MOTHERISK ROUNDS

The Effectiveness of Folate-Fortified Oral Contraceptives in Maintaining Optimal Folate Levels to Protect Against Neural Tube Defects: A Systematic Review

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Abstract

Objective: To conduct a systematic review evaluating the effectiveness of a folate-fortified oral contraceptive preparation in increasing blood folate concentrations to levels providing optimal protection against neural tube defects (> 906 nmol/L).

Methods: We searched Medline, EMBASE, Web of Science, and the Cochrane Library for human studies published from inception to June 2013 that evaluated oral contraceptive use and folate status. Case–control studies, cohort studies, and clinical trials were included. Efficacy and bioequivalence data were evaluated from included studies.

Results: Overall, efficacy and bioequivalence data for the folate-fortified oral contraceptive show that it is at least as effective as folic acid alone in raising blood folate concentrations, and that the concomitant administration of folate with the oral contraceptive component does not affect its absorption or kinetics.

Conclusion: A folate-fortified oral contraceptive preparation provides an option for women to maintain blood folate levels, especially those who may be planning a family after the cessation of oral contraceptive therapy.

Résumé

Objectif : Mener une analyse systématique de l'efficacité d'un contraceptif oral enrichi en folate pour ce qui est d'accroître les concentrations sanguines en folate jusqu'aux niveaux offrant une protection optimale contre les anomalies du tube neural (> 906 nmol/l).

Méthodes : Nous avons mené des recherches dans Medline, EMBASE, *Web of Science*, et la *Cochrane library* en vue d'en tirer les études menées chez l'homme, publiées entre le début de nos travaux et juin 2013, qui ont évalué l'utilisation de contraceptifs oraux et les taux de folate. Les études cas-témoins, les études de cohorte et les essais cliniques ont été admis aux fins de notre analyse. Les issues ont été soumises à une méta-analyse faisant appel à un modèle à effets aléatoires.

Résultats : De façon globale, les données sur l'efficacité et la bioéquivalence en ce qui concerne les contraceptifs oraux enrichis en folate indiquent que ceux-ci sont au moins aussi efficaces que l'acide folique administré seul pour ce qui est d'augmenter les concentrations sanguines en folate; elles indiquent également que l'administration concomitante de folate et d'un composé contraceptif oral n'en affecte ni l'absorption ni la cinétique.

Conclusion : Les contraceptifs oraux enrichis en folate offrent une option aux femmes pour le maintien de leurs taux sanguins de folate; cette option s'avère particulièrement adaptée aux femmes qui pourraient souhaiter devenir enceintes à la suite de l'abandon de la contraception orale.

Key Words: Family planning, oral contraceptive, folate, prenatals, pregnancy

Competing Interests: None declared.

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INTRODUCTION

Because an estimated one half of pregnancies are unplanned, many women are unable to undergo prenatal counselling and have supplementation with folic acid to prevent neural tube defects.[1,2] Current data suggest that 45.7% women of childbearing age become pregnant within three months of stopping use of oral contraception,[3] and only 28.1% take folic acid before conception.[4] Folic acid supplementation is associated with a reduction in the risk of NTDs that occur in the four weeks following conception; at this point, many women may not even know that they are pregnant.[5] Hence, it is critical that women begin supplementation with folic acid in the periconceptional period, at least three months before becoming pregnant.[6]

A novel folate-fortified oral contraceptive preparation (Yaz Plus) containing ethinyl estradiol 0.02 mg, drospirenone 3 mg, and levomefolate calcium 0.451 mg in each tablet, was approved by Health Canada in 2010 for the purpose of raising serum folate levels in women who are using it as a method of contraception.[7,8] The objective of this study was to systematically review the data available on this preparation in order to evaluate its potential as an alternative to current folic acid supplementation therapy.

METHODS

The databases Medline (from 2005 + in process/non-indexed), EMBASE (from 2005), Web of Science and the Cochrane Central Register of Controlled Trials (since 2005) were searched for articles published from their inception to June 2013. A health librarian was consulted to develop a comprehensive search strategy using the search terms "folic acid," "folate and derivatives," "pregnancy," "periconceptional period," "oral contraceptives," and related terms using the exploded versions of subject headings and their associated key words. No restrictions were placed on the language of the articles, the type of publication or study design, or the study model used (in vitro, animal, or clinical).

Studies were initially screened independently by two reviewers for relevance through title and abstract, and included all studies with the combination of the terms "oral contraceptives," "folate," "pregnancy," and their associated derivatives. Screening at the second stage required a review of the methods, and case reports, editorials, letters to the editor, and reviews were excluded, again by the two reviewers independently. Only clinical studies, both observational and interventional, were included if they evaluated folate status in women using oral contraceptives containing folic acid. Conference abstracts showing preliminary results that were part of a larger published study were excluded at this stage to prevent double-counting of data. All peer-reviewed publications that met the inclusion criteria (full articles or conference abstracts) were included.

Standardized Cochrane data extraction forms were used to collect study details and data from each included article, and were completed independently by two reviewers. No restrictions were placed on language during the search. Extracted data included information on study design, setting, sample size, participant characteristics, type of OC used, timing and measurement of exposure, blood folate concentrations and methods used to analyze them, a standardized study quality/bias assessment tool, and a summary of key results. PRISMA guidelines were followed throughout all steps within the systematic review.

ABBREVIATIONS

AUC	area under the curve
NTD	neural tube defect
OC	oral contraceptive
RBC	red blood cell

RESULTS

The pooled searches from all databases resulted in 23 340 citations being extracted. After the removal of 9897 duplicates, 68 articles were included based on selection for relevance, after a review of the title and the abstract as necessary. Of these, 33 articles were selected after a review of the title, abstract, and methods. Ultimately, five articles met the final inclusion criteria.[8–12]

The five studies presented in this category are summarized in the Table.

Bioequivalence studies

Wiesinger et al.[9] conducted a randomized, open-label, three-period, crossover study at a single centre in Germany to evaluate the bioequivalence of a new folate-supplemented oral contraceptive preparation (containing ethinyl estradiol, drospirenone, and levomefolate calcium) with its non-supplemented counterpart (containing ethinyl estradiol and drospirenone) and levomefolate calcium (5-methyl-THF) separately. Within this intra-individual crossover design, each participant was randomized to a treatment sequence that included:

1) ethinyl estradiol 0.03 mg/drospirenone 3 mg,
2) ethinyl estradiol 0.03 mg/drospirenone 3 mg/levomefolate calcium 0.451 mg, and
3) levomefolate calcium 0.451 mg.