

Venous thromboembolism in women

Citation for published version (APA):

Abbattista, M. (2022). *Venous thromboembolism in women: a focus on unusual sites, pregnancy and thrombophilia*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20220211ma>

Document status and date:

Published: 01/01/2022

DOI:

[10.26481/dis.20220211ma](https://doi.org/10.26481/dis.20220211ma)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Impact paragraph

Venous thromboembolism is a life-threatening condition and the leading cause of maternal mortality in developed countries. In many cases it can be prevented and adequately treated, but some areas of uncertainty remain. The contents of this thesis contribute to summarize the available evidences on the risk factors, clinical aspects, prevention and treatment of venous thromboembolism in women, particularly when it occurs at such unusual sites as cerebral veins and sinuses. This work also contributes to the knowledge on oral contraceptive use and pregnancy as risk factors for venous thrombosis and pregnancy outcomes with or without antithrombotic prophylaxis with low molecular weight heparin.

These data further strengthen the knowledge on how the duration of oral contraceptive use influences the risk of venous thromboembolism. The period within one year of use is associated with a higher risk of venous thromboembolism in women aged less than 30 years than in those over 30, particularly in the first-time users. Additionally, the risk of venous thromboembolism associated with the short duration of oral contraceptive use strongly interacts with the presence of thrombophilia abnormalities. The longer the use of hormonal contraception, the higher the number of transient risk factors other than oral contraceptive that act as main triggers of venous thrombosis, independently of women's age. The studies on cerebral venous thrombosis and pregnancy contribute to improve the knowledge on a poorly investigated topic, showing that women with previous cerebral vein thrombosis appear at increased risk of late obstetrical complications despite antithrombotic prophylaxis, however the risk of recurrent thrombosis and bleeding during pregnancy is low. Additionally, having had a cerebral vein thrombosis and being carrier of a thrombophilia abnormality greatly influenced the decision to terminate pregnancy. Although on one hand women with previous cerebral vein thrombosis should not be discouraged to become pregnant, on the other hand they should be informed and reassured on the possible risks. Investigating a large sample of women with the rare and severe thrombophilia abnormalities antithrombin deficiency, we observed a high risk of venous thromboembolism during pregnancy and puerperium both in those with positive and negative family history, and also an increased risk of late obstetrical complications. The efficacy of antithrombotic prophylaxis for the prevention of pregnancy-related venous thromboembolism but not obstetrical complications suggests that the causes underlying the two complications could be different. Finally, in women with or without thrombophilia abnormalities with the exception of antiphospholipid antibodies, antithrombotic prophylaxis is effective and safe in preventing recurrent thrombosis and miscarriage in the first pregnancy after venous thrombosis, but it does not prevent late obstetrical complications.

The provided data are added to the scarce available evidence, particularly in rare settings such as pregnant women after thrombosis at unusual sites or women with severe thrombophilia at risk of pregnancy-related venous thromboembolism. All the results included in this thesis have been submitted to peer-reviewed scientific journals in the area of Thrombosis and Haemostasis, and all but one have already been published online or printed. In the absence of randomized clinical trials in the setting of rare thrombosis and pregnancy, our data provide evidence in favor of the use of low molecular weight heparin prophylaxis to lower the risk of pregnancy-related recurrent thrombosis in women with previous cerebral vein thrombosis. We would also encourage international scientific societies to share therapeutic recommendation for rare thromboses that are often neglected by the guidelines. The increased risk of recurrent thrombosis during pregnancy in women who had had a previous thrombotic event during oral contraceptive use should motivate physicians to carefully evaluate pregnant women for the thrombotic history and the risk factors present at the time of previous event. These data highlight the importance of the assessment of an individual risk profile, as well as of the treatment-associated risks and benefits (i.e. risk of placenta-mediated obstetrical complications despite antithrombotic prophylaxis in women with previous cerebral vein thrombosis or carrier of antithrombin deficiency), suggesting a personalized approach. In addition, these data underline how having experienced a thrombotic event and being carrier of a thrombophilia abnormality can negatively affect the choice to carry a pregnancy to term. This should prompt awareness on a balanced counselling for women with a personal history of thrombosis taking into account psychological aspects. Pregnancy is a complex phenomenon which includes psychological changes and could be a stressful event, particularly for women who experienced a previous pregnancy-related thrombosis. In light of these findings, the scientific and social challenge should be directed towards new preventive measures, including adequate psychological support strategy for women who might get pregnant after a thrombotic event.

First and foremost, prompt recognition investing in communication campaigns and adequate treatment, which in the near future could include direct oral anticoagulants, will allow to reduce mortality. As well, any progress in the knowledge of risk factors for venous thromboembolism will ameliorate the risk stratification and optimize preventive strategies, increasing the benefits and limiting the harms of anticoagulant therapy. Observational and epidemiological studies, like those proposed in this thesis, fit into this framework adding evidence on the management of such unusual situations as rare thrombosis and pregnancy, and increasing the awareness of the gaps of knowledge. The pathophysiology of obstetrical complications, either in women who experience a previous cerebral vein thrombosis or women with antithrombin type I deficiency, should be elucidated. If the occurrence of

obstetrical complications in these settings will be confirmed, future studies should identify those women who could benefit from antithrombotic prophylaxis without harm.