A Prenatal Supplement with Methylfolate for the Treatment and Prevention of Depression in Women Trying to Conceive and During Pregnancy

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Abstract

Background: Women often seek alternatives to standard antidepressants for major depressive disorder (MDD) during pregnancy. In this preliminary study, EnBrace HR, a prenatal supplement containing methylfolate, was investigated in pregnant women or women planning pregnancy for (1) depressive relapse prevention and for (2) the acute treatment of MDD.

Methods: This 12-week open-label study included women with histories of MDD who were planning pregnancy or pregnant <28 weeks. **Group 1** participants were well (not in depressive episodes) and planned to discontinue antidepressants for pregnancy. **Group 2** participants were depressed at baseline. Primary outcome variables included MDD relapse and depressive symptoms, verified with the Mini International Neuropsychiatric Interview and the Montgomery-Ăsberg Depression Rating Scale (MADRS), respectively. Biomarkers of folic acid metabolism and inflammation were collected.

Results: Group 1 participants (N=11; well at baseline) experienced no significant decreases in MADRS scores and lower rates of depressive relapse (27.3%; p=0.005) than expected when compared to historical controls. **Group 2** (N=6; depressed at baseline) experienced significant improvements in MADRS scores (p=0.001), with five (83.3%) improving >50% and one improving 33.3%. One adverse event occurred, a hospitalization for depression.

Conclusions: Results suggest EnBrace HR is a well-tolerated intervention with potential efficacy for the prevention and treatment of perinatal depression. Larger controlled trials are necessary.

Introduction

Major Depressive Disorder (MDD) and Major Depressive Episodes (MDEs) in Women:

- MDD occurs approximately twice as often in women compared to men.[1,2]
- There is high risk for MDEs during pregnancy and the postpartum period.[3]
- Pregnant women often discontinue standard antidepressant medications prior to or during pregnancy because of safety concerns.[4-8]
- There are few evidence-based alternatives to antidepressant medications for the treatment and prevention of MDD during pregnancy, leaving pregnant women and clinicians with the clinical dilemma of weighing risks of fetal exposure to medication against impact of untreated maternal depression.

L-Methylfolate and Folate-Related Therapies:

- Evidence suggests various folate forms including folic acid, folinic acid, and methylfolate may have antidepressant effects.[9-12] These interconvertible folate forms constitute the one-carbon cycle and are postulated to exert an antidepressant effect by impacting neurotransmitter synthesis.[13]
- Because folate must be converted to its active form, methylfolate, for use in the body, polymorphisms impairing folate methylation may limit the efficacy of folate as an intervention targeting MDD.[9-16]
- Methylfolate may be more readily absorbed in the brain than folate, and methylfolate has potential as a non-psychotropic treatment for MDD.[17-18]
- L-methylfolate treatment in early trials has been found to induce significant improvement in depressive symptoms both when used as an adjunct to antidepressant therapy and when used as a monotherapy.[19-24]
- Folate-related compounds reduce rates of neural tube defects and improve child neurodevelopmental outcomes, conferring benefits and minimizing potential risks of antidepressants during pregnancy.[25-28]

EnBrace HR:

- EnBrace HR is a prescription prenatal/postnatal dietary management product that contains 5.53 mg L-methylfolate and other folate derivatives (1 mg folic acid, and 2.2 mg folinic acid), optimal for a population with high rates of polymorphisms that affect folic acid metabolism.

Methods

Group 1: Well at Baseline; Relapse Prevention Group

Inclusion Criteria:

- Age ≥18
- MDD as primary diagnosis
- Have prescribing clinician
- Planning to conceive or <28 weeks pregnant at enrollment
- *Planning to discontinue antidepressants or recently tapered off antidepressants*
- *No current major depressive episode on MINI*
- *"Well"; baseline MADRS score ≤10*

- **Primary Outcome:** To obtain preliminary data on the efficacy of EnBrace HR for depressive relapse prevention in women who discontinue antidepressants while trying to conceive or during early pregnancy

Group 2: Depressed at Baseline; Acute Treatment Group

Inclusion Criteria:

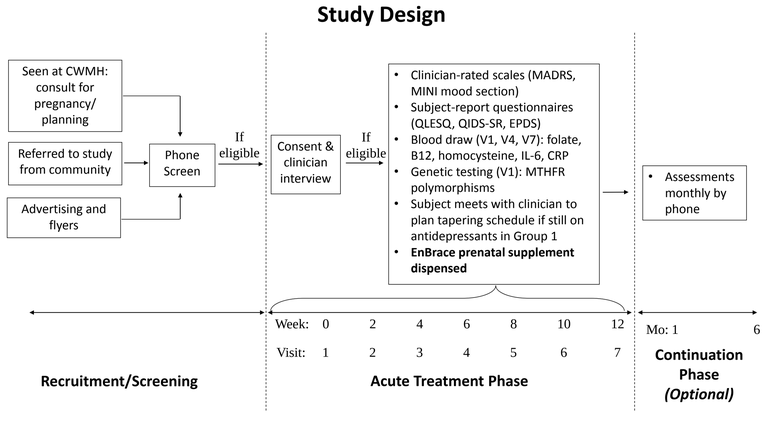
- Age ≥18
- MDD as primary diagnosis
- Have prescribing clinician
- Planning to conceive or <28 weeks pregnant at enrollment
- *No dose increase of current antidepressant or start of new antidepressant medication*
- *Currently depressed, as verified by MINI*
- *"Depressed"; baseline MADRS score ≥ 15*

- **Primary Outcome:** To obtain preliminary data on efficacy of EnBrace HR for treatment of acute MDEs in women who opt to avoid starting an antidepressant or increasing the dose of a current antidepressant while trying to conceive or during early pregnancy.

Exclusion Criteria for Both Groups:

- Significant risk for self-harm or harm to others;
- Diagnosis of schizophrenia or bipolar disorder; psychotic symptoms; active eating disorder; a cognitive disorder; an active substance and/or alcohol abuse disorder (within 6 months of screening);
- Pernicious anemia; gastric bypass surgery; a seizure disorder and/or anticonvulsant medication use;
- Allergy to study drug, inactive ingredients, beeswax, soy, fish, nuts, peanuts, egg, wheat, milk, or shellfish.

Study Design



Results

Demographics and Pregnancy Characteristics

TABLE 1 Subject characteristics of subjects who received medication (N=19)

Demographic characteristics N (%), unless otherwise noted		
Age (years), mean ± SD		32.8 ± 3.0
Race		
	White/Caucasian	16 (84.2%)
	Black/African American	1 (5.3%)
	Native Hawaiian or other Pacific Islander	0
	Asian	2 (10.5%)
	American Indian or Alaska Native	0
Ethnicity		
	Non-Hispanic or non-Latina	18 (94.7%)
	Hispanic or Latina	1 (5.3%)
Marital status		
	Married	16 (84.2%)
	Separated/divorced/widowed	1 (5.3%)
	Never married/single	2 (10.5%)
Education		
	Some high school	0
	High school or received GED	0
	Some college or Associate Degree	1 (5.3%)
	Graduated college (BA, BS)	4 (21.1%)
	Master's Degree	11 (57.9%)
	Doctoral Degree (PhD, MD, etc.)	3 (15.8%)
Employment status		
	Full-or part-time work	17* (89.5%)
	Homemaker	2* (10.5%)
	Student	2* (10.5%)
Pregnancy characteristics		
Pregnancy status		
	Planning pregnancy/Trying to conceive	12 (63.2%)
	Pregnant at enrollment	7 (36.9%)
Assisted Reproductive Technology (ART)		
	Use for conception/attempted conception	5 (26.3%)
	No use of ART	14 (73.7%)
Pregnancy events during trial		
	Became pregnant	4 (21.1%)
	Pregnancy Loss	2 (10.5%)
	Delivered	1 (5.3%)

Table 1. Demographics are listed for all 19 women who initiated study drug. Two women in Group 1, who were trying to conceive, intended to discontinue antidepressants upon becoming pregnant, but did not conceive during the trial. These women thus did not reduce or discontinue antidepressants during the acute treatment phase, and were not included in analyses.

Figure 1. Mood and Quality of Life Outcomes

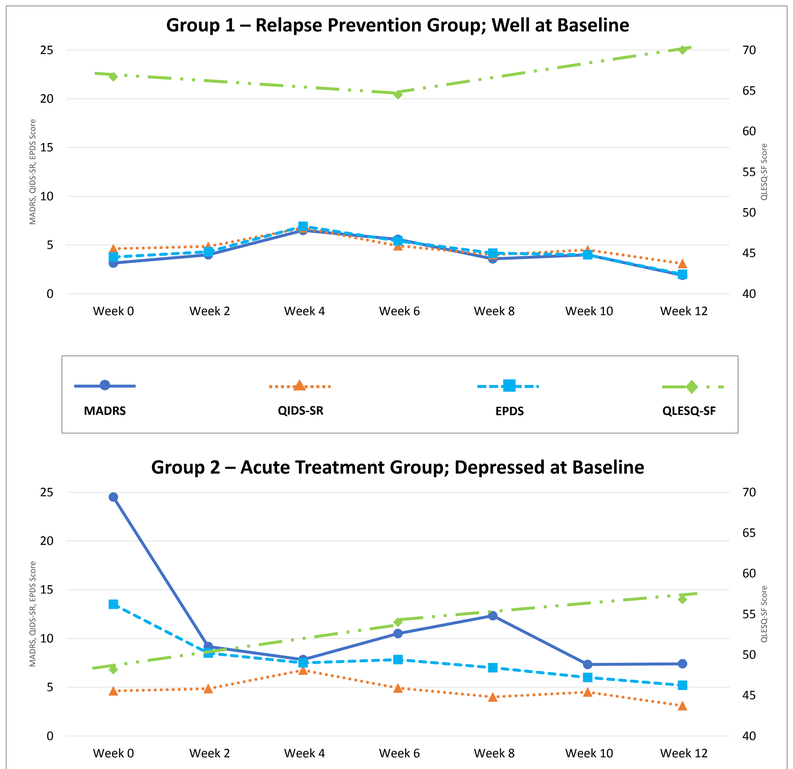


Figure 1. The aim for Group 1 was to prevent depression relapse, and the aim for Group 2 was to improve depression symptoms, measured through several mood and quality of life questionnaires. Trends shown by group for the primary mood outcome measure, the MADRS (Montgomery-Asberg Depression Rating Scale) in dark blue; for secondary mood measures, the QIDS–SR (Quick Inventory of Depressive Symptomatology-Self Report) in orange and the EPDS (Edinburgh Postnatal Depression Scale) in light blue; and for a quality of life outcome, the QLESQ-SF (Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form) in green. Group 1 experienced no significant changes in any of the four measures, and Group 2 experienced significant improvements in the mood questionnaires but not the quality of life questionnaire. All ANOVAs indicating significance are reported in Table 3.

Group	Measures							
	MADRS		EPDS		QIDS-SR		QLESQ-SF	
1	F(6,54)=1.13	p=0.357	F(6,54)=1.83	p=0.111	F(6,54)=1.58	p=0.171	F(2,17)=1.06	p=0.368
2	F(6,29)=5.16	p=0.001	F(6,29)=4.31	p=0.003	F(6,29)=6.49	p=0.0002	F(2,9)=2.88	p=0.108

Table 2. F-statistics for ANOVA tests and corresponding p-values. Statistical significance was established at the α = 0.05 level for all analyses. Group 1 experienced no significant differences on any of the questionnaires, as anticipated in hypotheses. Group 2 experienced significant improvements in mood, but not in quality of life as measured by these four instruments.

Relapse Rates

Group 1 Relapse Rates			
Major Depressive Episode Experienced Within 12-week Active Phase	Observed	Expected*	p-value
Yes	3	7.4	0.005
No	8	3.6	

Table 3: *Chi Square analysis (binary variable; relapse/no relapse) was performed to compare Group 1 MDD relapse rates (23.1%) to historical controls who had relapse rates of 67.7% for antidepressant medication discontinuation for pregnancy.[3]

Results (Cont.)

Adverse Events

Adverse Events Reported	
Adverse Event	**# of patients experienced**
Nausea	3 (15.8%)
Constipation	3 (15.8%)
Cough and nasal congestion	2 (10.5%)
Difficulty concentrating	2 (10.5%)
Urinary tract infection	2 (10.5%)
Miscarriage	2 (10.5%)
Headache	2 (10.5%)
Perioral dermatitis	1 (5.3%)
Abdominal muscle ache	1 (5.3%)
Dysgeusia (metallic taste)	1 (5.3%)
Suspected niacin flushing	1 (5.3%)
Mechanical fall	1 (5.3%)
Mild anemia	1 (5.3%)
Dyspepsia	1 (5.3%)
Worsening of depression symptoms with request for treatment referral	1 (5.3%)
Mild weight gain	1 (5.3%)
Chest tightness	1 (5.3%)
Total Adverse Events: 26; Unique Adverse Events: 17	

Discussion and Conclusions

Results Summary

- We assessed EnBrace HR in two samples of women planning pregnancy or during early pregnancy, to obtain data regarding:
  - 1) Prevention of depressive relapse in women with histories of MDD
  - 2) Acute treatment of MDD in women who were depressed and wanted to avoid the use of an antidepressant or did not want to increase the dose of one that they were already taking.
- Three of 11 women in Group 1 who reduced or discontinued their antidepressants and who were well at baseline experienced a relapse to an MDE (27.3%), a rate lower than expected when compared to historical controls who discontinued antidepressants for pregnancy (67.7%).[3]
- All participants in Group 2, who were depressed at baseline, experienced remission by the end of the study, and 5 of 6 (83.3%) experienced over a 50% improvement on the MADRS from baseline. One patient in Group 2 remitted, then relapsed, then again remitted prior to completing the study.
- We found EnBrace HR was well-tolerated in this sample. One serious adverse event occurred; a woman in Group 1 experienced a relapse of depression and was hospitalized.

Strengths

- We assessed a novel nutritional supplement for MDD prevention and treatment in women in the antenatal period, a critical goal among women seeking to avoid antidepressants during pregnancy.
- Other strengths include the rigorous assessments of history of MDEs and the diagnosis of MDD and the validation of MDE status at each study visit using the MINI. We collected biomarkers for assessment of exploratory variables.

Limitations

- The most important limitation is the lack of a placebo arm. We draw from historical controls assessing depressive relapse and symptom burden[3]. Concurrent parallel comparison groups were not available.
- Another major limitation is the small number of subjects overall and in each group.
- Our sample is largely composed of women who are white, non-Hispanic, married, and highly educated. It is not clear if our findings are generalizable to the larger population of reproductive-aged women.

Conclusions and Future Directions

- Study results suggest EnBrace HR is a novel and well tolerated intervention with potential efficacy for the prevention and treatment of depression among women planning pregnancy and who are pregnant
- Larger controlled trials are necessary to definitively determine efficacy and its role in the armamentarium of treatments for antenatal depression.

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