Endocrine determinants of haemostasis and thrombosis risk: Focus on thyroid hormone
Elbers, Laura

Citation for published version (APA):
Elbers, L. P. B. (2016). Endocrine determinants of haemostasis and thrombosis risk: Focus on thyroid hormone
Left-sided Predominance of Deep Venous Thrombosis in the Postpartum Period

Annemarie Venemans-Jellema
Laura PB Elbers
Saskia Middeldorp
Victor EA Gerdes
Suzanne C Cannegieter

Submitted for publication
Chapter 10

The risk of deep vein thrombosis (DVT) is 20-fold increased during the postpartum period compared with non-pregnancy. The underlying mechanism is currently unclear. During pregnancy, the preferred side is the left leg (88%), while a left-sided DVT is only slightly more common outside pregnancy. It is not known whether left-sided predominance is also present during the postpartum period, which could hint towards an explanation. The aim of this study was to determine the left-right and proximal-distal distribution of DVT postpartum women, compared with that in pregnant and non-pregnant women. We selected female DVT patients younger than 50 years, without recent malignancy. A total of 990 patients were included of whom 67 were postpartum and 34 were pregnant at the time of DVT. In the postpartum period 70% (95% Confidence Interval (CI): 58-80) had a left-sided DVT, compared with 85% (95%CI: 70-94) during pregnancy and 57% (95%CI: 53-60) in non-pregnant women. In the postpartum period more DVTs (28%; 95%CI: 16-45) were restricted to the iliofemoral region when compared with non-pregnancy (10%; 95%CI: 8-13). These findings suggest that a relevant proportion of DVTs that occur during the postpartum period has developed before delivery and has taken some time to cause clinical symptoms.

SUMMARY

The risk of deep vein thrombosis (DVT) is 20-fold increased during the postpartum period compared with non-pregnancy. The underlying mechanism is currently unclear. During pregnancy, the preferred side is the left leg (88%), while a left-sided DVT is only slightly more common outside pregnancy. It is not known whether left-sided predominance is also present during the postpartum period, which could hint towards an explanation. The aim of this study was to determine the left-right and proximal-distal distribution of DVT postpartum women, compared with that in pregnant and non-pregnant women. We selected female DVT patients younger than 50 years, without recent malignancy. A total of 990 patients were included of whom 67 were postpartum and 34 were pregnant at the time of DVT. In the postpartum period 70% (95% Confidence Interval (CI): 58-80) had a left-sided DVT, compared with 85% (95%CI: 70-94) during pregnancy and 57% (95%CI: 53-60) in non-pregnant women. In the postpartum period more DVTs (28%; 95%CI: 16-45) were restricted to the iliofemoral region when compared with non-pregnancy (10%; 95%CI: 8-13). These findings suggest that a relevant proportion of DVTs that occur during the postpartum period has developed before delivery and has taken some time to cause clinical symptoms.
INTRODUCTION

Venous thrombosis, i.e. the composite of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a serious complication during pregnancy and in the postpartum period, occurring in about 2 per 1000 deliveries (James, et al 2006). It accounts for 1.1 deaths per 100,000 deliveries, which corresponds to 10% of all maternal deaths in Western countries, thus being one of its leading causes (James, et al 2006). The elevated thrombosis risk continues into the postpartum period, and even has been reported to be as much as five times higher during the postpartum period than during pregnancy (Heit, et al 2005, Jackson, et al 2011).

During pregnancy, the most common side of DVT is the left leg. In a meta-analysis by Chan et al (Chan, et al 2010) involvement of the left leg was reported in 88% of the patients. Outside pregnancy, left-sided DVT is only slightly more frequent (about 55%) (Ouriel, et al 2000). Little is known about the left-right distribution in the postpartum period. This information would be of interest for better understanding the origination of DVT in the postpartum period: left predominance may indicate that postpartum DVT results at least in some cases from a thrombus that already developed during pregnancy or delivery, while a more equal left-right distribution would suggest another pathophysiology such as a hypercoagulable state or tissue damage during delivery (Greer 1999). In addition the location of the thrombus in the postpartum period may also inform us whether mechanical factors (reduced flow, compression) are important for the origination of DVT. In pregnant women with thrombosis, the majority of thrombi are restricted to the proximal veins, without involvement of calf veins; of these, about two third were restricted to the iliac and/or femoral vein (Chan, et al 2010). In non-pregnant women, isolated proximal vein thrombi (i.e., without calf vein involvement), are very uncommon.

The aim of this study was therefore to investigate the left-right distribution and location of DVT in women up to 12 weeks postpartum, compared with that in pregnant and in non-pregnant women.
METHODS

Participants
The Multiple Environmental and Genetic Assessment of risk factors for venous
thrombosis (MEGA) study is a large, population-based case–control study. Data and
blood collection, ascertainment of venous thrombotic events, and DNA analysis
have been previously described in detail (Blom, et al 2005). Briefly, the MEGA study
included consecutive patients with a first diagnosis of venous thrombosis. Between
March 1999 and September 2004, patients were recruited from six regional antico-
agulation clinics, which monitor the anticoagulant therapy of all patients within a
well-defined geographical area in the Netherlands. In order to participate, patients
were required to be between the age of 18 and 70. Patients with severe psychiatric
problems or those unable to speak Dutch were for practical reasons considered
ineligible. Partners of patients were asked to participate as control subjects and
an additional control group was obtained using the random digit dialling (RDD)
method (Waksberg 1978). These control groups were not used in the current analy-
sis. The MEGA study was approved by the medical ethics committee of the Leiden
University Medical Center and all participants provided written informed consent.

Data collection
All participants in the MEGA-study completed a detailed questionnaire on demo-
graphic and lifestyle-related factors as well as risk factors for venous thrombosis.
Items covered in the questionnaire included the use of oral contraception or hor-
mone replacement therapy in the year before the index date, pregnancy or delivery
in the three months before the index date, and malignancy in the five years before
the index date. We defined the postpartum period as the period up to 12 weeks
after delivery (Kamel, et al 2014). Information on the location of the affected leg
was retrieved from the questionnaire and from discharge letters. DVT of the veins
of the calf were considered distal and those involving the remaining vein segments
(popliteal, femoral, external iliac, internal iliac, common iliac, or inferior cava) were
considered proximal, according to Martinelli et al (Martinelli, et al 2007).
Of the 4956 patients who participated, 2679 were women of whom 2625 provided information on whether they had been pregnant or not before the thrombotic event. Individuals who were over 50 years of age or had had a malignancy in the five years before the thrombosis date were excluded for this analysis, leaving 1608 patients. Patients with pulmonary embolism without DVT (n=501) or patients with thrombosis on both sides (n=7) or patients of whom the site of thrombosis was not known (n=86) were also excluded. In addition, 14 patients of whom delivery dates were unavailable and 10 patients who delivered between 13 weeks and 1 year before the index date were not included in the analyses, leading to 990 patients. We calculated proportions and their 95% confidence intervals (CIs) as well as differences in proportions and their 95% CIs.

RESULTS

Of the 990 included patients with a mean age of 37.2 years, 877 women were diagnosed with deep venous thrombosis of the leg and 113 with both deep venous thrombosis and pulmonary embolism. 67 out of 990 women (7%) were postpartum and 34 (3%) were pregnant at the time of thrombosis.

The majority of postpartum DVT occurred in the left leg (Table 1). In the entire postpartum period 70% (47 out of 67, 95% CI: 58-80) of women had a left-sided DVT. In week 1-3 postpartum, 71% (95% CI: 57-82) of the DVTs were left-sided, while this proportion was 64% (95% CI: 35-85) in week 4-6 and 75% (95% CI: 35-97) in week 7-12. During pregnancy, 85% of women (29 out of 34, 95% CI: 70-94) had a left-sided DVT. In contrast, in women who were not pregnant, the left-right difference was less strong with 57% (503 out of 889, 95% CI: 53-60) diagnosed with a left-sided DVT. Hence, the difference in proportions was -15% (95% CI: -30 - +3) between postpartum and pregnancy and 14% (95% CI: 1-24) between postpartum and non-pregnancy.
Table 1. Left-right distribution of postpartum, pregnant and non-pregnant DVT-patients.

<table>
<thead>
<tr>
<th></th>
<th>Left (n)</th>
<th>Right (n)</th>
<th>% left (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postpartum</td>
<td>47</td>
<td>20</td>
<td>70 (58-80)</td>
</tr>
<tr>
<td>Week 1</td>
<td>7</td>
<td>3</td>
<td>70 (40-89)</td>
</tr>
<tr>
<td>Week 2</td>
<td>19</td>
<td>6</td>
<td>76 (57-89)</td>
</tr>
<tr>
<td>Week 3</td>
<td>8</td>
<td>5</td>
<td>62 (36-82)</td>
</tr>
<tr>
<td>Week 4</td>
<td>4</td>
<td>1</td>
<td>80 (28-99)</td>
</tr>
<tr>
<td>Week 5</td>
<td>2</td>
<td>0</td>
<td>100 (16-100)</td>
</tr>
<tr>
<td>Week 6</td>
<td>1</td>
<td>3</td>
<td>25 (1-81)</td>
</tr>
<tr>
<td>Week 7 – 12</td>
<td>6</td>
<td>2</td>
<td>75 (35-97)</td>
</tr>
</tbody>
</table>

N indicates number; CI, confidence interval.

Table 2 shows the location of the thrombus in postpartum, pregnant and non-pregnant women of 656 patients of which data of thrombus location was available. In women in the postpartum period 28% of the DVTs (95% CI: 16-45) were restricted to the iliac and/or femoral region, compared to 55% (95% CI: 35-73) in pregnant women and 10% (95% CI: 8-13) in non-pregnant women.

Table 2. Location of thrombosis of postpartum, pregnant and non-pregnant DVT-patients.

<table>
<thead>
<tr>
<th></th>
<th>Postpartum (N=32)</th>
<th>Pregnant (N=22)</th>
<th>Non-pregnant (N=602)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% (CI)</td>
<td>N</td>
</tr>
<tr>
<td>Proximal</td>
<td>28</td>
<td>88 (72-95)</td>
<td>22</td>
</tr>
<tr>
<td>Iliac/femoral</td>
<td>9</td>
<td>28 (16-45)</td>
<td>12</td>
</tr>
<tr>
<td>other</td>
<td>19</td>
<td>59 (42-74)</td>
<td>10</td>
</tr>
<tr>
<td>Distal</td>
<td>4</td>
<td>13 (5-28)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Based on 656 cases of which data of thrombus location were available. N indicates number; CI, confidence interval.

The majority (78%) of the DVTs in the iliofemoral region during the postpartum period was at the left side, whereas DVTs in the distal region were more or less evenly distributed (Table 3). The left-right distribution according to location for post-partum women was in between that of pregnant (where 92% of the iliofemoral thrombi was left-sided) and non-pregnant women (68%).
In this study we found that in postpartum women with DVT 70% (47 out of 67) of the DVTs were left-sided. Although this predominance was less pronounced compared with the left predominance during pregnancy, it was still much higher than in non-pregnant women. Furthermore, the left-right distribution at proximal locations of the DVT was also in between that of pregnant and non-pregnant women. This overall pattern of post-partum DVT, that partly, but not completely, follows that of pregnant women, suggests that some DVTs may have developed already before delivery, and have taken some time to cause clinical symptoms.

The mechanism of left-sided predominance of DVT during pregnancy is not exactly known. One obvious explanation is the compression of the left iliac vein by the overlying right iliac artery (Cockett and Thomas 1965). Pressure by the enlarged uterus on the left iliac vessels likely potentiates this situation leading to local stasis or injury, resulting in left and proximal predominance during pregnancy. However, since left predominance has also been observed in the first and second trimester (Blanco-Molina, et al 2007, James, et al 2005) when an effect of an enlarged uterus is hardly as strong, a second mechanism needs to be considered. Possibly, this is a result of a decreased blood flow velocity during pregnancy. Macklon et al found that this flow velocity from week 15 of pregnancy was significantly slower in the left leg (Macklon, et al 1997).

For the consideration that some postpartum DVTs have developed already before delivery, knowledge on the time course of thromboembolic events after other triggers may be helpful. In patients with total hip or knee arthroplasty, the median

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**Table 3.** Left-right distribution and location of postpartum, pregnant and non-pregnant DVT-patients

<table>
<thead>
<tr>
<th></th>
<th>Postpartum (N=32)</th>
<th>Pregnant (N=22)</th>
<th>Non-pregnant (N=602)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>left</td>
<td>right</td>
<td>% left</td>
</tr>
<tr>
<td>Proximal</td>
<td>18</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>iliac/femoral</td>
<td>7</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>other</td>
<td>11</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>Distal</td>
<td>2</td>
<td>2</td>
<td>50</td>
</tr>
</tbody>
</table>

* Based on 656 cases of which data of thrombus location were available. N indicates number.
time of diagnosis of thromboembolism was 17 days and 7 days after surgery, respectively (White, et al 1998). Van Adrichem et al (van Adrichem, et al 2014) studied the time between the date of lower leg cast application and development of venous thrombosis. Almost two-thirds of the patients were diagnosed with venous thrombosis in the first month after immobilization (62.5%), about one-quarter in the second month (24.2%), and 13.3% in the third month. Peak incidence was two weeks after cast application. Also, in a case-control study on travel and venous thrombosis clinical symptoms occurring up to 12 weeks after travel were observed (Cannegieter, et al 2006). The occurrence of venous thrombosis was highest in the first week after travel, and slowly declined afterwards. Based on the examples above there seems to be a lag time of up to approximately three months between a trigger and a diagnosis of DVT with a peak between one and two weeks after the trigger. It is plausible that this also applies for pregnancy-related DVTs triggered by pregnancy, hence explaining the pattern that partly follows that of pregnancy.

An alternative explanation of the persisting left predominance during the postpartum period is persisting stasis in the left iliac vein after delivery. Macklon et al (Macklon and Greer 1997) observed an increased diameter and reduced blood flow in the left leg compared with the right leg in the postpartum period. They demonstrated that only by the 42\textsuperscript{nd} postnatal day the diameter and flow velocity had returned to levels observed in early pregnancy. In a study by Calderwood et al (Calderwood, et al 2007) significant venous dilatation was also still present at 6 weeks post-partum compared with the 15 weeks gestation value. However, this study found no significant difference between measurements in the right leg compared with the left leg. Finally, we cannot exclude the possibility that the delivery itself may be associated with a temporary increased compression of the left iliac vein and stasis.

The left right distribution of DVTs in the postpartum period has not been studied extensively. James et al (James, et al 2005) found slightly more DVTs in the left leg (9/7, 56%) compared with the right leg. This is in accordance with Blanco-Molina et al (Blanco-Molina, et al 2007), who found that the left leg was affected in 55% (26/21) of the patients in the postpartum period. Our proportion of left DVTs is higher (70%) compared with these publications. This might be due to the smaller
sample sizes or different characteristics of the study populations (e.g. 64% of postpartum patients had caesarean section in the study by Blanco-Molina).

Our study has some limitations. First, we studied a relatively small number of cases. Therefore the confidence intervals were wide. Nevertheless, we found consistently increased percentages of thrombosis on the left side in the postpartum period compared with non-pregnancy. Furthermore, an underestimation of the number of cases in the first and second trimester may have occurred, since we recruited participants from anticoagulation clinics. Women with a thrombosis in the first or second trimester are more likely to be treated with low molecular weight heparin only than women with a thrombosis in the third trimester, who are referred to the anticoagulation clinic for additional treatment after child delivery. While this should not have affected the left-right distribution, the number of cases in the first and second trimester in this study was indeed low, so these results should be interpreted with caution. A third limitation is the absence of information about the mode of delivery and length of labour in our study. It would have been interesting to investigate differences in left-right distribution of thrombosis for these factors.

In summary, we found that the left predominance of DVT seen in pregnancy persisted in the postpartum period. This suggests that some DVTs already developed before delivery, but only led to clinical symptoms in the postpartum period.

Acknowledgements
S.C. Cannegieter, L.P.B. Elbers and V.E.A. Gerdes designed the study. A. Venemans-Jellema and S.C. Cannegieter analyzed the data. A. Venemans-Jellema wrote the paper. L.P.B. Elbers, S. Middeldorp, V.E.A. Gerdes and S.C. Cannegieter revised the paper critically. A. Venemans-Jellema, L.P.B. Elbers, S. Middeldorp, V.E.A. Gerdes and S.C. Cannegieter did the approval of the version to be published. The authors wish to thank the directors of the Anticoagulation Clinics of Amersfoort (M.H.H. Kramer), Amsterdam (M. Remkes), Leiden (F.J.M. van der Meer), The Hague (E. van Meegen), Rotterdam (A.A.H. Kasbergen), and Utrecht (J. de Vries-Goldschmeding), who made the recruitment of patients possible. The interviewers J. C.M. van den Berg, B. Berbee, S. van der Leden, M. Roosen and E. C. Willems of Brilman also

We express our gratitude to all individuals who participated in the MEGA study. This study was supported by grant NHS 98.113 from the Netherlands Heart Foundation, grant RUL 99/1992 from the Dutch Cancer Foundation, and grant 912-03-033|2003 from the Netherlands Organization for Scientific Research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
REFERENCE LIST


