

Editorial

Women's Health Issues in Thrombosis and Haemostasis

Birgit Linnemann¹ Christina Hart² and Speakers
of the GTH Working Group "Women's Health"

¹Division of Angiology, University Center of Vascular Medicine,
University Hospital Regensburg, Regensburg, Germany

²Department of Haematology and Oncology, Internal Medicine III,
University Hospital Regensburg, Regensburg, Germany

Hamostaseologie 2022;42:285–286.

In the last couple of years sex specific health issues have continually been gaining attraction by physicians of different medical specialities. Sex differences have been described e.g. in the pathogenesis and mortality in patients affected by COVID-19, in metabolic regulation and cancer mechanisms.^{1–3} In the field of haemostasis, many aspects concerning risk factors, clinical presentation and management of thromboembolic disease and bleeding disorders also display sex differences.

This special issue of *Hämostaseologie- Progress in Haemostasis – Women's Health Issues in Thrombosis and Haemostasis* hosts six review articles covering the wide range of coagulation specific aspects in women. The aim of the selection of conceptional reviews in this issue is to draw attention to the elevated thromboembolic risk during a woman's life, to address women specific side effects of anticoagulation therapy and to focus on female specific aspects in von Willebrand disease (VWD).

The lifetime risk of venous thromboembolism (VTE) has been described to be slightly higher in women than in men.⁴ This refers especially to women of reproductive age. In their review, **Birgit Linnemann** and members of the GTH Working Group „Women's Health“ have addressed „Venous Thromboembolism Issues in Women“ such as hormonal contraception, pregnancy, infertility treatment, postmenopausal hormonal replacement therapy and the risk of VTE recurrence.⁵ Based on an extensive literature research, the authors provide a comprehensive review on hormonal contraceptive methods including new formulations with a better safety profile with regard to VTE. In addition, the authors emphasize the necessity of effective and safe contraception in women of reproductive age who are treated with direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA) for treatment or secondary prophylaxis of VTE. There is an increasing number of venous and arterial thromboembolic events after infertility treatment (syn. artificial reproduction technologies; ART) reported in the

literature in recent years. The risk of VTE is particularly increased in women with moderate and severe ovarian hyperstimulation syndrome (OHSS) so that first trimester pharmacoprophylaxis should be considered in these cases. Finally, the authors explore the risk of recurrent VTE after a first thromboembolic event in women when compared to men and especially focus on the risk of recurrence after hormone-related VTE.

Specific consideration should be given to transgender people receiving gender-affirming hormone therapy (GAHT), especially in those desiring feminization.⁶ However, data on long-term outcome and thrombotic risk in transgender people are still scarce. Introduced by a clinical case of a transgender woman, **Christa van Bunderen et al.** outline the current pharmacological interventions and highlight the impact of hormonal treatment in transgender medicine on the risk of VTE.⁷ Whereas GAHT in non-transgender women is discontinued after hormone-related VTE in the majority of cases, this is not the case for transgender women. In addition, elaborate discussion is provided on thromboprophylaxis in transgender people with additional VTE risk factors as well as in the perioperative setting such as hereditary thrombophilia or a history of VTE.

Thromboembolic events are a common complication in patients with haematologic and solid malignancies and a leading cause of mortality. Especially women with sex-specific malignancies like breast and uterine cancer who develop VTE have an elevated mortality risk compared to patients with pancreatic or lung cancer.⁸ In his review article „VTE in women with VTE in Women with cancer“, **Axel Matzdorff** starts with a case-report on a woman suffering from breast cancer and a catheter-related VTE.⁹ The author addresses the incidence and risk factors of VTE in women with cancer and hereinafter focusses on prophylactic and therapeutic challenges regarding anticoagulation therapy in women with cancer. Additionally, the author critically evaluates the use of DOAC in this setting and highlights specific issues, e.g. bleeding risk, possible drug-

Address for correspondence

PD Dr. Christina Hart, University
Hospital Regensburg,
Department of Haematology and
Oncology, Internal Medicine III,
Regensburg, Germany
(e-mail: christina.hart@klinik.uni-
regensburg.de).

© 2022. Thieme. All rights reserved.
Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI <https://doi.org/10.1055/s-0042-1757549>.
ISSN 0720-9355.

drug interactions and thrombocytopenia that have to be considered in choosing the appropriate anticoagulation regimen for these women.

Only recently, members of the GTH Working Group „Women's Health“ released recommendations on pharmacological thromboprophylaxis during pregnancy and the puerperium.¹⁰ In this theme issue, **Christina Hart** and colleagues focus on women with antithrombin (AT) deficiency and summarize current knowledge and management strategies reported in case control and observational studies.¹¹ Hereditary AT deficiency is a major burden of hereditary thrombophilia and a rare condition in the general population. Approximately 50% of individuals with hereditary AT deficiency will develop thrombotic events. Especially women with AT deficiency experiencing pregnancy and delivery are at high risk of maternal VTE.^{12,13} The management of pregnant women with AT deficiency poses a particular challenge because the efficacy of heparins, that are the anticoagulants of choice for women at risk or diagnosed with acute VTE, may be attenuated in individuals with AT deficiency.

VWD is the most common inherited bleeding disorder. Though women and men are affected equally, women face special challenges regarding menstruation and child birth and show a significant diagnostic delay in comparison to men.¹⁴ **Fagr Eladly and Wolfgang Miesbach** give a detailed overview on specific bleeding manifestations in women with VWD, laboratory diagnostics and management strategies.¹⁵ The authors describe therapeutic options in treating heavy menstrual bleeding (HMB) and provide information on the management of pregnancy and the ante- and postpartal period.

In recent years, there has been an increasing awareness of bleeding issues in women receiving anticoagulant therapy.^{16,17} **Lida Kalmanti and Edelgard Lindhoff-Last** explore the clinical significance of abnormal uterine bleeding (AUB) which comprises HMB as well as bleeding and spotting between periods, after sex or after menopause.¹⁸ In their review, the authors specifically focus on HMB occurring under treatment with DOAC and summarize the current evidence mainly obtained from retrospective or single center studies or from post hoc analysis of the corresponding phase III studies. The authors demonstrate therapeutic approaches to manage women with AUB or HMB and finally present the rationale and design of the HEMBLEMED registry, an ongoing prospective observational study investigating the incidence of HMB in women of reproductive age treated with different direct oral anticoagulants due to VTE.

It was a great pleasure for us to organize and serve as Guest Editors of this theme issue of *Hämostaseologie – Progress in Haemostasis* and to write the editorial introduction on „Women's Health Issues in Thrombosis and Haemostasis“.

On behalf of the Editorial Board, we highly appreciate the efforts of the authors and like to thank them cordially for their time spent in preparing their exciting contributions. Further on, we like to express our gratitude to the reviewers for their comments.

We hope that the choice of our topics and the insights provided by the presented reviews will be of interest for you, the readers of this theme issue, and will be helpful for your daily work.

References

- 1 Rubin JB, Lagas JS, Broestl L, et al. Sex differences in cancer mechanisms. *Biol Sex Differ* 2020;11(01):17. Doi: 10.1186/s13293-020-00291-x
- 2 Tramunt B, Smati S, Grandgeorge N, et al. Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia* 2020;63(03):453–461. Doi: 10.1007/s00125-019-05040-3
- 3 Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. *Cardiovasc Res* 2020;116(14):2197–2206. Doi: 10.1093/cvr/cvaa284
- 4 Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. *Eur J Epidemiol* 2022;37(02):195–203. Doi: 10.1007/s10654-021-00813-w
- 5 Linnemann B, Rott H, Zotz R, Hart C. Venous Thromboembolism Issues in Women. *Hämostaseologie* 2022;290–299. Doi: 10.1055/a-1919-9558
- 6 de Blok CJ, Wiepjes CM, van Velzen DM, et al. Mortality trends over five decades in adult transgender people receiving hormone treatment: a report from the Amsterdam cohort of gender dysphoria. *Lancet Diabetes Endocrinol* 2021;9(10):663–670. Doi: 10.1016/S2213-8587(21)00185-6
- 7 Van Bunderen CC, Leentjens J, Middeldorp S. Transgender Medicine and Risk of Venous Thromboembolism. *Hämostaseologie* 2022 doi: ???
- 8 Mahajan A, Brunson A, Adesina O, Keegan THM, Wun T. The incidence of cancer-associated thrombosis is increasing over time. *Blood Adv* 2022;6(01):307–320. Doi: 10.1182/bloodadvances.2021005590
- 9 Matzdorff A. Venous Thromboembolism in Women with Cancer. *Hämostaseologie* 2022;309–319. Doi: 10.1055/a-1913-2873
- 10 Hart C, Bauersachs R, Scholz U, et al. Prevention of Venous Thromboembolism during Pregnancy and the Puerperium with a Special Focus on Women with Hereditary Thrombophilia or Prior VTE-Position Paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH). *Hämostaseologie* 2020;40(05):572–590. Doi: 10.1055/a-1132-0750
- 11 Hart C, Rott H, Heimerl S, Linnemann B. Management of Antithrombin Deficiency in Pregnancy. *Hämostaseologie* 2022;320–329. Doi: 10.1055/a-1841-0399
- 12 Martinelli I, Mannucci PM, De Stefano V, et al. Different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: a study of 150 families. *Blood* 1998;92(07):2353–2358
- 13 Abbattista M, Giannelli F, Novembrino C, et al. Risk of pregnancy-related venous thromboembolism and obstetrical complications in women with inherited type I antithrombin deficiency: a retrospective, single-centre, cohort study. *Lancet Haematol* 2020;7(04):e320–e328. Doi: 10.1016/S2352-3026(20)30007-7
- 14 Atiq F, Saes JL, Punt MC, et al; WiN, RBiN and TiN study groups. Major differences in clinical presentation, diagnosis and management of men and women with autosomal inherited bleeding disorders. *Eclinical-Medicine* 2021;32:100726. Doi: 10.1016/j.eclinm.2021.100726
- 15 Eladly F, Miesbach W. Von Willebrand Disease – Specific Aspects in Women. *Hämostaseologie* 2022;330–336. Doi: 10.1055/a-1891-9976
- 16 Huq FY, Tvarkova K, Arafa A, Kadir RA. Menstrual problems and contraception in women of reproductive age receiving oral anticoagulation. *Contraception* 2011;84(02):128–132. Doi: 10.1016/j.contraception.2010.12.011
- 17 Klok FA, Schreiber K, Stach K, et al. Oral contraception and menstrual bleeding during treatment of venous thromboembolism: Expert opinion versus current practice: Combined results of a systematic review, expert panel opinion and an international survey. *Thromb Res* 2017;153:101–107. Doi: 10.1016/j.thromres.2017.03.013
- 18 Kalmanti L, Lindhoff-Last E. Bleeding Issues in Women under oral Anticoagulation. *Hämostaseologie* 2022;337–347. Doi: 10.1055/a-1891-8187