Anti-androgen contraceptive pills and higher risk of venous thromboembolism

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Venous thromboembolism (VTE) is associated with the use of combined oral contraceptives (OCs). Older contraceptives, containing the second-generation progestogens levonorgestrel or norethisterone, are associated with up to a three-fold increased risk of VTE compared with otherwise similar non-users. Third-generation progestogens, such as desogestrel or gestodene, are in turn associated with a two-fold higher risk of VTE compared to second-generation OCs. However, the association of newer formulations, including OCs containing the anti-androgen cyproterone acetate (CPA) and the fourth-generation progestin, drospirenone (DRSP) which also has anti-androgenic activity, with VTE, may be less well known in New Zealand. In a study reported in The New Zealand Medical Journal in 2004, we compared the frequency of specific COC use in patients with VTE with the expected frequency derived from national prescription data, and found that the association of VTE with anti-androgen use is at least as strong as with third-generation OC use.

In this study, we report a secondary analysis of case-control studies of the association of VTE with use of OCs containing CPA or DRSP.

The two case-control studies combined for this study used similar methodology and questionnaires to investigate the association between occupational seated immobility and other factors, and VTE. The first study used data from 196 consecutive patients with VTE attending the Capital & Coast District Health Board (CCDHB) VTE clinics and 197 controls admitted to the CCDHB Coronary Care Unit (CCU) between February 2007 and February 2009. The second study used data from 200 new consecutive patients attending the CCDHB VTE clinics and 200 controls attending the CCDHB fracture clinic with upper limb injuries between October 2011 and January 2013.

In both studies, cases were patients to be aged between 18 and 65 years, with a confirmed diagnosis of VTE within the last 6 months. Controls were patients aged between 18 and 65, admitted to CCU in the first study, or with a traumatic upper limb injury for any reason other than VTE, in the second study.

The data collected included age, sex, information about the index event and risk factors for VTE. Thrombophilia screens were only inconsistently available in some cases, were not available for the controls, and were not included as a risk factor. Logistic regression estimated the association between oral contraceptive use and VTE adjusted for age, BMI, family history of VTE, personal history of VTE, history of recent surgery, and history of recent travel. SAS version 9.3 was used.

There were 189 cases and 145 controls who were women. The univariate and multivariate analyses confirmed the known associations of VTE with obesity, personal and family history of VTE, and surgery. No OC was used in 141/189 (75%) cases and 135/145 (93%) controls. Anti-androgen OC use (CPA or DRSP) was present in 12 (6%) cases and 1 (0.7%) controls; and other OC use in 36 (19%) cases and 9 (6.2%) controls. The multivariate odds ratio (OR) for association between VTE and anti-androgen OC use compared to none was 20.0 (95% CI 2.4 to 165), P=0.006; and for other OC use compared to none 5.5 (95% CI 2.3 to 13.2), P<0.001.

This secondary analysis found a strong association with anti-androgen COC use or other OC use and VTE in New Zealand women. Limitations of the study are that this was a post hoc analysis, the estimates...
have very wide confidence intervals related to the small sample size, and that the control groups (CCU patients and those with upper limb fractures) may have a biased use of the OC due to age or other factors.

The association with VTE identified here is consistent with a large study reported from UK primary care datasets, which included data about COCs containing desogestrel, gestodene, CPA and DRSP. The reported associations in that study were that the newer COCs were associated with a risk of VTE between 3.6- to 4.3-fold compared with non-use and by around two-fold compared with COCs containing second generation progestogens. This is also consistent with the report of a Cochrane systematic review and meta-analysis.

Media commentary around VTE risk and OCs can have a strong focus on individual experiences and outcomes, resulting in highly emotional debates, concern and confusion for women. For example, it may not be reported that pregnancy and the post-partum period have a stronger association with VTE than that reported for any COC. No currently available COC, or any likely to be developed in the future, will be 100% effective at preventing conception, be completely risk free, tolerated by all users, and associated with non-contraceptive benefits that justify and facilitate their long-term use. However, prescribers should be aware of the differential risk, and in particular that the anti-androgen agents CPA and DRSP, together with third generation COCs, have a greater VTE risk than the second generation COCs. As in all health-care practice, apply this evidence to the practicalities of advice and prescription of contraception based on individual risk-benefit assessments and informed patient choice and decisions.

**REFERENCES:**


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