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RESEARCH ARTICLE

A prenatal supplement with methylfolate for the treatment and prevention of depression in women trying to conceive and during pregnancy

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BACKGROUND: Women often seek antidepressant alternatives for major depressive disorder (MDD) in anticipation of or during pregnancy. In this preliminary study, EnBrace HR, a prenatal supplement containing methylfolate, was investigated for depressive relapse prevention and for acute treatment of MDD in women planning pregnancy or during pregnancy.

METHODS: This 12-week open-label study included women with histories of MDD who were planning pregnancy or pregnant <28 weeks. At enrollment, Group 1 participants were well (not depressed) and planned to discontinue antidepressants for pregnancy. Group 2 participants were depressed. Primary outcome variables by group included MDD relapse and depressive symptoms, verified with the Mini-International Neuropsychiatric Interview and the Montgomery-Åsberg Depression Rating Scale (MADRS), respectively. Biomarkers of inflammation and the folate cycle were collected.

RESULTS: Group 1 participants (N = 11) experienced lower rates of depressive relapse (27.3%; $P = .005$) than expected from a historical comparison group and no significant changes in MADRS scores. Group 2 participants (N = 6) experienced significant improvements in MADRS scores ($P = .001$), with 5 (83.3%) improving >50% and 1 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 prevention and treatment of perinatal depression. Larger controlled trials are necessary.

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INTRODUCTION

Major depressive disorder (MDD) occurs approximately twice as often in women compared with men.[1] As an often chronic and recurrent condition, MDD represents a high burden of illness for many women of reproductive age.[2] Therefore, the identification of safe and effective treatments for depression before, during, and after pregnancy is a critical public health concern.

Contrary to previous assumptions that pregnancy is protective against depressive relapse, women often experience major depressive episodes (MDEs) during pregnancy, and they are especially at risk for depressive relapse in the postpartum period.[3] The current standard of treatment for recurrent MDD in non-pregnant patients is maintenance antidepressant therapy.[4,5] These guidelines are derived from the high risk of recurrence among patients who discontinue maintenance antidepressant therapy.[6]

Although antidepressants are frequently used during pregnancy, women and their health care providers may have concerns regarding potential adverse outcomes associated with fetal exposure to psychotropic medications.[7-11] Despite the potential risk of depressive relapse, women treated with antidepressants frequently elect to discontinue antidepressant medications while trying to conceive or during pregnancy to avoid medication exposure to their children *in utero*.[3] Also, women who experience acute depressive episodes while trying to conceive or during pregnancy often forgo antidepressant use.[12]

Women and their health care providers are therefore faced with the difficult clinical dilemma of weighing the potential risks of fetal exposure to medication against the impact of untreated maternal depression during pregnancy. Additional evidence-based non-psychotropic interventions to treat or prevent depressive episodes while trying to conceive or during pregnancy would increase the range of options available to mothers and their providers as they seek to avoid potential adverse outcomes during pregnancy.

Increasing evidence shows a role for various folate-related treatments in the prevention and acute treatment of depression.[13-16] To date, there is an evidence base for antidepressant effects of folic acid, folinic acid, and methylfolate, and similar findings may be attributable to the shared interconversion potential of these folate forms in the complex set of pathways that comprise the one-carbon cycle. These are postulated to exert an antidepressant effect by impacting the synthesis of

TABLE 1
Demographic and pregnancy characteristics of participants who received medication (N = 19)

Characteristic	N (%)[a]
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
Other	0
Decline to answer	0
Ethnicity	
Non-Hispanic or non-Latina	18 (94.7%)
Hispanic or Latina	1 (5.3%)
Decline to answer	0
Marital status	
Married	16 (84.2%)
Separated/divorced/widowed	1 (5.3%)
Never married/single	2 (10.5%)
Decline to answer	0
Education	
Some high school	0
High school or received GED	0
Vocational/training school after high school	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[b] (89.5%)
Homemaker	2[b] (10.5%)
Disabled	0
Not working, unemployed	0
Student	2[b] (10.5%)
Volunteer	0
Retired	0
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%)

[a]N (%), unless otherwise noted.
[b]Overlap between self-identified categories (ie, a student who worked part-time, and a homemaker who worked part-time).

SD: standard deviation.

TABLE 2
Adverse events reported

Adverse effect	N (%)
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.

neurotransmitters such as norepinephrine, dopamine, and serotonin.[17] Given the evidence base for the positive impact of folate-related treatments in the prevention of neural tube defects and the potential positive impact on neurodevelopmental outcomes, these compounds represent a promising potential treatment for depression in pregnancy that might help to avoid or minimize the potential risks of antidepressants in pregnancy and would also confer important benefits to pregnancy and child development outcomes.[18]

Some but not all studies suggest efficacy of folate augmentation for MDD, but this intervention may be limited by the common occurrence of polymorphisms in the general population that make folate a less efficient one-carbon cycle constituent than L-methylfolate.[13-16,19-21] Since certain polymorphisms that impair methylation processes and conversion of folate into its active form, methylfolate, have been found to be common in those with MDD, methylfolate may be a more effective form of folate supplementation to target MDD.[22] Also, methylfolate may be more readily absorbed in the brain compared with other folate forms.[23]

Recently, Papakostas et al[24] demonstrated that adjunctive L-methylfolate is significantly more efficacious compared with placebo for the treatment of MDD in patients who failed to respond to antidepressant therapy alone. In addition, several other studies of methylfolate monotherapy in various depressed populations have found that patients experienced significant improvement in depressive symptoms with good tolerability.[25-29] Although more data are needed from controlled trials, preliminary studies indicate methylfolate may be a safe and effective option for treatment of MDD, especially in populations vulnerable to medication-related adverse events, and those who are folate-deficient or have elevated folate needs, such as pregnant women.

In this context, EnBrace HR is a prescription prenatal/postnatal dietary management product containing vitamins and minerals, including folic acid, folinic acid, and methylfolate, that may have efficacy for MDD indications. It meets the above criteria as a candidate for the prevention and treatment of MDD in pregnancy. It contains 5.53 mg L-methylfolate and smaller quantities of 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. Folic acid supplementation has been associated with reduced risk of neural tube defects and is recommended for use in women of reproductive potential to reduce risk of birth defects.[30-32]

Few studies have examined folate-related treatments specifically to assist patients who wish to avoid or discontinue antidepressants, and none have examined this during the time proximate to attempts to conceive or during pregnancy, which is particularly relevant due to safety concerns of medication exposure *in utero*. The adaptation of such a treatment for use in women who are pregnant or planning pregnancy who choose to avoid or discontinue antidepressant treatment would broaden treatment choices available during this important time.

The primary objectives of this study were specific to each group. In Group 1, the aim was to obtain preliminary data on whether EnBrace HR appears to have efficacy in depressive relapse prevention in women who discontinue antidepressant medications in anticipation of pregnancy or during early pregnancy. In Group 2, the aim was to obtain preliminary data on whether EnBrace HR appears to have efficacy in the treatment of acute depressive episodes in women who opt to avoid starting an antidepressant or increasing the dose of a currently used antidepressant while trying to conceive or during early pregnancy.

TABLE 3
Relapse rates in Group 1

Group 1			
Major depressive episode experienced within 12-week active phase	**Observed**	**Expected[a]**	***P***
Yes	3	7.4	.005
No	8	3.6	

[a]Chi-square analysis (binary variable; relapse/no relapse) was performed to compare the major depressive disorder (MDD) relapse rates (27.3%) of analyzable women in Group 1 (11 women who discontinued or decreased antidepressant dose during the study) with literature values of expected relapse rates (67.7%) for antidepressant medication discontinuers from a large population of women with MDD and past or current use of antidepressant medications while pregnant or planning pregnancy.[3] A significantly lower rate of depressive relapse rates than that reported in the literature in similar populations was observed. The 2 women in Group 1 who did not discontinue antidepressants were not included in this analysis.

METHODS

Study design

This was a 12-week open-label study of EnBrace HR in women age ≥18 with MDD who were trying to conceive or were pregnant (<28 weeks gestational age at enrollment, calculated using last menstrual period). English-speaking women who were planning pregnancy or were <28 weeks pregnant with histories of MDD and who had prescribing clinicians for MDD treatment were eligible for the study if they met criteria for one of 2 groups. All assessments relevant for inclusion and exclusion criteria were conducted by a study physician.

Inclusion in Group 1 (the "well" group, planning to discontinue antidepressants) required that women currently meet criteria for stable remission from MDD as defined by a baseline score of ≤10 on the Montgomery-Åsberg Depression Rating Scale (MADRS), have recent or current antidepressant use that they had elected to discontinue for pregnancy, have histories of an MDE as verified using the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV, and have MDD as one of their primary diagnoses.

Inclusion criteria for Group 2 (the "depressed" group, planning not to start an antidepressant or increase the dose of a current antidepressant after consultation with their prescribing provider) required that women be currently experiencing clinically significant depressive symptoms as defined by a baseline score of ≥15 on the MADRS, be currently experiencing an MDE as verified using the MINI, and have MDD as one of their primary diagnoses. Women who endorsed any suicidal ideation were not included in the study, and follow-up care was swiftly coordinated.

Exclusion criteria specific to Group 1 included a current MDE, as diagnosed on the MINI mood module. Exclusion criteria for both groups included a significant risk for self-harm or harm to others; psychotic symptoms; a primary diagnosis of a psychotic disorder or bipolar disorder; an active eating disorder; a cognitive disorder; presence of an active substance and/or alcohol use disorder within 6 months prior to screening; pernicious anemia or a history of gastric bypass surgery; a seizure disorder and/or on anticonvulsant medications; and an allergy to the study drug, any inactive ingredients, beeswax, soy, fish, nuts, peanuts, egg, wheat, milk, and/or shellfish.

After the baseline screening visit, participants received the EnBrace HR supplement to be taken once per day for the duration of the 12-week active treatment phase in addition to their normal prenatal vitamins. Study medication was packaged in bottles, and each bottle included 30 gelatin capsules with 5.23 mg of L-methylfolate. If a participant was unable to tolerate EnBrace HR due to adverse effects or expressed a preference to discontinue the study supplement, she was withdrawn from the study. To collect information regarding changes in biomarker levels for the folate cycle, changes in inflammatory marker levels, and participant response to the supplement by status of methylene tetrahydrofolate reductase (MTHFR) polymorphisms, blood and pharmacogenetic analyses were performed. Following Visit 1, subsequent study visits were scheduled every 2 weeks, for a total of 7 study visits across the 12-week period. An option of remote study visits was added for participant convenience during visits that did not require a blood draw. All medication was stored and dispensed by physician investigators at the Massachusetts General Hospital Center for Women's Mental Health following standard, pharmacy-approved procedures. A standard prenatal vitamin was offered to participants in addition to EnBrace HR to ensure equal access to prenatal vitamins. Pill counts were used to ensure the study supplement was being taken as prescribed through the study.

The study protocol was approved by the Partners Healthcare System Institutional Review Board (IRB). Written informed consent was obtained from all participants.

An Investigational New Drug application (129890) was obtained from the US FDA for this study, and the study is registered on clinicaltrials.gov at https://clinicaltrials.gov/ct2/show/NCT02676882. Participants were enrolled from January 24, 2017 to February 20, 2018.

Measures

Primary outcome measures for each group included: Group 1—relapse of major depression, as defined by the MINI mood portion "current major depressive episode" criteria[33] and confirmed by research clinician interview; and Group 2—treatment of current MDE, defined by a response (≥50% improvement in depressive symptoms) to EnBrace HR therapy as assessed by the MADRS and other mood questionnaires. The MADRS was the primary outcome measure of depressive symptoms. For assessments related to depression, secondary outcome scales included the Quick Inventory of Depressive Symptomatology–Self Report (QIDS–SR) and the Edinburgh Postnatal Depression Scale (EPDS), both self-report questionnaires. Quality of life was assessed with the Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF). Symptoms were re-assessed every other week following initiation of EnBrace HR. Participant psychiatric and medical histories were collected and MDD diagnosis was verified using the MINI at baseline, conducted by a study clinician. Adverse events were assessed with a standard IRB-approved form at every study visit.

At weeks 0, 6, and 12, blood samples were collected to quantify inflammatory biomarkers (interleukin-6 [IL-6] and C-reactive protein [CRP]) and biomarkers related to folate metabolism (folate, vitamin B12, and homocysteine). C-reactive protein was measured with latex immunoturbidimetry, folate and vitamin B12 were each measured with an electrochemiluminescence immunoassay, IL-6 was measured with an enzyme-linked immunosorbent assay (ELISA), and homocysteine was measured with an enzymatic assay. Pharmacogenetic testing for MTHFR polymorphisms related to folic acid metabolism was performed at baseline.

Biostatistical analyses

This was a preliminary open-label study, not powered to show definitive results for the efficacy of EnBrace HR for all outcome measures; however, this pilot study was designed to demonstrate the preliminary efficacy of EnBrace HR for the primary outcome (prevention of depressive relapse or treatment of current depressive symptoms).

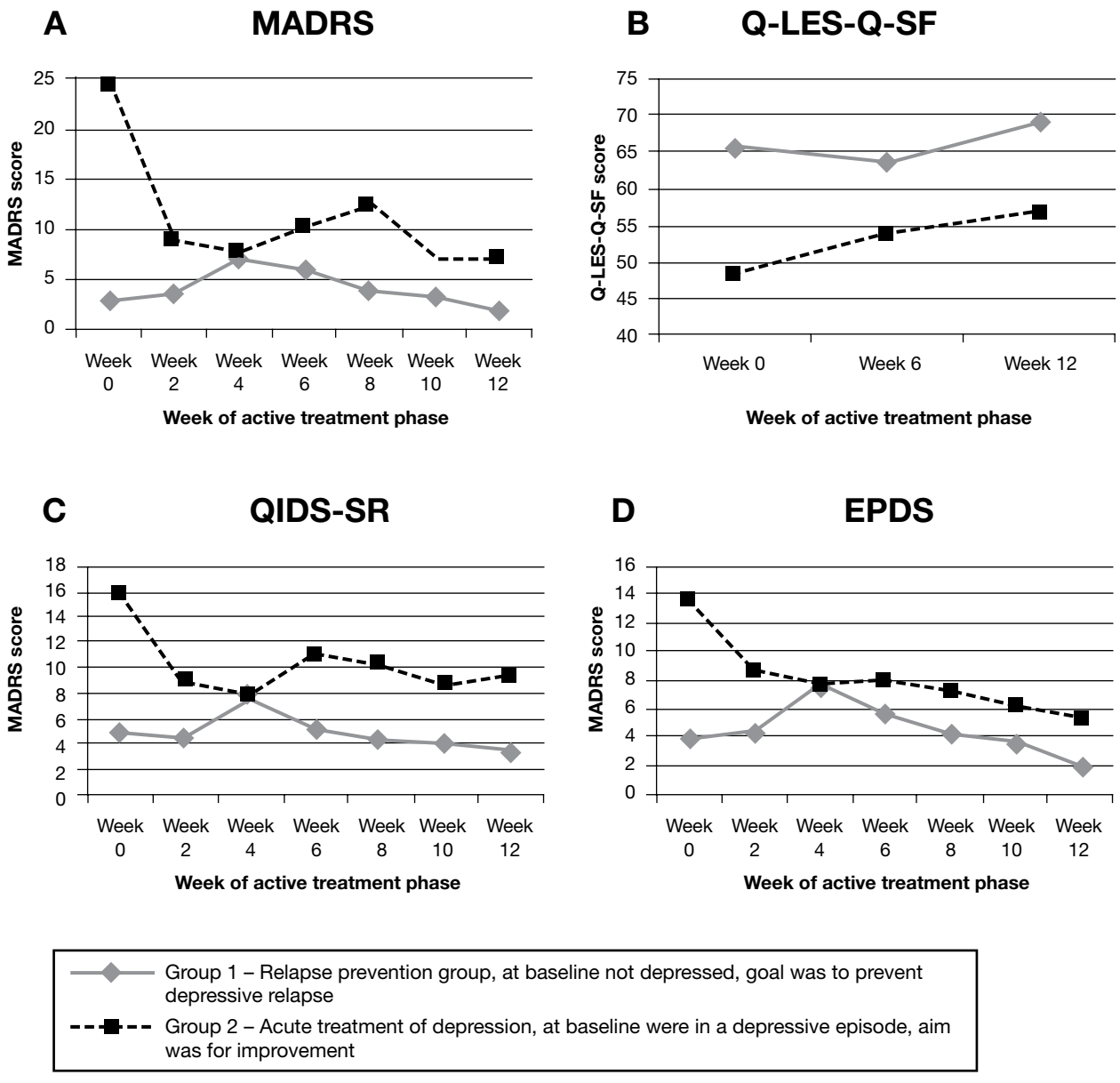
Participants were considered responders to EnBrace HR if their MADRS score was reduced by ≥50% from baseline to the end of treatment and remitters if they did not meet criteria for a current depressive episode on the MINI after having previously met criteria. Participants were considered evaluable for a last observation carried forward (LOCF) analysis if they completed at least 1 assessment after starting treatment with EnBrace HR. Two participants in Group 1 did not discontinue antidepressants as planned and were not included in these analyses.

Primary outcomes included depressive relapse rates specifically in Group 1, and measures of depression using the MADRS across groups. Depressive relapse rates were reported as percentages. To determine the efficacy of EnBrace HR in preventing depressive relapse, relapse rates for those taking the intervention in the well group (Group 1) were compared with relapse rates in the literature using Chi-square analysis.[3] One-way repeated measures analysis of variance (ANOVA) tests were run separately for both groups (Group 1: N = 11; Group 2: N = 6) to determine if there were differences in MADRS scores over time from baseline due to the intervention. Trends over time were additionally graphed for each group, and the changes in baseline and final visit mean MADRS scores for each group were analyzed using two-tailed *t* tests.

One-way repeated measures ANOVAs were also run separately for both groups (Group 1: N = 11; Group 2: N = 6) to determine if there were differences in secondary measures, including the QIDS-SR, Q-LES-Q-SF, and EPDS scores over time from baseline due to the intervention.

It was hypothesized that there would be no significant difference in scores at baseline and follow-up for Group 1 participants, who entered the study for prevention of depressive relapse, and that MADRS scores would significantly decrease for Group 2 participants, who entered the study in acute depressive episodes. It was hypothesized that Group 1 participants would have no significant change in these measures from baseline, while Group 2 participants would see a decrease in MADRS, QIDS-SR, and EPDS scores and an increase in Q-LES-Q-SF scores.

FIGURE 1
Mood and quality of life outcome trends



Trends are shown for **A)** primary mood measure outcome and for **B)** to **D)** secondary outcomes regarding quality of life and mood. MADRS, QIDS-SR, and EPDS scores were measured at Weeks 0, 2, 4, 6, 8, 10, and 12, and QLESQ-SF scores were measured at Weeks 0, 6, and 12. Decreases in MADRS, QIDS-SR, and EPDS scores are associated with improved depressive symptoms, and increases in Q-LES-Q-SF scores are associated with improved quality of life. Group 1 experienced no significant changes in any of the 4 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 4**.

ANOVA: analysis of variance; EPDS: Edinburgh Postnatal Depression Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; QIDS-SR: Quick Inventory of Depression Symptomatology–Self Report; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form.

TABLE 4
Mood and quality of life outcome measures by group[a]

	Measures							
	MADRS		EPDS		QIDS-SR		Q-LES-Q-SF	
Group 1	F(6,54) = 1.13	*P* = .357	F(6,54) = 1.83	*P* = .111	F(6,54) = 1.58	*P* = .171	F(2,17) = 1.06	*P* = .368
Group 2	F(6,29) = 5.16	*P* = .001	F(6,29) = 4.31	*P* = .003	F(6,29) = 6.49	*P* = .0002	F(2,9) = 2.88	*P* = .108

[a]F-statistics for ANOVA tests and corresponding *P* values (statistical significance was established at the $\alpha = .05$ level for all analyses) are listed. Decreases in MADRS, EPDS, and QIDS-SR scores are associated with improvements in depressive symptoms. Increases in Q-LES-Q-SF scores are associated with increased quality of life. 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 4 instruments.

ANOVA: analysis of variance; EPDS: Edinburgh Postnatal Depression Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; QIDS-SR: Quick Inventory of Depression Symptomatology–Self Report; Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form.

Statistical significance was established at the $\alpha = .05$ level for all analyses.

RESULTS

Participants

Twenty-five participants consented to participate in the study, and 20 were eligible to initiate treatment following the screening visit. The participants who were not eligible after screening did not meet criteria for either group on the MADRS (N = 2, with a score not ≤10 or ≥15), did not have a diagnosis of MDD validated using the MINI (N = 1), had an active substance use disorder (N = 1), or intended to increase their antidepressant dose (N = 1). Of the 20 participants eligible after baseline, 19 (95%) continued to the open-label EnBrace HR treatment phase of the study and received the study medication. The participant who did not start medication dropped out prior to medication initiation. Of the 19 women initiating treatment with EnBrace HR, all were evaluable for a LOCF analysis, as all returned for at least 1 assessment after starting EnBrace HR. Fifteen participants (78.9%) completed the study, having attended all 7 study visits across the 12-week active treatment phase.

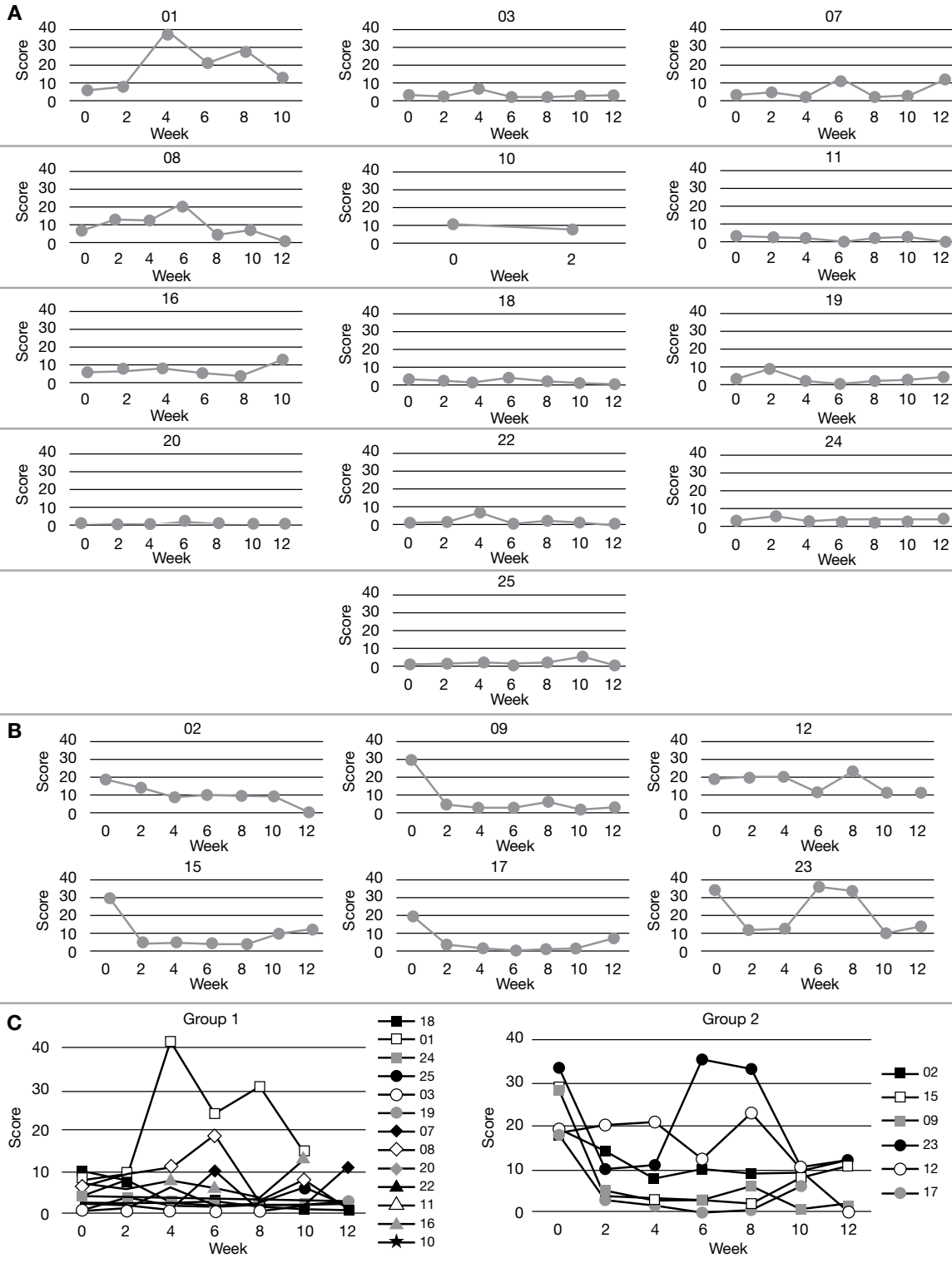
Four participants initiated EnBrace HR and were evaluable but not study completers. Of the 4 participants who initiated EnBrace HR but did not complete the study, 1 was deemed lost to follow-up and was dropped between the sixth and seventh visits, 1 withdrew due to concerns about pregnancy safety between the sixth and seventh visits, 1 withdrew due to delivery of her baby prior to study completion between the sixth and seventh visits, and 1 was dropped due to a depression relapse requiring inpatient hospitalization between the second and third visits.

The demographic and relevant pregnancy characteristics of the 19 women initiating treatment with EnBrace HR are listed in **TABLE 1**. The mean age was 32.8 years (standard deviation [SD] 3.0; range 28 to 39 years). The overall sample included 13 women in remission from depression symptoms at enrollment (Group 1), and 6 in a depressive episode at enrollment (Group 2). Four participants became pregnant during the trial.

Of the participants in Group 1 (N = 13), 5 had discontinued their antidepressants before the baseline visit, 4 tapered off antidepressants completely during the study, 2 tapered off one antidepressant completely and were midway through the taper off a second antidepressant at the end of the active treatment phase, and 2 did not change their antidepressant dose during the study. The 2 participants in Group 1 who intended to discontinue antidepressants during the trial did not taper as they had initially planned and continued taking their antidepressants at their baseline dose. The participants were actively trying to conceive and planned to stop their medications when they tested positive for pregnancy but did not become pregnant during the trial. Therefore, these 2 participants were removed from these analyses but are included in the demographics and adverse event reporting. Neither participant experienced a depressive relapse during the 12 weeks of study monitoring. Of the participants in Group 2, 3 had discontinued their antidepressants before the baseline visit, and 3 maintained their baseline dose during the study.

There was one serious adverse event in the study. A Group 1 participant experienced a depressive relapse requiring inpatient hospitalization and her study participation was ended, although her relapse was included in

FIGURE 2
MADRS score trajectories



Montgomery-Åsberg Depression Rating Scale score trajectories are displayed by participant in **(A)** Group 1–the relapse prevention group, **(B)** Group 2–the acute treatment group, and **(C)** composites of each group across weeks of participation in the trial.

TABLE 5
Depression, pregnancy, and genetic status of participants who received EnBrace HR (N=19)

Participant ID	Psychiatric medications and dose at study entry	Months in remission at study entry	Taper of medications: timing of final dose/discontinuation (d/c)	Planning pregnancy status at study entry or weeks gestation
Group 1				
01	None	12	--	Starting fertility treatment
03	None	39	--	12 weeks
07	Escitalopram 7.5 mg/d	4	D/c between Visit 2 and Visit 3	Trying to conceive
08	Sertraline 150 mg/d	7	D/c between Visit 1 and Visit 2	15 weeks
10	None	2	--	9.5 weeks
11	None	10	--	Trying to conceive
16	Citalopram 40 mg/d Clonazepam .25 mg/d	Unknown	Did not taper medications although initially planned to do so[a]	Starting fertility treatment
18	Fluoxetine 20 mg/d	80	D/c between Visit 2 and Visit 3	Trying to conceive
19	Escitalopram 5 mg/d	37	D/c between Visit 5 and Visit 6	Planning to conceive
20	Bupropion 300 mg/d Escitalopram 20 mg/d	80	D/c bupropion between Visit 3 and Visit 4	Planning to conceive
22	None	84	--	Planning to conceive
24	Fluoxetine 20 mg/d	33	Did not taper medications although initially planned to do so[a]	Trying to conceive
25	Venlafaxine 150 mg/d Bupropion 200 mg/d	2	Tapered bupropion to 100 mg/d, venlafaxine to 112.5 mg/d	Planning to conceive
Group 2				
02	None	0	--	Trying to conceive
09	None	0	--	7.5 weeks
12	Bupropion SR 150 mg/d	0	--	27 weeks
15	Duloxetine 120 mg/d	0	--	16 weeks
17	None	0	--	26 weeks
23	Fluoxetine 20 mg/d	0	--	Trying to conceive

[a]Two participants were actively trying to conceive and planned to stop antidepressant medications when they tested positive for pregnancy but did not become pregnant during the trial.

Medication and length of remission status were recorded at baseline. Participants in Group 1 who had discontinued antidepressant medications proximal to study entry tapered off antidepressant medications within the past year prior to enrollment. MTHFR (methylene tetrahydrofolate reductase) enzyme activity was based upon single nucleotide polymorphism bases at C677T and A1298C.

	Pregnancy changes/events	MTHFR enzyme activity	C677T A1298C polymorphisms
	Pregnant between Visit 6 and Visit 7	Intermediate	C/T A/A
	--	Intermediate	C/T A/C
	--	Normal	C/C A/C
	Therapeutic abortion at 18 weeks due to Trisomy 18	Intermediate	C/T A/C
	--	Normal	C/C A/A
	--	Intermediate	C/T A/C
	Stopped trying to conceive at Visit 6	Intermediate	C/T A/A
	Pregnant between Visit 1 and Visit 2	Normal	C/C A/A
	Trying to conceive	Normal	C/C A/C
	Trying to conceive	Normal	C/C A/A
	--	Intermediate	C/T A/A
	--	Intermediate	C/T A/C
	Trying to conceive	Low	T/T A/A
	Pregnant between Visit 2 and Visit 3	Normal	C/C A/C
	--	Intermediate	C/T A/C
	--	Normal	C/C A/C
	--	Intermediate	C/T A/C
	Delivered	Intermediate	C/T A/A
	Became pregnant; miscarried	Intermediate	C/T A/A

study outcomes. She was pregnant and off of antidepressant medications at the time of relapse. **TABLE 2** summarizes the adverse events reported by participants during the trial.

Mood and quality of life

Of the 11 participants included in analyses in Group 1, 3 (27.3%) participants relapsed to an MDE, and of those 3, 2 remitted after relapse while still in the study and 1 was withdrawn from the study due to inpatient hospitalization. One participant was pregnant, 1 participant was in fertility treatment, and 1 participant had terminated pregnancy at time of relapse. All 3 were off of antidepressant medications when they relapsed, and the 2 participants who remained in the study elected not to restart antidepressants in the context of pregnancy planning. This relapse rate (**TABLE 3**) was significantly lower than historical controls of a similar population in the literature, which showed a 67.7% relapse rate for women discontinuing antidepressants in the context of preparation for conception and early pregnancy.[3]

Of the 6 participants in Group 2, all 6 (100%) remitted from MDEs. One participant in Group 2 remitted, relapsed, and remitted again over the course of the study**,** with relapse and remission defined by criteria for a current depressive episode on the MINI. One participant was pregnant, and 1 participant had just experienced a pregnancy loss at time of relapse. Both elected to remain on their antidepressant medications at the same dose in the context of pregnancy and efforts to conceive, utilizing the study supplement as an adjunctive treatment.

In Group 2 (N = 6), the mean change in MADRS score from baseline was -17.33 (SD = 7.17; $P = .0005$), representing a significant improvement in depression symptoms from baseline to the final visit. Five of the 6 participants in Group 2 (83.3%) achieved >50% improvement in MADRS score from baseline to the final visit. The participant who did not achieve a >50% improvement experienced a 33.3% improvement in MADRS score.

In examining the overall course of Group 2 participants' MADRS scores using a one-way repeated measures ANOVA, the results showed that the intervention elicited statistically significant decreases in mean MADRS total scores over time ($F[6, 29] = 5.16$, $P = .001$). Group 1 did not show statistically significant differences from baseline as analyzed through ANOVA ($F[6, 54] = 1.13$, $P = .357$) and through a direct comparison of mean MADRS score at

baseline and final visit. Trend in MADRS scores over time can be seen in **FIGURE 1**.

Separate one-way repeated measures ANOVAs, shown in **TABLE 4**, were run to determine if there were differences due to the EnBrace HR intervention in total scores for Group 1 (N = 11) or Group 2 (N = 6) in any of the following questionnaires: QIDS-SR, Q-LES-Q-SF, and EPDS. As anticipated, there were no statistically significant changes in scores for Group 1 participants. All but the Q-LES-Q-SF showed significant improvements in Group 2. Graphs of score trends for secondary outcomes can be seen in **FIGURE 1**. Trajectories for MADRS scores are displayed in **FIGURE 2**.

Laboratory and genetics results

Contrary to our hypotheses, we did not observe significant increases of vitamin B12 nor decreases in homocysteine or CRP associated with EnBrace HR supplementation. Because participants mainly had folate blood levels above the assay limit of detection, we were not able to assess changes across participation. A similar limitation concerned IL-6 levels, as many participants had levels below the assay limit of detection. The sample size of each group (Group 1: N = 9; Group 2: N = 6) was too small to perform specific analyses on laboratory measures and response to treatment, but there did not appear to be distinct observable patterns. Blood was not collected from 2 participants in Group 1 due to discomfort with blood-draw procedures. There were no clear patterns observed in pharmacogenetic results by group and no clear associations between polymorphisms in the MTHFR gene and depressive symptoms measured via mood questionnaires (**TABLE 5**).

DISCUSSION

In this preliminary study, we assessed EnBrace HR in 2 samples of women planning pregnancy or during pregnancy, to obtain data regarding: 1) the prevention of depressive relapse in women with histories of MDD, and 2) the acute treatment of depression in women who were depressed and either wanted to avoid the use of an antidepressant or did not want to increase the dose of one that they were already taking.

While the numbers of participants were small in each group, these data support further study for these indications. We found that among the women who entered the study in Group 1 who reduced or discontinued their antidepressants (N = 11) and who were not depressed and were interested in a treatment to prevent depressive relapse, 3 experienced a relapse to an MDE (27.3%). To provide context, in a previous observational study of women who either maintained or discontinued antidepressant medication for pregnancy who began pregnancy in remission from MDD, medication discontinuers experienced a relapse rate of 67.7%, medication continuers experienced a rate of depressive relapse of 26%, and the overall relapse rate was 43%.[3] In a separate meta-analysis examining depressive relapse rates in individuals with MDD who discontinued antidepressant treatment, the overall relapse rate was 41%.[6] While many participants in our sample were women who were trying to conceive and who became pregnant during the trial, thus having different inclusion criteria than this previous observational study, our finding is suggestive of a protective effect of EnBrace HR in depressive relapse prevention in women who plan to stop antidepressant medication in anticipation of pregnancy or while pregnant.

In Group 2 (those who entered the study in an MDE), we found that all the participants experienced remission by the end of the study, and 5 of 6 (83.3%) experienced a >50% improvement on the MADRS from baseline. One patient in Group 2, however, remitted, then relapsed briefly, then again remitted prior to completing the study. These findings similarly suggest an antidepressant effect of EnBrace HR.

In addition to the potential efficacy observed, we also found that EnBrace HR was well tolerated in this sample. One serious adverse event occurred during the study; 1 woman with a history of depression in Group 1 experienced a relapse of depression and was hospitalized. Considering the chronic and recurrent course of MDD, it was not unexpected based on existing evidence that women stopping antidepressants could experience worsening of MDD.

The strengths of this study include the assessment of a novel nutritional supplement for the prevention and treatment of depression in women planning pregnancy or who are pregnant. This is critical due to the high rate of depressive relapse among individuals who have MDD, as well as the frequent wish to avoid antidepressant medication among women who are pregnant or trying to conceive. Other strengths of the study include the rigorous assessments of history of MDEs and the diagnosis of MDD, and the validation of whether a patient was in an MDE at each study visit by a study psychiatrist using a validated

diagnostic tool, the MINI. We also collected biomarkers, which contributed to our assessment of exploratory variables for this pilot study.

Limitations

There are important limitations to this study. A major limitation is the lack of a placebo arm. For comparison, we can draw from other studies assessing depressive relapse and symptom burden in similar populations,[3] but concurrent parallel comparison groups were not available. Another major limitation is the small number of participants overall and in each group. Additionally, our study sample is largely represented by women who were White, non-Hispanic, married, and highly educated. Therefore, it is not clear if our findings are generalizable to the larger population of women of reproductive age. There was notable heterogeneity in pregnancy status, medication regimens, and taper schedules of enrolled participants. Finally, the study supplement contains multiple vitamins and minerals, including folic acid, L-methylfolate, and folinic acid, so study results cannot be attributed to one component of the supplement.

CONCLUSIONS

In summary, the results of this preliminary study suggest that 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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