venous thrombosis associated with drospirenone compared with either nonuser of oral contraceptives or users of mainly oral contraceptives containing levonorgestrel (reviewed by Wu et al).[25] Most individual studies included few cases of thrombosis resulting in wide confidence intervals around the risk estimates; thus, there is still uncertainty about the associated risks. Nevertheless, all but 1 study assessing the risk of drospirenone compared with levonorgestrel, point towards an increased risk of venous thrombosis associated with oral contraceptives containing drospirenone compared with oral contraceptives containing levonorgestrel. Recently, we performed a network meta-analysis with the aim to provide an overview of the risk of venous thrombosis associated with different combined oral contraceptive preparations.[26] Results from this analysis showed that oral contraceptives containing cyproterone acetate, were associated with a 1.7-fold increased risk of venous thrombosis when compared with a combined preparation containing levonorgestrel with the lowest amount of estrogen (20 μg). A similar risk estimate was reported for users of a combined oral contraceptive containing drospirenone. A network meta-analysis allowed us to compare the risk of venous thrombosis between all different compositions of frequently used oral contraceptives. This allowed us to draw a conclusion about the safest type of oral contraceptives with regard to venous thrombosis risk. Combined oral contraceptives containing levonorgestrel and 30 or 20 μg of ethinylestradiol were among the safest preparations.

Intermediate endpoints There has been a rapid development of new types of oral contraceptives and their composition is constantly changing. The mechanism by which ethinyloestradiol leads to an increased risk of venous thrombosis and the role of progestogen in this association needs to be unraveled to enable the development of safer preparations. Owing to the low incidence of venous thrombosis in young women, studies on assessing the difference in the risk of venous thrombosis between different types of oral contraceptives require a very large sample size of women or a long duration of follow-up. Consequently, especially for hormonal contraceptive preparations that were recently introduced on the market, studies with clinical endpoints are as yet lacking.

Oral contraceptives have clear effects on the coagulation system; however, the mechanism behind this effect remains unclear. These effects include increases in the levels of procoagulant proteins and reductions in the anticoagulant proteins[27,28]; therefore, all these protein changes predict a shift towards a more prothrombotic state. This shift was also confirmed in studies using global coagulation tests, such as activated protein C (APC)-resistance or endogenous thrombin generation.[27-29] Users of oral contraceptives with a high thrombotic risk have higher plasma levels of sex hormone-binding globulin (SHBG) than users of low-risk oral contraceptives, and SHBG plasma levels were positively associated with resistance to APC.[30-32] Therefore, elevated levels of SHBG may be seen as a marker of the thrombogenicity of combined hormonal contraceptives. Using these results, relative safety of new preparations may be established much sooner after a preparation is marketed and, therefore, less women will be unnecessarily exposed to an increased risk of venous thrombosis. Two recent studies based on intermediate endpoints only, i.e., markers of clotting activation, have shown that estradiol valerate, in contrast to ethinyloestradiol, may not be associated with an increased risk of thrombosis.[33,34] Nevertheless, studies using clinical endpoints are still lacking and urgently needed.

Conclusions Currently, the discussion regarding safety of combined oral contraceptives has gone as far as governments discussing the possibility of banning combined preparations containing cyproterone acetate from the market. However, whether certain types of oral contraceptives should be banned from the market is a political question which is not easily answered. Nevertheless, both physicians and users of oral contraceptives should carefully consider efficacy and side effects. Since all different types of hormonal contraceptives work equally well in preventing pregnancy, the type of oral contraceptive that is associated with the lowest risk of major side effects such as venous thrombosis should be preferred. Therefore, currently, when a combined oral contraceptive preparation is considered, an oral contraceptive with the lowest tolerated dose of estrogen combined with levonorgestrel should be the first choice.

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