Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis

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CRD summary
The authors concluded that progestin-only contraception use was not associated with increased risk of venous thromboembolism compared with hormonal contraception non-use; the association between injectable progestins and thrombosis required further study. With a caveat regarding unclear presence of individual study biases, the conclusions seem reliable but may not be entirely generalisable to high thrombotic risk populations.

Authors' objectives
To evaluate the risk of venous thromboembolism associated with progestin-only contraception, and whether risk differs according to mode of drug delivery.

Searching
PubMed, EMBASE, and the Cochrane Database of Systematic Reviews were searched to December, 2011. The search was restricted to studies in English; search terms were reported. Reference lists of included articles from a previous relevant meta-analysis and a review were handsearched to locate further studies.

Study selection
Eligible studies had one of the following study designs: randomised trial or case-control, cohort, or cross-sectional study (prospective or retrospective). Treatment arms needed to include use of progestin-only contraceptives and control arms with no hormone use. Independent analysis of pre-menopausal women was required for the incidence outcome of venous thromboembolic events. One or more of three administration routes (oral, injectable, intrauterine) were considered.

All but one of the included studies evaluated patients taking a progesterone-only pill; some included patients with a depot or intrauterine progestin-only contraceptive. Inclusion criteria differed across the studies. Various progestin drugs had been administered in varying doses. Most studies reported average baseline risk of venous thromboembolic event in patients; two studies reported this risk as being high (based on subjective assessment according to inclusion criteria).

Two reviewers independently screened studies for inclusion and two additional reviewer checked the sub-set of included studies. Mutual consensus was required for the inclusion of a study in the analysis.

Assessment of study quality
Quality of included studies (all observational) was assessed according to comparison of exposed and unexposed patients or case and control groups, use of matching or stratification, and covariates used for adjustment in analyses.

Two reviewers independently assessed the quality of the included studies.

Data extraction
Data were extracted for users of progestin-only oral contraceptives versus non-users to calculate risk ratios and 95% confidence intervals. Based on previous reports, venous thromboembolic events were assumed to have a low incidence (<10% a year) in women under 50 years of age taking oral contraceptives.

Two reviewers independently extracted the data.

Methods of synthesis
Risk ratios and 95% confidence intervals were pooled using the random-effects DerSimonian and Laird method. Statistical heterogeneity was assessed using the $I^2$ statistical test. Secondary analysis involved calculation of adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for subgroups (according to route of administration) and for raw event data. Sensitivity analyses (excluding selected subgroups) were performed.
Results of the review

Eight observational studies were included in the review (8,900 patients, where reported): five case-control studies (6,658 patients) and three retrospective cohort studies (2,242 patients). Total number of patients per study ranged from 202 to 3,052 (where reported). All case-control studies had matched patients by age; two also matched according to medical record number or general practice. Two studies performed stratification. All of the studies had adjusted for covariates in multivariate analyses.

No statistically significant difference was found between users of progestin-only contraception versus non-users for risk of venous thromboembolic event (adjusted RR 1.03, 95% CI 0.76 to 1.39; eight studies). Low statistical heterogeneity was shown ($I^2=24\%$). A similar result, with no statistical heterogeneity ($I^2=0\%$), was shown when the analysis was re-performed using crude data (excluding one study for which this was unavailable).

There were no statistically significant differences in venous thromboembolic risk between users and non-users of progestin-only pills (RR 0.90, 95% CI 0.57 to 1.45; seven studies) or between users and non-users of a progestin intrauterine device (RR 0.61, 95% CI 0.24 to 1.53; two studies).

Risk of a venous thromboembolic event was statistically significantly higher for users of injectable progestin versus non-users (RR 2.67, 95% CI 1.29 to 5.33; two studies). No statistical heterogeneity was indicated ($I^2=0\%$).

Authors' conclusions

Overall, the use of progestin-only contraception was not associated with an increased risk of venous thromboembolism compared with non-users of hormonal contraception. The potential association between injectable progestins and thrombosis requires further study.

CRD commentary

The review question was clear and inclusion criteria appeared sufficiently replicable. Relevant databases were accessed and efforts were made to reduce error and bias during the review process. The rating system for quality was not clearly reported, however observational studies were liable to multiple potential biases. Study details were presented where possible.

Clinical and methodological differences existed between the studies, but low levels of statistical heterogeneity between studies were indicated (where reported). A sensitivity analysis using crude data also revealed similar results for the main meta-analysis on which the authors' conclusion was based. The authors admitted that only two of the studies in the main meta-analysis specifically enrolled high thrombotic risk populations and they were of small sample sizes, so it was unclear whether such findings might also apply to high-risk populations. The authors also stated that studies were limited in their adjustment for confounding factors in analyses and that the small number of individual studies restricted them from assessing publication or reporting biases. Selection bias was possible with studies investigating injectable progestins. With a caveat regarding unclear presence of individual study biases, the conclusions appear reliable though they may not be entirely generalisable to high thrombotic risk populations.

Implications of the review for practice and research

Practice: The authors stated that the presented evidence supported use of all modes of progestin contraception for women at all levels of thrombotic risk, but that only two of the studies enrolled high risk populations. In the interim they suggested consideration of non-injectable forms of progestin-only contraception for highest risk women.

Research: The authors stated that further research was required to confirm findings linking use of injectable progestins with increased thrombotic risk.

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Bibliographic details

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.