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.

Studies on the novel folate-fortified oral contraceptive

Reference, year, and location	Study design and sample size	Patient characteristics	Intervention/Drug	Outcomes	Assessment of folate status	Timing of outcome evaluation	Supplement use and nutritional status	Summary of results
Blode et al., 2012[10] *Netherlands*	Randomized, open-label, intra-individual crossover study 40 women	– Healthy adult female volunteers with regular menstrual cycles – Supplement use was part of exclusion criteria	Single dose ingestion: – EE 0.02 mg/drsp 3 mg – EE 0.02 mg/drsp 3 mg/ levomefolate Ca 0.451 mg – levomefolate Ca 0.451 mg	AUC_{∞} C_{max} Other pharmacokinetic variables	LC/MS	Treatments started b/w day 3–6 of menstrual cycle 1 cycle washout period	Extensve dietary restrictions 3-day weighted diet records	– Bioequivalence was demonstrated for all components: EE, drsp and levomefolate calcium, since the GMRs and CIs were within 80–125% for AUC_{∞} and C_{max} values of each component
Wiesinger et al., 2012[9] *Germany*	Randomized, open-label, intra-individual crossover study 41 women	– Healthy women with regular menstrual cycles – Excluded if formerly used supplements	Single dose ingestion: – EE 0.03 mg/drsp 3 mg – EE 0.03 mg/drsp 3 mg/ levomefolate Ca 0.451 mg – levomefolate Ca 0.451 mg	C_{max} AUC Other pharma-cokinetic variables for EE, drsp, L-5-methyl-THF	LC/MS	Treatments started b/w day 3–6 of menstrual cycle 1 cycle washout period	Extensive dietary restrictions 3-day dietary records	– The GMRs and CIs were between 80–125% for AUC and C_{max} values, thus demonstrating bioequivalence for EE, drsp and levomefolate calcium – No sig. effects on the rate and extent of absorption of L-5-methyl-THF following concomitant administration with EE and drsp.
Bart Sr et al., 2012[11] *United States*	Randomized, double-blind, parallel-group study 196 EE/drsp/ levomefolate 66 EE/drsp	– Healthy women from urban and rural centres, as well as diverse ethnicities included – 3:1 randomization scheme	EE 0.02 mg/drsp 3 mg/levomefolate Ca 0.451 mg vs. EE 0.02 mg/drsp 3 mg	RBC folate Plasma folate	L.casei microbio-logical assay	Blood samples b/w day 25–28 of menstrual cycle	Folate supplement use recorded but not reported Short folate frequency questionnaire	– No sig. difference in demographic characteristics or treatment compliance between the two groups. – RBC folate conc. were sig. higher in the EE/drsp/levomefolate group compared to EE/drsp ($P < 0.0001$) after 24 weeks of supplementation – Plasma folate conc. were also sig. different between the two groups by week 24 ($P < 0.0001$)
Diefenbach et al., 2013[12] *Germany*	Randomized, double-blind, parallel-group study 75 EE/drsp/ levomefolate 75 EE/drsp+ folic acid	– Healthy women recruited from the local population – Excluded if regularly used supplements – 1:1 randomization scheme – 2 phases in the study: invasion phase (24 weeks), then elimination phase (20 weeks)	EE 0.03 mg/drsp 3 mg/levomefolate Ca 0.451 mg + placebo vs. EE 0.03 mg/drsp 3 mg + folic acid	RBC folate Plasma folate	Microbio-logical assay	Fasting blood samples	Supplements not used Standardized food questionnary (University of Bonn)	– Mean dietary folate intake and compliance was similar between the two groups – The GMRs for the AUC of plasma and RBC folate were comparable between the two groups. – Mean conc. of plasma and RBC folate were similar between groups by week 24, but were slightly higher in the EE/drsp/levomefolate group. – In the elimination phase, plasma and RBC folate conc. were similar in the two groups after 20 weeks of stopping tx, with slightly higher conc. in the EE/drsp/levomefolate group.
Castano et al., 2014[8] *United States*	Secondary analysis from randomized, double-blind study 196 EE/drsp/ levomefolate 66 EE/drsp	Same as Bart et al. (2012)[11]	EE 0.02 mg/drsp 3 mg/ levomefolate Ca 0.451 mg vs.EE 0.02 mg/drsp 3 mg	Dietary folate equivalents (DFEs) based on diet, supplement use and OC contribution % of pop. with optimal NTD protection	Same as Bart et al. (2012)[11]	Same as Bart et al. (2012) [11]	26% of participants reported supplement use Short food frequency questionnaire (Columbia University)	– No sig. difference in DFEs when accounting for diet and supplement use between the EE/drsp/ levomefolate vs. EE/drsp group – Sig. differences between groups by 24 weeks when accounting for folate contribution by OC – After 24 weeks of supplementation, 91% in the fortified-OC group vs. 60% in the regular OC group had protective RBC folate conc. against NTDs

Each treatment commenced between the third and sixth days of the participant's menstrual cycle, and each treatment was administered as a single dose orally, along with extensive dietary restrictions that were standardized across all participants. Each consecutive treatment was separated by a washout period of one menstrual cycle. Food diaries were maintained by participants to record their food consumption three days before the treatment, and dietary folate intake was estimated by three-day dietary records. The authors evaluated plasma levels of L-methyl-THF through blood samples drawn at 0.5, 1, 1.5, 2, 3, 4, 5, 8, 10, 12, 16, 24, 34, 48, 72, 96, 120, 144, and 168 hours post-treatment, and measured through a validated liquid chromatography/tandem mass spectrometry method. Given that bioequivalence is typically established through measures of bioavailability and comparable pharmacokinetic profiles, the authors measured $AUC_{\infty}/AUC_{last,}$ as a measure of bioavailability, and C_{max}, to compare max serum drug concentrations, as primary variables, with all other pharmacokinetic parameters as secondary variables. Among 41 women in the per-protocol set, the baseline-corrected pharmacokinetics of L-5-methyl-THF in those taking ethinyl estradiol/drospirenone/levomefolate calcium were (geometric mean [geometric coefficient of variation]): C_{max} = 51.7 nmol/L (30.6%) and AUC_{last} = 236 nmol•h/L (26.3%), and was closely comparable to the respective values in 43 women taking levomefolate calcium alone: C_{max} = 48.7 nmol/L (30.4%) and AUC_{last} = 239 nmol•h/L (26.5%). Both of the pharmacokinetic measures in the two groups were quite comparable, given that C_{max}—assessment of magnitude of peak drug response—was similar, and their AUC—measure of drug absorption, and hence duration of response—was also quite similar. More specifically, the geometric mean ratios and the 90% confidence intervals for the AUC and C_{max} were between 80% and 120%, which met the criteria for bioequivalence and demonstrated that the bioavailability of 5-methyl-THF after the administration of the ethinyl estradiol/drospirenone/levomefolate calcium preparation vs. after levomefolate calcium alone was similar.

Blode et al.[10] conducted another randomized, open-label, three-arm, intra-individual crossover bioequivalence study at a single centre in the Netherlands. Healthy volunteers who had not used folic acid supplements for at least two menstrual cycles before the study were recruited. The study aimed to demonstrate bioequivalence for all active ingredients of the ethinyl estradiol/drospirenone/levomefolate calcium preparation, specifically its levomefolate calcium component. Three different treatments were used:

1) ethinyl estradiol 0.02 mg/drospirenone 3 mg,
2) ethinyl estradiol 0.02mg/drospirenone 3 mg/levomefolate calcium 0.451 mg, and
3) levomefolate calcium 0.451 mg.

The administration of each treatment sequence was randomized, and each treatment was separated by a washout period of at least one menstrual cycle. Each treatment was self-administered as a single oral dose, with extensive standardized dietary restrictions within the protocol, and began between the third and sixth day of the menstrual cycle. Dietary folate intake was recorded through three-day weighted diet records, and blood samples were collected at −0.5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 34, 48, 72, 96, 120, 144, and 168 hours after administration. Finally, the concentrations of L-5-methyl-THF were analyzed using liquid chromatography/tandem mass spectrometry, and the AUC and C_{max} were the primary variables. Within the per-protocol set, 40 women completed the study, and the baseline-corrected geometric means (geometric coefficient of variation) for the ethinyl estradiol/drospirenone/levomefolate calcium combination were C_{max} = 44.3 nmol/L (32.7%) and AUC_{last} = 214 nmol•h/L (28.7%), compared with C_{max} = 44.2 nmol/L (39.4%) and AUC_{last} = 217 nmol•h/L (28.1%) for levomefolate calcium alone. Both these measures were comparable between the two groups; their point estimates and 90% confidence intervals were within the 80% to 120% necessary to demonstrate bioequivalence.

Efficacy Studies

Bart et al.[11] conducted a multicentre, randomized, double-blind, active-controlled, parallel-group study in the United States to measure folate status (red blood cell and plasma folate) in women taking the folate-supplemented OC preparation (ethinyl estradiol/drospirenone/levomefolate calcium) and in women taking the non-supplemented OC preparation (ethinyl estradiol/drospirenone). Healthy adult women were randomized 3:1 to taking either ethinyl estradiol 20 = μg/drospirenone 3 mg/levomefolate calcium 0.451 mg (n = 196) or ethinyl estradiol 20 μg/drospirenone 3 mg (n = 66) for 24 weeks. The study was composed of three phases:

1) screening and baseline,
2) blinded treatment phase for 24 weeks, and
3) follow-up phase (weeks 26 to 28).

Fasting blood samples were retrieved at baseline, at 4, 8, 12, 16, 20, and 24 weeks, and then during follow-up, between days 25 and 28 of each treatment (menstrual)

cycle. Plasma and RBC folate concentrations were analyzed using a validated microbiological assay, and adherence was evaluated through patient diaries and pill counts. Dietary intake was also evaluated using a short folate food-frequency questionnaire. Mean RBC folate concentrations increased in women taking the ethinyl estradiol/drospirenone/levomefolate calcium combination, from 990 ± 390 nmol/L at baseline to 1406 ± 440 nmol/L at week 24. These levels were significantly different ($P < 0.001$) from the levels in women taking ethinyl estradiol/drospirenone (1014 ± 308 nmol/L at baseline to 1024 ± 293 nmol/L). Similarly, mean plasma folate concentrations increased significantly ($P < 0.001$) from baseline in women taking the ethinyl estradiol/drospirenone/levomefolate calcium combination, from 45.0 ± 17.6 nmol/L at baseline to 60.8 ± 19.9 nmol/L, compared to the changes in women taking ethinyl estradiol/drospirenone, whose plasma folate concentrations increased from 43.1 ± 16.1 nmol/L at baseline to 41.0 ± 17.6 nmol/L.

Castano et al.[8] published post-hoc subanalysis from the study of Bart et al.,[11] to incorporate dietary folate data as well as data on supplement use in establishing the efficacy of the folate-supplemented OC preparation (ethinyl estradiol/drospirenone/levomefolate calcium) compared with controls, who were taking a comparable oral contraceptive without folate (ethinyl estradiol/drospirenone). The authors found that dietary folate intake did not differ between the two groups at baseline ($P = 0.6$) or at week 24 ($P = 0.4$). Only 26% of the study participants used folate supplements, regardless of their assigned treatment. Interestingly, the authors evaluated total daily folate intake through diet, supplements, and OC contribution, and found that the women in the folate-fortified OC group had a significantly higher daily mean folate intake (1225.9 μg ± 346.2) than women in the control group (500.6 μg ± 361.2), who were not receiving folate in their OC, by 24 weeks of therapy. The authors also analyzed the proportion of the study population achieving RBC folate concentrations that were adequately protective against NTDs (> 906 nM) by 24 weeks of use of OCs. They found that 91% of women in the folate-fortified OC group were optimally protected against NTDs, compared with 60% in the regular OC group.

Diefenbach et al.[12] conducted a double-blind, double-dummy, randomized, parallel-group study comparing the effect of ingestion of the folate-fortified oral contraceptive preparation (ethinyl estradiol/drospirenone/levomefolate calcium) with ethinyl estradiol/drospirenone + folic acid for 24 weeks (invasion phase), and ethinyl estradiol/drospirenone alone for an additional 20 weeks (elimination phase) at a single centre in Germany. The objective of the invasion phase was to study the AUC for plasma folate and RBC folate levels, and the authors studied the elimination phase to investigate blood folate concentrations after the cessation of treatment with ethinyl estradiol/drospirenone/levomefolate calcium. In this study, healthy women who were not previously taking folic acid supplements or any other medications contraindicated for OC therapy were recruited and randomized equally between the two groups for the two phases of the study. Seventy-five women taking the folate-fortified oral contraceptive preparation also took a placebo, whereas 75 women received ethinyl estradiol/drospirenone + folic acid, and the pills were identical between these two groups. Compliance in the study was evaluated through patient diaries and pill counts, and dietary folate intake was estimated through a standardized food questionnaire. Blood samples were collected at baseline and then at biweekly intervals, and blood folate concentrations were measured using the microbiological assay. The geometric means (% geometric coefficient of variation) were comparable for plasma and RBC folate between the two treatment groups in the invasion phase: baseline-corrected plasma folate $AUC_{0–24wk}$ for ethinyl estradiol/drospirenone/levomefolate calcium was 640 nmol•week/L (29.0%) versus $AUC_{0–24wk}$ for ethinyl estradiol/drospirenone + folic acid of 561 nmol•week/L (32.7%). Baseline-corrected RBC folate $AUC_{0–24wk}$ for ethinyl estradiol/drospirenone/levomefolate calcium was 10 427 nmol•week/L (34.3%), versus $AUC_{0–24wk}$ for ethinyl estradiol/drospirenone + folic acid of 8863 nmol•week/L (24.6%). Plasma and RBC folate concentrations in women taking either ethinyl estradiol/drospirenone/levomefolate calcium or ethinyl estradiol/drospirenone + folic acid plateaued after eight weeks, and were comparable in both groups, with slightly higher concentrations in the ethinyl estradiol/drospirenone/levomefolate calcium group. At week 24, plasma folate concentrations were 49.9 ± 15.5 nmol/L in the ethinyl estradiol/drospirenone/levomefolate calcium group and 43.3 ± 13.3 nmol/L in the ethinyl estradiol/drospirenone + folic acid group. Similarly, RBC folate concentrations in the ethinyl estradiol/drospirenone/levomefolate calcium group (1361 ± 322 nmol/L) were comparable to those in the ethinyl estradiol/drospirenone + folic acid group (1207 ± 217 nmol/L) at 24 weeks. With respect to the elimination phase, mean red cell folate concentrations 20 weeks after cessation of treatment (i.e., week 44) were 739.8 ± 197.6 nmol/L

in the ethinyl estradiol/drospirenone/levomefolate calcium group versus 701.1 ± 170.6 nmol/L in the ethinyl estradiol/drospirenone + folic acid group. Plasma folate concentrations also decreased at similar rates between the two groups. The authors reported that the median time from cessation of ethinyl estradiol/drospirenone/levomefolate calcium therapy to RBC folate concentrations falling below 906 nM was 10 weeks (i.e., week 34).

DISCUSSION

Overall, the data from the bioequivalence studies associated with the ethinyl estradiol/drospirenone/levomefolate calcium preparation (Yaz Plus)[9,10] demonstrate bioequivalence for each of this preparation's components. This confirms that the concomitant administration of the OC component (ethinyl estradiol/drospirenone) does not alter the pharmacokinetics of the folate component (levomefolate calcium), and vice versa. Similarly, the efficacy studies demonstrate that the folate-fortified OC significantly increased blood folate concentrations over 24 weeks,[11,12] in comparison to a regular OC preparation (the same OC preparation without the folate component).[11] While this study was well-controlled, and did analyze dietary folate intake as a potential influence on blood concentrations, it employed an unequal randomization scheme (3:1) without citing a rationale for this. Such an unequal allocation is associated with a loss of statistical power for comparisons of treatment, and should be noted when considering the significance of the positive effect cited by the authors. Diefenbach et al.[12,13] compared concomitant supplementation with an equimolar dose of folic acid and the folate-fortified OC preparation in their two-arm randomized clinical trial, and found comparable RBC folate levels in both groups (with slightly higher levels in the folate-fortified OC group) after 24 weeks of use, suggesting that the folate-fortified OC is at least as effective as folic acid in raising blood folate concentrations. Interestingly, through the elimination phase of their study, they found that RBC folate levels fell below 906 nmol/L by 10 weeks after stopping folate supplementation.[12]

Thus, the folate-fortified OC preparation is comparable to supplementation with 400 μg folic acid daily in women of childbearing age. However, it also offers several advantages over regular supplementation, described below.

Compliance

Recent data from the Canadian Health Measures Survey show that only 28.2% of women use folate supplements.[4] Since OC users tend to be reliable pill-takers (because of the potentially significant consequences for the user of missing a pill), the folate-fortified OC preparation offers an appropriate vehicle for folate supplementation. Rates of consistent OC use range from 92.6% to 95.7%,[14] thus making the folate-fortified OC preparation an ideal delivery method for daily folate intake among women.

Target Population

Unlike broad-spectrum strategies for folate supplementation such as dietary fortification, the folate-fortified OC preparation actually targets the population of women who need it most: women of childbearing age. Thus, in the event of an unplanned pregnancy it provides blood folate levels that are optimally protective against NTDs.[8,11] Even without pregnancy, it provides the appropriate daily folate dose for women to maintain good health.

Levomefolate Calcium Versus Folic Acid

The use of levomefolate calcium (5-methyl-THF) in the fortified OC preparation offers several advantages over the use of folic acid, given that it is at least as effective as folic acid in raising blood folate levels. Since it is the metabolically active form of folate in plasma, levomefolate calcium does not need to be metabolized (unlike folic acid), and it is beneficial for women who may have mild to severe deficits in folate metabolism. Further, it is less likely to mask symptoms of vitamin B12 deficiency, which is a theoretical concern with folic acid supplementation.[15] In addition, it potentially decreases the amount of unmetabolized folic acid in the blood as a result of folic acid supplementation.

A recent systematic review and meta-analysis suggests that OCs do have a folate-lowering effect on blood folate concentrations. In addition, the fact that one half of all pregnancies are unplanned[1] implies that folate-fortified OC preparations offer a unique and significant option for women of childbearing age.

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