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Chapter 8

Discussion and recommendations

This thesis focussed on the role of hormonal contraceptives in the pathogenesis of venous thrombosis and its association with a first and recurrent venous thrombosis. We set out to research the mechanisms behind combined oral contraceptive-associated venous thrombosis, to assess the association between hormonal contraceptive use and recurrent venous thrombosis and to provide an overview of the risk of a first venous thrombosis per type of combined oral contraceptive. In this section, the research questions of the thesis and its implications will be discussed.

Mechanism behind combined oral contraceptive-associated venous thrombosis

Sex hormone binding globulin (SHBG) levels are said to be a marker of venous thrombosis in combined oral contraceptive users reflecting the difference in risk between different contraceptives[1,2]. For instance, SHBG levels are higher in users of contraceptives with a third generation progestagenn (desogestrel, gestodene and norgestimate) than in users of a second generation (levonorgestrel), reflecting the difference in venous thrombosis risk. Although the association between SHBG levels and contraceptive use has been established, the question remained whether SHBG level is an intermediate, i.e., meaning both a marker and a cause, or only a marker for venous thrombosis risk. In chapter 2, we used a Mendelian randomization approach to show that SHBG level was only a marker and not a cause of venous thrombosis. A disadvantage of this analysis is the requirement that the changes in protein levels caused by genetic variation, which may be minor, are also causative of the disease of interest. However, we observed changes in SHBG levels caused by genetic variation in the SHBG gene in the same magnitude as changes caused by oral contraceptive use, rendering this approach feasible. We were able to include only 23 women with venous thrombosis, and over 200 women without venous thrombosis. Despite this

low number of patients, our three-pronged approach consistently showed that increased SHBG levels were not causally related with venous thrombosis.

The association between SHBG levels and different progestagens in combined oral contraceptives has been well established [1,2], but the association with the ethinylestradiol dose remains to be determined. The ethinylestradiol dose in combined oral contraceptives is positively associated with the risk of venous thrombosis [3,4]. For SHBG levels to be considered as a useful marker of venous thrombosis in combined oral contraceptive users, the ethinylestradiol dose should also be reflected in SHBG levels. In chapter 3, we were able to show that with increasing ethinylestradiol dose, SHBG levels increased as well. Although we were not able to restrict our analysis to one specific progestagen, we did adjust for the progestagen. Furthermore, the observed SHBG levels were similar as previously reported.

The relevance of the first-pass metabolism of ethinylestradiol for the risk of venous thrombosis was assessed through haplotypes in genes coding for enzymes involved in this metabolism and their effect on SHBG levels. We found that carrying two copies of haplotype D in the gene *UGT2B7* was associated with an increased risk of venous thrombosis, described in chapter 4. We only assessed genetic variation in this metabolism through common variation (SNPs with a minor allele frequency of more than 5%). However, these common SNPs could code for rare haplotypes (frequency below 5%). The first-pass metabolism may not be as pivotal in the pathogenesis of venous thrombosis as previously thought. Other contraceptives were developed to bypass the first-pass metabolism of ethinylestradiol, namely the transdermal patch and the vaginal ring. Users of these contraceptives, however, still have an increased risk of venous thrombosis [5]. Therefore, although we show that genetic variation in the first pass metabolism may explain part of the pathogenesis of combined oral contraceptive-associated venous thrombosis, currently we cannot fully explain how combined oral contraceptives cause

venous thrombosis.

Hormonal contraceptive use after a first event

Guidelines[6–8] recommend that women should refrain from using combined preparations after a first event of venous thrombosis. Progestagen-only preparations could be used instead. Are these guidelines followed in daily practice? We found that about 25% of women continued using hormonal contraception after a venous thrombotic event, either by continuing their oral contraceptive or by switching. This includes women changing to a progestagen-only contraceptive which is according to the guidelines. However, we found that 21% continued or changed to another combined oral contraceptive. Women without a positive family history of venous thrombosis, or women with thrombosis following surgery or a plaster cast were more likely to continue or switch contraceptives. Because venous thrombosis is a multicausal disease, it is difficult to indicate one factor that solely causes venous thrombosis. From our data it is not possible to know exactly why decisions to continue or stop were made. However, 12% of women who received advice from a physician to stop their contraceptive, still continued or changed to another combined oral contraceptive.

Current guidelines are from 2009 and do not include a study from 2010 showing that continuing or restarting hormonal contraceptives after a first event increases the risk of recurrence[9]. In our study, we found 21 recurrences while women were using hormonal contraceptives. In line with this previous publication, we observed a three-fold increased risk of a recurrent venous thrombosis while using hormonal contraceptives. Whether or not the first event occurred during use of hormonal contraceptives did not affect the risk of recurrence. Regarding different preparations, we found that combined oral contraceptive use increased the risk of a recurrence about three-fold. The risk of a recurrence was highest (about eight times increased) in users

of triphasic contraceptives. Furthermore, results indicated that a levonorgestrel-releasing IUD could be safely used after a first event.

Overview per type of contraceptive

The literature was searched for studies that assessed the risk of a first venous thrombosis per type of combined oral contraceptive. Through a network meta-analysis, we were able to combine direct and indirect evidence in a weighted average. All hormonal contraceptives increased the risk of venous thrombosis. The dose effect of ethinylestradiol depended on the progestagen. We observed no difference in risk between 20 µg ethinylestradiol with desogestrel or 30 µg ethinylestradiol with desogestrel users. Furthermore, users of 20 µg ethinylestradiol with gestodene seemed to have the same risk of venous thrombosis as 20 µg ethinylestradiol with levonorgestrel. Although only one study had data on 20 µg ethinylestradiol with gestodene users, it is worth investigating this observation further. Previous reports have already suggested the risk of venous thrombosis for gestodene users is not equal to desogestrel but somewhere between levonorgestrel and desogestrel use, for an equal dose of ethinylestradiol[3]. The effects of these compounds on SHBG levels point in the same direction[1,2].

Conclusion

The research outlined in this thesis has contributed to our understanding of the pathogenesis of venous thrombosis in combined oral contraceptive users. SHBG levels are only marker for venous thrombosis and not a cause and are affected not only by the type of progestagen but also by the ethinylestradiol dose in combined oral contraceptive. Genetic variation in the first-pass metabolism of ethinylestradiol was associated with venous thrombosis in combined oral contraceptive users. A substantial

proportion of women disregard the advice of a physician to stop their contraceptive use after a venous thrombosis, while continuing hormonal contraceptive use, in particular combined oral contraceptives, after a first venous thrombotic event increased the risk of a recurrence. A levonorgestrel-releasing intra-uterine device may be a safe option after a venous thrombotic event.

Recommendations

Clinical recommendations

- Regardless of exposure to risk factors for venous thrombosis, women should stop using combined hormonal contraceptives after a venous thrombosis.
- After a venous thrombosis, the use of a levonorgestrel-releasing IUD is likely to be a safe option.
- In women without a history of venous thrombosis, switching to a contraceptive with a higher ethinylestradiol dose, for control of breaktrhough bleeding, is not rational and likely to be detrimental.

Scientific recommendations

- When evaluating the risk of venous thrombosis, refrain from any classification of contraceptives.
- Regarding the mechanism behind combined oral contraceptive-associated venous thrombosis, variation in protein levels, caused by factors other than genetic, or variation in ethinylestradiol levels may be pivotal in the pathogenesis of combined oral contraceptive-associated venous thrombosis.
- A proportion of women disregards the advice of a physician to stop their contraceptive use after a venous thrombosis. It would useful to know why they disregard this advice.
- Triphasic contraceptives increase the risk of recurrence in hormonal contraceptives more than monophasic preparations containing the same progestagen. The mechanism behind this is unknown.

- Literature on progestagen-only contraceptives is sparse, because only a small group of women are using these contraceptives. Therefore, large studies are needed to evaluate the effect of these contraceptives, both for a first event and a second event of venous thrombosis

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