The hormonal influence on the haemostatic system and the risk of thrombosis
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CHAPTER 1

General Introduction and Outline of the thesis

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**GENERAL INTRODUCTION**

Approximately 100 years ago the word ‘hormone’ was coined by Ernest Starling (1866–1927).<sup>1,2</sup> Hormones, derived from the Greek meaning ‘to set in motion’ (ormao), were defined as chemical internal messengers carried from the cell where they are produced to the cells which they affect by means of the bloodstream. It was thought that different parts of the body are able to take up these hormones from the blood, and transform them into other materials.<sup>2</sup> Since then, hormones and hormone receptors have become an exciting and important field in multidisciplinary research. It has led to various pharmacological and therapeutic strategies for the treatment of both endocrine and non-endocrine diseases. It has also brought social and economic progress with, for example, providing methods for limiting the growth of the human population and by promoting the supplies of food.<sup>2</sup>

Most hormones initiate a cellular response by initially combining with either a specific intracellular or cell membrane-associated receptor protein. This receptor can be present on different tissues throughout the body explaining hormones’ numerous effects, therapeutic options and various complaints in individuals in whom there is an over- or underproduction of a specific hormone.<sup>4</sup> In this thesis we aimed to further explore the hormonal influence on the haemostatic system.

Haemostasis is a complex and elegant process that keeps blood in a fluid state within the circulation, thereby preventing individuals from experiencing excessive bleeding or thrombosis. The haemostatic balance can be disrupted by, as described by Virchow, an alteration in blood flow, change in vessel wall, or change in haemostatic protein composition of the blood.<sup>5</sup> The cross-talk amongst these three components determines propensity for both thrombosis and bleeding. Many factors that influence this cross-talk are known, and more and more are discovered each year.<sup>6</sup>

Endocrine disorders are common diseases in the general population and have been found to increase the risk of both arterial and venous thrombosis, however the underlying mechanisms are different. The risk of arterial thrombosis is increased by indirect effects on lipids, blood pressure and body weight and direct effects on the process of atherogenesis and plaque instability, whereas the risk of venous thrombosis is enhanced by modulating both primary and secondary haemostasis.<sup>7,8</sup> Primary haemostasis firstly includes platelet adhesion to damaged endothelium thereby activating the platelets, secondly platelet aggregation to form a platelet plug, and thirdly degranulation of the platelets to continue this process in a positive feedback loop.<sup>9</sup> Both the process of activation and aggregation of platelets has been found
to be responsive to hormonal influences.10 During secondary haemostasis the coagulation cascade is activated leading to the formation of fibrin strands to stabilize the platelet plug. The hormone receptor complex is thought to increase or decrease gene transcription of coagulation and fibrinolytic proteins at both the hepatic and endothelial level, thereby influencing the coagulation and fibrinolytic activity.11-13

The first hormonal risk factors known to be associated with venous thrombosis include oral contraceptives and hormone replacement therapy, containing the hormones oestrogen and progesterone.14,15 Since then, a wide variety of endocrine disorders have been associated with both mild abnormalities in laboratory coagulation tests and clinical thrombotic manifestations. Hyperthyroidism has been found to induce a hypercoagulable and hypofibrinolytic state, thereby increasing the risk of venous thrombosis.16,17 Hypothyroidism has been related to a bleeding tendency varying from mild mucocutaneous bleeding to severe posttraumatic bleeding with acquired von Willebrand syndrome as the main underlying pathophysiologic mechanism. However, the exact incidence of this complication is unknown, thereby making it difficult to provide useful clinical advice.16 Endogenous hypercortisolism in Cushing’s syndrome has been proposed to increase the risk of both arterial and venous thrombosis, although the exact risk, especially after surgery is unknown.18 Also, a link has been suggested between the use of exogenous glucocorticoids and the risk of venous thromboembolism.19 Several studies suggest a direct activation of coagulation and inhibition of fibrinolysis, however this seems to depend on the clinical situation in which these drugs are given. Given the high prevalence of glucocorticoids prescribed in all areas of modern medicine this effect could be clinically relevant. Finally, several conditions that are characterised by high levels of prolactin, such as pregnancy, puerperium, the use of oral contraceptive agents, hormone replacement therapy, and antipsychotic drugs are associated with an increased risk of venous thrombosis.20,21 Also, in prolactinoma patients a hypercoagulable and hypofibrinolytic state has been observed and these patients demonstrated a higher incidence of venous thrombosis than the general population.22 However, to which extent prolactin itself affects the haemostatic system and whether it plays a causal role in the aetiology of venous thrombosis, has only been scarcely investigated.

At present, thrombosis is considered as a “multi-causal” disease in which multiple genetic or environmental elements coincide to push over a so called ‘thrombotic threshold’.6 An individual thromboembolic risk factor may therefore be ‘the last drop that makes the cup run over’ (cover). Such a risk factor may become clinically relevant, especially if treatable. This is true for endocrine disorders. Although several studies have looked at the association between
endocrine dysfunction and the haemostatic system, important methodological drawbacks drastically reduce the strength of evidence and do not allow for definitive conclusions on the clinical relevance of these findings. This thesis aims to bring further insights into the intriguing link between the hormonal and haemostatic system. By focussing on the thyroid hormone, cortisol, and prolactin, we aimed to unravel both the underlying mechanisms by which the hormones affect the haemostatic system and the clinical thrombotic manifestations.

**Outline of this thesis**

This thesis consists of 3 parts. In the first part, we study the effects of the glucocorticoid hormone cortisol on the haemostatic system. **Chapter 2** describes the findings of a large retrospective multicentre cohort study on the overall incidence of venous thrombosis in patients with Cushing's syndrome, with special emphasis on the three years prior to the start of treatment and the postoperative period. As glucocorticoids are prescribed to millions of patients worldwide for many underlying diseases, we aimed to evaluate whether an association exists between use of glucocorticoids and risk of symptomatic pulmonary embolism in **Chapter 3**.

The second part of this thesis concerns the thyroid hormone. In **Chapter 4** we systematically review and meta-analyse the available studies on the effects of hyperthyroidism on coagulation and fibrinolysis. In **Chapter 5**, we describe a young woman who attempted suicide by auto-intoxication with levothyroxine, which presented a unique situation of assessing the haemostatic effects during extreme thyroid hormone excess. **Chapter 6** concerns the effects of hyperthyroidism and hypothyroidism on thrombin-activatable fibrinolysis inhibitor, a protein that links the coagulation and fibrinolytic systems. To further enhance the understanding of the mechanisms responsible for an increased bleeding tendency in hypothyroidism and a thrombotic environment during hyperthyroidism, we studied fibrin clot structure and fibrinolysis in hyperthyroidism and hypothyroidism *ex vivo* in **Chapter 7**. Although acquired von Willebrand syndrome is thought to be the main pathophysiological mechanism responsible for the bleeding tendency in hypothyroid patients, the prevalence and clinical relevance of this coagulation disorder is studied in a large cohort study in **Chapter 8**. In **Chapter 9**, the effect of subclinical hypothyroidism on vitamin K antagonist stability and sensitivity is investigated. To understand the clinical implications of the association between hyperthyroidism and venous thrombosis, the incidence of venous thrombosis in patients with overt hyperthyroidism and the risk of recurrent venous thrombosis associated with different levels of thyroid hormone is assessed in **Chapter 10** and **Chapter 11**. To gain further insights into the association between thyroid hormone and the risk of arterial thrombosis, we describe the change in lipid levels in two cases with hypothyroidism-induced dyslipidemia before
and after substitution with thyroid hormone in Chapter 12. Recently, the development of synthetic thyroid hormone mimetic compounds and metabolites that preferentially elicit the favourable metabolic effects of thyroid hormone without inducing unfavourable effects of the hormone, have received attention as potential treatment modalities for hypercholesterolemia and obesity. As thyroid hormone treatment has been found to induce a hypercoagulable state, we aimed to study the effect of the thyromimetic compound 3,5-diiodothyronine (T2) on coagulation and fibrinolysis in a randomized controlled trial in Chapter 13.

The final part of this thesis addresses the hormone prolactin. In Chapter 14, the association between increasing levels of prolactin and venous thrombosis is assessed in a case-control design. The effects of hyperprolactineamia on atherothrombotic parameters in prolactinoma patients is described in Chapter 15.

Last, in Chapter 16, we tested the hypothesis, formed during the course of this thesis, that there is a serious underreporting of venous and arterial thrombosis in randomized clinical trials.
Reference List