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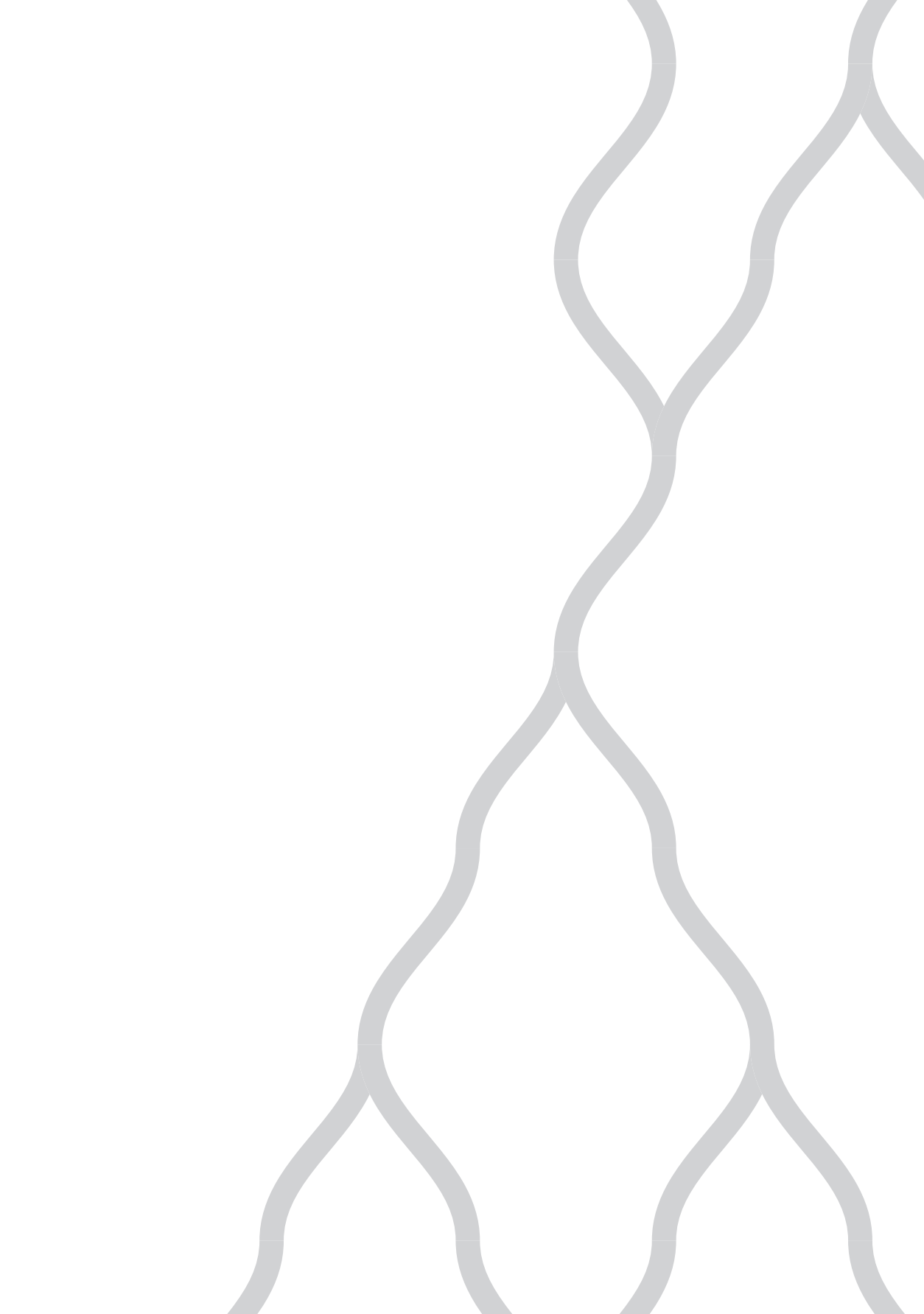



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Effect of ethinylestradiol
dose and progestagen in
combined oral contraceptives
on plasma sex hormone
binding globulin levels in
premenopausal women

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The effect of a combined oral contraceptive (COC) on sex hormone binding globulin (SHBG) levels may be an indicator for venous thrombosis risk of the COC involved (1;2). SHBG is a plasma glycoprotein primarily produced in hepatocytes that binds the sex steroid hormones testosterone and 17 β -estradiol but not ethinylestradiol. Users of COC containing a third generation progestagen have higher SHBG levels than second generation progestagen users (1;2) reflecting the difference in venous thrombosis risk. In accordance with the hypothesis that SHBG levels are a marker of venous thrombosis risk, SHBG levels in COC users are positively associated with thrombin generation-based activated protein C resistance (APC resistance) (2). APC resistance has been shown to predict venous thrombosis risk in both men and women.

If SHBG levels can be considered a marker for venous thrombosis and ethinylestradiol is the main compound in COC causing venous thrombosis, then the ethinylestradiol dose in COC should be reflected in SHBG levels. The main aim of this study was to determine whether an increase in ethinylestradiol dose result in higher SHBG levels in healthy premenopausal women.

Participants were selected from a large case-control study on venous thrombosis, i.e., the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study (3) and from a crossover study where women were asked to switch from their current contraceptive to either a COC containing drospirenone or levonorgestrel, i.e., the DRSP (drospirenone/ethinylestradiol) study (2). From the MEGA study, female control subjects, i.e. women without venous thrombosis were selected. From the DRSP study, data of women before switching to a specific COC were used. We excluded women with known environmental thrombotic risk factors. A total of 191 healthy premenopausal women using COC were included (181 from the MEGA study and 101 the DRSP study).

In the MEGA study, whether the women were menstruating at venipuncture was recorded; however, blood was drawn randomly during the four week cycle of pill use (3 weeks of pill use followed by a pill-free week). In the DRSP study, blood was drawn between days 18 and 21 of the four week cycle of pill-use. SHBG levels (nmol/L) were measured with an immunometric assay (Immulite; Siemens Healthcare Diagnostics, Tarrytown, NY, USA) and without knowledge of the COC used or any other of the participant's characteristics.

The ethinylestradiol dose was categorised into 20 μ g, 30 μ g, \geq 35 μ g per pill and triphasic preparations, which have a varying ethinylestradiol and progestagen doses over 21 days. The effect of progestagen and dose of ethinylestradiol on SHBG levels was assessed using linear regression analysis. The analysis was adjusted for study and to ensure that the effect of ethinylestradiol dose on SHBG levels is independent of the progestagen used, we adjusted this analysis for the progestagen used in COC. Regarding the effect of progestagen in COC on SHBG levels, the analysis was restricted to subjects taking 30 μ g ethinylestradiol per contraceptive pill. To reduce random variation in SHBG levels, the analyses were adjusted for whether women were menstruating at the time of venipuncture, and for age and BMI which can influence SHBG levels. Results were expressed as mean differences with 95% confidence interval.

Overall, women were about 33 years (range: 18-49) and had a BMI of 23.3 kg/m² (range: 15.7-37.9). The mean SHBG plasma level was 139.5 nmol/L (95%CI: 131.2-147.8, IQR 99.8, range 28.0-390.9). In the MEGA study, SHBG levels were compared between menstruating women versus women taking a pill at venipuncture. 11 women were menstruating at time of venipuncture and the mean SHBG level was 102.1 nmol/L (95%CI: 59.1-145.0) whereas the level in women who were taking a pill (N=163) was 145.4 nmol/L (95%CI: 134.3-156.6); mean difference: 43.4 nmol/L (95%CI: -1.0 -87.7). When we restricted our analysis to women receiving 30 µg of ethinylestradiol, users of desogestrel, gestodene, and drospirenone had approximately 100 nmol/L higher SHBG levels than users of levonorgestrel (Table). Adjustment for factors influencing SHBG levels did not change these results. After adjustment for progestagen, users of ≥35 µg of ethinylestradiol had higher SHBG levels than users of 20 µg (Table). Also users of triphasic contraceptives had higher SHBG levels than users of 20 µg of ethinylestradiol. The SHBG levels were only slightly higher in users of 30 µg compared with 20 µg of ethinylestradiol. Adjustment for factors influencing SHBG levels did not change these results. The same results were observed when the analysis of ethinylestradiol dose and SHBG levels was restricted to most commonly used progestagens (levonorgestrel, desogestrel and gestodene) or separately per these progestagens, although the number of women per category became very small. Furthermore, similar results were observed when the analysis was performed per study. Additional to the progestagens levonorgestrel, gestodene, desogestrel, and drospirenone, 30 women used cyproterone acetate. The mean SHBG level in users of cyproterone acetate was high at 215.9 nmol/L (95%CI: 199.7-232.1); much higher than in users of COC containing levonorgestrel with 30 µg ethinylestradiol (mean difference: 135.4 nmol/L, (95%CI: 116.9-153.9) adjusted for study and menstruating at venipuncture).

One other paper evaluated the effect of different COC on SHBG levels and provided information on ethinylestradiol dose per progestagen (4). However, no direct comparisons between ethinylestradiol dose and SHBG levels were made; therefore, no conclusions could be drawn on whether the ethinylestradiol dose in different COC was reflected in SHBG levels. The positive association between ethinylestradiol dose and SHBG levels is in line with previous findings regarding venous thrombosis risk. Lidegaard *et al.* (5) reported that compared to users of oral contraceptive preparations containing 30-40 µg ethinylestradiol, the risk of venous thrombosis was higher in users of 50 µg ethinylestradiol (OR 1.6, 95%CI: 0.9-2.8) and lower in users of 20 µg (OR 0.6, 95%CI: 0.4-0.9). In the MEGA study, we also demonstrated that within users of oral contraceptives containing levonorgestrel, the risk of venous thrombosis was higher in users of 50 µg ethinylestradiol than in users of 30 µg (OR adjusted for age 2.2, 95%CI: 1.3-3.7) (6). The risk of venous thrombosis was lower in users of 20 µg than in users of 30 µg; both in users of progestagens gestodene (OR 0.3, 95%CI: 0.2-0.7) and desogestrel (OR 0.7, 95%CI: 0.4-1.2).

Unfortunately, ethinylestradiol levels could not be measured directly because the blood was drawn at random during the four week cycle of pill use in the MEGA study and without considering the hours after a pill was taken, which both have a significant influence on ethinylestradiol levels (7). The hours after a pill was taken do not influence the SHBG levels, because of a half-life of SHBG of about 7 days. However, data were available on factors that were previously shown to

influence SHBG levels and on whether women were menstruating at venipuncture. Furthermore, regarding the analysis between ethinylestradiol dose and SHBG levels, we would have preferred to restrict our analysis to one progestagen; however, the number of women per category became very small leading to unreliable estimates. We combined two studies that differed in their design, which may have affected our results. However, the same results were observed in an analysis per study. Strengths of our study were that we included a relative large number of COC users who were using many different types of prescriptions. Furthermore, mean SHBG levels as well as the difference in SHBG levels between different progestagens in COC users were in the same range as observed in other studies.

In conclusion, SHBG levels reflect the ethinylestradiol dose used in COC independent of the progestagen used. Since ethinylestradiol is important in the pathogenesis of venous thrombosis in COC users, these findings strengthen the idea that SHBG levels in COC users may be seen as a marker for venous thrombosis risk.

Table: Mean SHBG levels and adjusted differences per progestagen or per ethinylestradiol dose

| Variable | N (%) | Mean SHBG levels * (95% CI) | Adjusted difference * (95% CI) | Adjusted difference † (95% CI) |
|----------------------|----------|--------------------------------|-----------------------------------|-----------------------------------|
| Progestagen ‡ | | | | |
| Levonorgestrel | 99 (60) | 80.3 (72.3 to 88.2) | Reference | Reference |
| Desogestrel | 36 (22) | 193.0 (179.9 to 206.2) | 112.8 (97.3 to 128.2) | 116.9 (101.1 to 132.7) |
| Gestodene | 13 (8) | 160.9 (138.8 to 183.0) | 80.6 (57.3 to 104.0) | 81.5 (56.3 to 106.6) |
| Drospirenone | 17 (10) | 191.3 (171.8 to 210.9) | 111.1 (89.8 to 132.3) | 114.3 (93.1 to 135.5) |
| EE dose | | | | |
| 20 µg | 31 (11) | 101.6 (80.4 to 122.8) | Reference | Reference |
| 30 µg | 165 (60) | 115.3 (103.9 to 126.8) | 13.8 (-7.1 to 34.6) | 13.9 (-8.3 to 36.2) |
| ≥35 µg | 45 (16) | 247.0 (200.6 to 293.4) | 145.4 (87.1 to 203.7) | 136.4 (64.5 to 208.3) |
| Triphasic | 32 (12) | 152.5 (132.7 to 172.4) | 51.0 (22.8 to 79.1) | 50.9 (20.7 to 81.1) |

CI, confidence interval; EE, ethinylestradiol.

* Adjusted for progestagen in the case of ethinylestradiol dose and adjusted for study

† Further adjusted for age, BMI and menstruating at venipuncture

‡ Restricted to 30 µg ethinylestradiol

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