**Moderate cross-sex hormone-induced changes of hemostatic variables in transgender individuals. (Cardiovascular)**

N.L.D. Selier, S.C. Cannegieter MD PhD¹, A. Venemans-Jellemans PhD¹, M. den Heijer MD PhD²,³

¹Department of Clinical Epidemiology LUMC, ²Department of Endocrinology VUmc, ³Center of Expertise on Gender Dysphoria VUmc.

**Background**

- Oral contraceptives (OC) expose women to changes in the coagulation system and a higher risk of venous thrombosis.¹
- Different effects of transdermal and oral estrogen are observed in OC users and transgender individuals.¹ ²
- Cross-sex hormone treatment (CSHT) is associated with venous thrombosis.² ³
- The effect of testosterone suppletion (TS) on coagulation still remains to be elucidated ² ⁴

**Objective**

- Assess whether CSHT induces similar changes in hemostatic factors in transgender individuals as observed in biological men and women receiving hormone suppletion. In addition, it will be assessed whether dosage form influences the change in hemostatic factors.

**Methods**

- Analyzing plasma samples of 100 female-to-male (FTMs) and 98 male-to-female (MFTs) individuals at baseline and after 12 months of CSHT.
- Determining the levels of hormone-sensitive factors, e.g. factor II, IX, XI, fibrinogen, protein C, free protein S and normalized activated protein C sensitivity ratio (nAPCsr).
- Investigating whether the dosage form affects the alteration in coagulation.
- Comparing the observed changes with those reported in oral contraceptives and androgen suppletion.

**Results**

- **FTMs**: Increase in factor IX, free protein S and nAPCsr, decrease in factor II, XI, protein C and fibrinogen.
- **MFT**: Increase in factors II, IX, XI, fibrinogen, free protein S and nAPCsr, decrease in protein C.
- No differences in hemostatic factor alterations between dosage forms. There was no influence of age (data not shown).

**Discussion**

- **FTMs**: The prothrombotic factor IX increases, while the rest seems to shift towards an anti-thrombotic state.
- **MFTs**: The nAPCsr shifts to an anti-thrombotic state, in contrast to the remaining factors.
- **No difference in change between dosage forms found.**

**Conclusion**

- **FTMs**: No anti- or prothrombotic state is induced in FTMs under CSHT, with similar changes compared to those found in TS.
- **MFTs**: Moderate CSHT-induced prothrombotic state in MFTs, with similar changes compared to those observed in OC users, except for protein C and the nAPCsr.

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3Proctor et al. Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transgender people. J Clin Endocrinol Metab. 2020;95(12):8723-8
4Jayon et al. Comparative safety of testosterone dosage forms. JAMA Int Med. 2015;175(7):1187-97

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**Table 1. Linear regression coefficients and 95%CI for the differences in the ratios of the measured hemostatic factors between the dosage forms in MFT and FMT individuals, nAPCsr: normalized APC sensitivity ratio, FMTs: female-to-males individuals, intramuscular injection vs. transdermal use, MFT: male-to-females individuals, oral vs. transdermal use.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>MFT subjects (n=98)</th>
<th>FMT subjects (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>0.014 (0.025, 0.057)</td>
<td>-0.028 (-0.076, 0.019)</td>
</tr>
<tr>
<td>Factor IX</td>
<td>-0.068 (-0.166, 0.033)</td>
<td>-0.065 (-0.171, 0.041)</td>
</tr>
<tr>
<td>Factor XI</td>
<td>-0.045 (-0.183, 0.087)</td>
<td>-0.055 (-0.074, 0.064)</td>
</tr>
<tr>
<td>Protein C</td>
<td>0.004 (0.036, 0.064)</td>
<td>-0.051 (-0.107, 0.004)</td>
</tr>
<tr>
<td>Protein S</td>
<td>0.045 (0.003, 0.085)</td>
<td>0.034 (-0.063, 0.112)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.070 (0.023, 0.154)</td>
<td>-0.061 (-0.178, 0.056)</td>
</tr>
<tr>
<td>nAPCsr</td>
<td>-0.004 (-0.069, 0.062)</td>
<td>-0.033 (-0.080, 0.073)</td>
</tr>
</tbody>
</table>