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Transcranial direct current stimulation (tDCS) for depression in pregnancy: A pilot randomized controlled trial

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ABSTRACT

Background: Depression in pregnancy negatively affects maternal-child health. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation treatment for depression, has not been evaluated in pregnancy.
Objective: To conduct a pilot randomized controlled trial (RCT) to evaluate tDCS for antenatal depression.
Methods: In this pilot RCT in Toronto, Ontario (October 2014 to December 2016), adult pregnant women 14–32 weeks gestation with major depressive disorder who had declined antidepressant medication were considered for inclusion. Participants were randomly assigned 1:1 to tDCS or sham-control. Active tDCS comprised 30-min sessions of 2 mAmp direct current delivered over the dorsolateral prefrontal cortex, 5 days per week, for 3 weeks. Sham was administered similarly, but with current turned off after 30 s. Main outcomes were feasibility, acceptability, and protocol adherence. Maternal Montgomery Asperg Depression Rating Scale (MADRS) was measured post-treatment and at 4 and 12 weeks postpartum.
Results: Of 20 women randomized, 16 completed treatment and provided data (124 tDCS, 122 sham sessions). Views of treatment were positive with no serious adverse events. Post-treatment estimated marginal mean MADRS scores were 11.8 (standard error, SE 2.66) for tDCS and 15.4 (SE 2.51) for sham ($p = 0.34$). At 4 weeks postpartum, 75.0% of tDCS women were remitted versus 12.5% sham-control ($p = 0.04$).
Conclusions: Results support proceeding to a definitive RCT to evaluate tDCS for antenatal depression. The preliminary efficacy estimates immediately post-treatment and in the postpartum, are encouraging with respect to the potential use of tDCS to improve treatment rates in this population. The trial was registered at: clinical trials.gov (NCT02116127).

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Introduction

Major depression affects up to 10% of pregnant women and is associated with adverse outcomes for mother and developing child [1]. These include negative impact on maternal well-being and quality of life, and poor neonatal outcomes such as preterm birth and problems with fetal growth and development [2]. Depression in pregnancy is the strongest predictor of postpartum depression (PPD), a condition linked to problems with maternal-child interactions and child motor, language and socioemotional development [2]. Standard depression treatments are not ideal for pregnant women. Psychotherapies require time to take effect, and are often ineffective for severe depression [3]. Antidepressants (e.g. selective serotonin reuptake inhibitors) can be effective within

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weeks, but fetal exposure may increase risk for adverse child outcomes [4]. Accordingly, acceptability of current treatments is low, likely contributing to undertreatment of depression in this population, where as few as 20% of patients receive adequate care for their illness [5].

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation treatment for depression that changes regional brain activity in the prefrontal cortex without impacting autonomic or thermoregulatory functions [6,7], thus posing no theoretical risk to a developing fetus when applied in pregnancy. A recent meta-analysis of 6 trials (289 non-pregnant patients with depression) found active tDCS superior to sham-control with response rates of 34% vs. 19%, remission rates of 23.1% vs. 12.7% [8] and no differences between groups in treatment acceptability or drop-out rate [9]. A systematic review of neurostimulation treatments for antenatal depression revealed no randomized controlled trials (RCTs) assessing the safety and efficacy of tDCS in pregnancy [10]. Herein, we report on the first RCT of tDCS for depression in pregnancy. The objective of the study was to assess the feasibility, acceptability and adherence to an RCT protocol for tDCS to treat depression in pregnancy.

Methods and materials

Study design

Following informed consent, we randomized pregnant women to active tDCS or sham-control between October 2014 and December 2016. Follow-up was completed in July 2017.

Ethics statement

All authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants were approved by the Research Ethics Boards at Women's College Hospital (WCH) and Sinai Health System (SHS), fully-affiliated University of Toronto hospitals in Toronto, Ontario, Canada. The trial was registered at clinical trials.gov (NCT02116127). The study protocol is at: https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-366 [11].

Participants

Women were referred to the trial by their psychiatrists at the participating hospitals (WCH and SHS). Pregnant women (aged 18 years or older) 14–32 weeks gestation, who had been offered but declined to use antidepressant medication in pregnancy were considered for inclusion. The lower gestational age limit was selected to minimize risk for spontaneous abortion; the upper limit to increase probability that the intervention phase (~3 weeks in length) would be completed before delivery. Included participants met criteria for major depressive disorder and were in a current major depressive episode, moderate or severe, without psychotic features, as per Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.

Exclusion criteria were: (1) alcohol or substance use disorder in the previous 6 months, (2) major and unstable medical or neurologic illness or history of seizure, (3) metal implants in the cranium or electrical implants, (4) benzodiazepine (except for intermittent use of low-dose lorazepam) or anticonvulsant use (these interfere with anodal tDCS), and (5) non-intact skin on scalp areas at stimulation electrode sites. To enroll women with lower risk pregnancies, we also excluded women with: (6) previous very preterm delivery (<32 weeks gestation), and (7) a current fetal anomaly or major obstetrical complication.

Consent statement

Written informed consent was obtained from all participants.

Interventions

For active tDCS, 2 mA of direct current was delivered using a battery-driven constant current stimulator (Magstim) [12–14]. To target the dorsolateral prefrontal cortex, the anode was placed over F3 and cathode over F4 (10–20 international system for EEG placement) in 5×7 cm saline soaked sponge electrodes, as in a previous study by members of our team [12]. In this previous study, sessions were 20 minutes long, however better efficacy was subsequently demonstrated with 30-minute sessions by another investigator group [15,16]. As such, fifteen 30-minute sessions were delivered over approximately 3 weeks (one per working day) by a trained obstetrical research nurse. Participants were instructed to sit quietly, and nurses instructed to limit engagement with participants, other than to provide instructions directly relevant to delivery of the intervention, to prevent co-intervention and accidental unblinding. Sham stimulation was administered with the same parameters and at the active treatment site, but the current was turned off after 30 s in a slow ramp down that mirrors sensory adaptation in ongoing stimulation, as in prior tDCS clinical trials [16]. Participants received clinical care from their regular mental health and obstetrical providers, who were blind to group allocation. Concurrent pharmacologic and non-pharmacologic depression treatments were documented.

Outcomes

To assess feasibility, we recorded the number of eligible participants, proportion recruited, reasons for non-participation, the number of participants who completed all 15 active study sessions, reasons for discontinuation, and the proportion of follow-up questionnaires completed immediately post-treatment (primary endpoint) and at 4 and 12 weeks postpartum.

To assess in-treatment safety, maternal blood pressure, maternal heart rate and fetal heart rate were recorded prior to and following each session. For pregnancies of <24 weeks gestation, fetal heart rate was measured using a hand-held doppler monitor. For pregnancies ≥24 weeks gestation, continuous fetal monitoring was performed for 10 min prior to the procedure, during the session, and for 10 min afterward using a non-stress test. We administered the Toronto Side Effects Scale at the end of each of weeks 1, 2 and 3 to systematically assess for side effects commonly observed with antidepressant treatment [17]. A pregnancy complications questionnaire was administrered weekly during treatment. This questionnaire asked women whether they had experienced any of severe nausea, infection, bleeding, placenta previa, placental abruption, hypertensive disorders of pregnancy (inlcuding eclampsia/pre-eclamplsia) or any other complication. Spontaneously reported side effects during treatment sessions were recorded in treatment session logs.

Post-treatment, the research coordinator administered a semi-structured treatment perceptions questionnaire (Table S1). The pregnancy complications questionnaire was administered every 4 weeks until delivery. At 4 weeks postpartum, we administered a neonatal outcomes questionnaire that queried type of labour (including premature rupture of membranes and labour induction) and delivery, complications of labour and delivery, gestational age

and weight at birth, and neonatal complications, including specific severe conditions and neonatal intensive care unit admissions [18].

The main maternal clinical outcome was the 10-item clinician-administered Montgomery Asberg Depression Rating Scale (MADRS) [19,20]score. Other outcomes were the Edinburgh Postnatal Depression Scale (EPDS), a self-report perinatal depression scale ([21]) and the State-Trait Anxiety Inventory (STAI), a self-report anxiety measure validated in perinatal populations. These were administered immediately post-treatment and at 4 and 12 weeks postpartum ([22]). Infant clinical outcomes were measured since both infant temperament and infant development can be adversely affected by untreated maternal depression [2]. At 12 weeks postpartum, we administered the Infant Characteristics Questionnaire [23] (ICQ) to assess parental perceptions of difficult infant temperament and the Ages and Stages Questionnaire (ACQ) (3-month) to assess infant development [24,25].

Sample size

At least 20 participants are generally required to allow for sufficient variability in assessing the implementation of procedures involved in an intervention delivery ([26]). For the MADRS, a minimal clinically important difference between groups is considered to be 1.6–1.9 points, with slightly larger observed differences in tDCS trials with non-pregnant samples [27]. Twenty participants would be too small to detect these clinically significant differences, so we did not expect to observe a statistically significant effect in the pilot study on the MADRS or on any other clinical outcome.

Randomization and blinding

Randomization was in a 1:1 ratio (tDCS: sham) stratified by gestational age at enrollment (<24 weeks; $\geq$ 24 weeks) so a similar number of participants in each group could receive continuous fetal monitoring. A research assistant external to the study generated the allocation sequence using a random permuted block randomization table and placed group allocations into sealed envelopes. The study coordinator selected an envelope to include in the participant's chart, thus remaining blind to group allocation. The obstetrical research nurse opened the envelope to determine group allocation and programmed the tDCS device accordingly (i.e. active tDCS or sham). The nurse, not blind to group allocation, recorded objective outcome measures (i.e. physiological parameters). Participants, their health care providers and the study research personnel who collected maternal and infant clinical outcome data were blind to group allocation.

Statistical analysis

The number of participants screened, eligible, consented and randomized were reported. The number of participants who started treatment, completed treatment and completed each set of follow-up questionnaires were tabulated for each treatment allocation. Baseline demographic and clinical characteristics were described for each group.

Maternal and fetal physiologic parameters were reviewed at the treatment session level for any observed abnormalities. We analyzed the frequency of spontaneously-reported in-treatment side effects at the participant level, comparing active tDCS to sham-control using generalized estimating equations to account for clustering within participant. Results from the Toronto Side Effects Scale, pregnancy complications and neonatal outcome questionnaires, ICQ and ASQ were reported at the participant level where means were compared between groups using t-tests for independent samples and Fisher's exact chi-square tests of association for categorical variables. Women's views of treatment derived from the semi-structured interview were summarized.

Maternal symptom scores (MADRS, EPDS, STAI) at each time point were compared between active tDCS and sham-control using analysis of covariance to adjust for baseline score, with marginal means reported to account for differences at baseline. Missing data were not imputed. The proportion of participants in remission (MADRS < 10) at 4 and 12 weeks postpartum (i.e. the proportion without postpartum depression, PPD) were compared between groups using chi-square tests of association.

Results

Feasibility of recruitment, retention and protocol adherence

From 33 eligible participants, 20 (61%) consented and were randomized to tDCS ($n = 10$) or sham-control ($n = 10$) (Fig. 1). Reasons for non-participation included difficulty with the study time commitment, travel to the hospital and competing childcare responsibilities. Participants ranged in age from 26 to 43 years (mean 32.3, standard deviation 4.15), with a median gestational age at enrolment of 21 weeks (interquartile range 20–26 weeks). Most participants had recurrent depression, comorbid anxiety disorders, and mean MADRS scores in the moderate range. Characteristics were similar by treatment allocation (Table 1).

Two participants, one in each group, withdrew prior to starting the protocol; one due to an obstetrical complication, the other due to childcare conflicts. Sixteen of the remaining (88%) completed the 15 sessions. One participant allocated to tDCS attended 4 sessions and 1 participant allocated to sham-control attended 1 session; both withdrew due to difficulty with travel commitment, resulting in 124 tDCS session and 122 sham-control sessions for analysis. Follow-up questionnaires were completed by 17 out of 18 (94%) immediately post-treatment, and by 16 out of 18 (88%) at 4 and 12 weeks postpartum. The mean time to delivery from the immediate post-treatment assessment was 123.4 days (SD 32.4) and 134.5 days (SD 20.1) in the active and sham groups respectively ($F = 0.571$, $p = 0.462$). No unblinding of participants nor outcome data collectors occurred during the trial. The strength of the blind is not reported, as it is difficult to determine whether participant guesses about their treatment allocation would reflect failure of blinding, or accurate assumptions about the efficacy of the intervention [28].

Safety and tolerability

Maternal heart rate, maternal blood pressure and fetal monitoring were all within normal limits in both groups. There were 46 sessions where pregnancies were $\geq$24 weeks gestation and continuous fetal monitoring was possible (31 tDCS, 15 sham-control) with no abnormalities noted. In-treatment, minor, transient, maternal side effects were reported in 22 out of 124 (17.7%) of tDCS vs. 5 out of 122 (4.7%) of sham-control sessions ($p = 0.001$). The only side effect reported more than 3 times in either group was “buzzing” or “tingling” at the electrode site, reported in 9 (7.3%) of tDCS sessions and no sham-control sessions ($p = 0.003$). On the Toronto Side Effects Scale, 9 women in each group provided data for at least 1 week of treatment. No significant differences were observed when comparing the proportion of women in each group who reported a specific side effect as occurring often or always or very or extremely troublesome in any of weeks 1, 2 or 3 (Table 2a).

No serious pregnancy complications were reported in either group. Mean (SD) gestational age at birth was 39.0 (1.4) in tDCS and 38.9 (1.1) in sham-control ($p = 0.84$). Mean (SD) birth weight was 7.0 lbs (0.54) vs. 7.1 lbs (1.2) in tDCS vs. sham-control groups

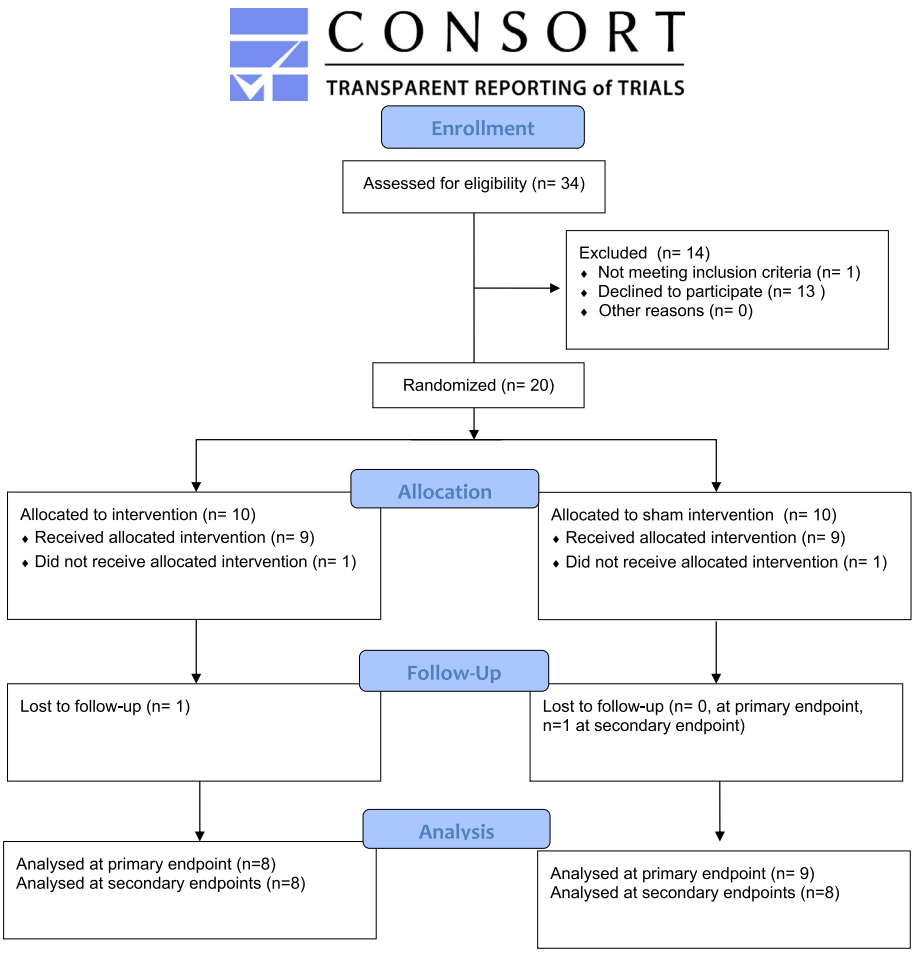

Fig. 1. CONSORT trial flow diagram.

($p = 0.80$). There was 1 infant in each group with an Apgar score less than 8 at 1 min after birth and no infants with an Apgar score less than 8 at 5 min after birth. One infant in the tDCS group had a spontaneous preterm birth (36 weeks and 5 days gestation), was monitored in the neonatal intensive care unit, and discharged with no known further sequelae. There were no other neonatal complications in either group. There were no differences between groups on any of the infant developmental-behavioural outcome indicators (Table 2b).

Women's views of treatment

Seven out of 8 (87.5%) of participants allocated to tDCS were satisfied or extremely satisfied with treatment, as were 7 out of 9 (77.8%) of those allocated to the sham-control. Participants commented that flexible scheduling of daily appointments was helpful, but daily travel made this a large commitment. Seven women (41.2%; 2 allocated to tDCS, 5 allocated to sham-control) indicated that they would have preferred a different treatment schedule (i.e. not daily, evenings or weekends). All women allocated to tDCS ($n = 8$) and 6 (77.8%) of those in the sham-control felt that it was an acceptable alternative to antidepressants. Selected comments are in Box 1 (Patient Perspectives).

Maternal symptoms

At the primary endpoint, the mean MADRS score dropped from 23.5 (SD 5.15) to 11.4 (SD 7.11) in the tDCS group and from 26.8 (SD 7.48) to 15.8 (SD 7.65) in the sham control group. Using analysis of covariance adjusting for baseline MADRS score in the primary analysis, estimated marginal mean (EMM) MADRS score was 11.8 (standard error, SE, 2.66) immediately post-treatment for those in the tDCS group, about 4 points lower than in the sham-control group (EMM 15.4, SE 2.51) ($F = 0.97$, $p = 0.34$) (Fig. 2). The pattern of non-significantly lower scores in the tDCS group persisted at the secondary endpoints. At the primary endpoint, there were 3 out of 8 (37.5%) participants with MADRS < 10 in the tDCS group versus 2 out of 9 (22.2%) in sham-control ($p = 0.62$). At 4 weeks postpartum, 6 out of 8 (75.0%) participants receiving tDCS had reached remission vs. 1 out of 8 (12.5%) receiving sham-control (Chi-square 6.35, Fisher's exact $p = 0.04$). At 12 weeks postpartum, remission rates were 75.0% (6 out of 8) and 25.0% (2 out of 8) for tDCS and sham-control respectively (Chi-square 4.00, Fisher's exact $p = 0.13$).

The tDCS group had lower EPDS scores than the sham-control group at all time points that were non-significant statistically (Table 3). There was minimal apparent effect of tDCS on anxiety scores as measured by the STAI (also in Table 3). No participants took antidepressants during pregnancy. Two participants allocated to active tDCS group and 3 allocated to sham-control started antidepressants by 12 weeks postpartum.

Discussion

To our knowledge, this pilot trial is the first RCT of tDCS for depression in pregnancy. This study demonstrated feasibility of recruitment, adherence to protocol and acceptability of a clinical

Table 1
Baseline Characteristics, presented as N (%) unless otherwise stated, for the active transcranial direct current stimulation (tDCS) and sham-control groups.

	Active tDCS (n = 10)	Sham control (n = 10)
Sociodemographics		
Age in years (mean, SD)	31.2 (4.0)	33.3 (4.3)
Married or cohabitating/common-Law	8 (80)	9 (90)
Completed a university degree	8 (80)	9 (90)
Employed outside the home	7 (70)	7 (70)
Annual Household Income >$80,000	6 (60)	8 (80)
Obstetrical Characteristics		
Median (interquartile range) gestational age in weeks	21 (20–26)	21 (19–26)
Median (interquartile range) number of pregnancies	3 (2–3)	2 (1–4)
Median (interquartile range) number of previous births	1 (0–1)	0 (0–1)
Pre-existing medical condition*	3 (30)	3 (30)
Medications, vitamins or supplements**:		
Antihistamine	3 (30)	3 (30)
Prenatal Vitamin	8 (80)	10 (100)
Current smoker	0	1 (10)
Current alcohol use	0	1 (10)**
Psychiatric Characteristics		
Two or more episodes of depression (including current)	8 (80)	8 (80)
Comorbid generalized anxiety disorder	8 (80)	8 (80)
Comorbid panic disorder	1 (10)	2 (20)
Comorbid obsessive-compulsive disorder	1 (10)	2 (20)
Comorbid post-traumatic stress disorder	1 (10)	0
Current individual psychotherapy	4 (40)	5 (50)
Current group psychotherapy	1 (10)	1 (10)
Lifetime use of antidepressant medication	6 (60)	4 (40)
Lifetime psychiatric hospitalization	2 (20)	1 (10)
Lifetime suicide attempt	3 (30)	2 (20)
Baseline Symptom Scores		
Montgomery-Asperg Depression Rating Scale, Mean (SD)	23.5 (5.15)	26.8 (7.48)
Edinburgh Postnatal Depression Score, Mean (SD)	17.5 (5.02)	14.7 (6.77)
State-Trait Anxiety Inventory – State, Mean (SD)	49.4 (11.8)	50.7 (7.68)
State-Trait Anxiety Inventory – Trait, Mean (SD)	57.2 (10.0)	56.2 (12.9)

*Participant-reported medical conditions: asthma, eczema, gallstones and hypothyroidism for the active treatment group; anemia, asthma, arthritis, gastro-esophageal reflux, hypoglycemia and osteoporosis in the control group; **Other medications were: Active tDCS - asthma medication (n = 1), iron supplement (n = 1), thyroid replacement (n = 1); sham-control – antibiotic (n = 1), proton pump inhibitor (n = 1), hypnotic (n = 1)***Participant reported 1 alcoholic beverage per week; note that 1 participant in the tDCS group reported no alcohol at baseline, but ~1 beverage/week at follow-up interviews during pregnancy.

Table 2a
Toronto Side Effect Scale, side effects reported as occurring often or always or very or extremely troublesome in any of week 1, 2 or 3 in N (%), comparing active tDCS (n = 9 participants) to sham (n = 9 participants).

Side Effect	Active tDCS (n = 9)	Sham control (n = 9)	X^2	Fisher's exact p
Nervousness	6 (66.6)	7 (77.7)	0.28	1.00
Agitation	5 (55.6)	4 (44.4)	0.64	1.00
Tremor	0	0	–	–
Twitching/myoclonus (muscle contraction)	0	0	–	–
Abdominal Pain	2 (22.2)	2 (22.2)	0.00	1.00
Dyspepsia (upset stomach)	1 (11.1)	3 (33.3)	1.29	0.58
Nausea	1 (11.1)	4 (44.4)	2.49	0.29
Diarrhea	1 (11.1)	2 (22.2)	0.40	1.00
Constipation	2 (22.2)	0	2.25	0.47
Decreased Appetite	2 (22.2)	2 (22.2)	0.00	1.00
Increased Appetite	3 (33.3)	5 (55.6)	0.90	0.64
Weakness or Fatigue	5 (55.6)	3 (33.3)	0.90	0.64
Dizziness	4 (44.4)	3 (33.3)	0.23	1.00
Postural Hypotension (dizzy getting up)	2 (22.2)	3 (33.3)	0.28	1.00
Drowsiness/daytime somnolence	6 (66.6)	7 (77.7)	0.28	1.00
Increased Sleep	3 (33.3)	3 (33.3)	0.00	1.00
Decreased Sleep	4 (44.4)	6 (66.6)	0.90	0.64
Sweating	0	0	–	–
Flushing	0	0	–	–
Edema (fluid retention)	0	1 (11.1)	1.06	1.00
Headache	3 (33.3)	3 (33.3)	0.00	1.00
Blurred Vision	2 (22.2)	1 (11.1)	0.40	1.00
Dry Mouth	0	2 (22.2)	2.25	0.47
Anorgasmia (no orgasm)	0	0	–	–
Increased Libido	1 (11.1)	1 (11.1)	0.00	1.00
Decreased Libido	2 (22.2)	3 (33.3)	0.28	1.00
Other	2 (22.2)	3 (33.3)	0.28	1.00

Weight gain and weight loss questions not reported as these are difficult to interpret as side effects in the context of pregnancy (i.e. number of pounds gained or lost).

Table 2b
Infant outcomes following a tDCS protocol for depression in pregnancy comparing active tDCS (n = 8 participants) to sham (n = 8 participants).

	Active tDCS (n = 8)	Sham Control (n = 8)	p-value
Infant Characteristics Questionnaire (higher = more impairment)			
Mean (SD) Fussy Subscale [norm: 17.8 (5.88)]	16.9 (4.73)	19.8 (6.20)	0.32
Mean (SD) Unadaptable Subscale [norm: 8.90 (1.85)]	8.00 (3.07)	8.75 (3.32)	0.65
Mean (SD) Dull Subscale [norm: 5.88 (1.85)]	7.88 (2.90)	6.38 (1.51)	0.22
Mean (SD) Unpredictable subscale [norm: 7.32 (2.69)]	9.88 (1.72)	10.1 (4.70)	0.89
Ages and Stages Questionnaire			
Mean (SD) Communication (< 35 is below norm)	45.6 (9.04)	49.4 (7.29)	0.38
Mean (SD) Gross Motor (< 40 is below norm)	47.5 (8.00)	47.5 (8.00)	1.00
Mean (SD) Fine Motor (< 30 is below norm)	32.5 (16.7)	40.6 (12.7)	0.29
Mean (SD) Problem Solving (< 35 is below norm)	46.9 (9.61)	46.3 (5.18)	0.87
Mean (SD) Personal-Social (< 35 is below norm)	40.6 (6.78)	46.3 (12.2)	0.27

Box 1
Patient Perspectives

Selected participant responses to the question: "Was this an acceptable alternative to antidepressant medication use during your pregnancy?"

"Absolutely 100%. I was apprehensive about taking meds in pregnancy, especially antidepressants even though I know the research doesn't show negative effects. I still think it is better to avoid meds while pregnant. Plus, this may turn out to be more effective with fewer risks" *active tDCS*

"I never would have considered an antidepressant in a million years" *sham*

"Tried medication before and it never worked, with this I can see a little bit of improvement" *active tDCS*

"This (no meds) was the main motivation" *sham*

"Using an antidepressant was never a reasonable option for me during my pregnancy" *active tDCS*

"Would never prefer to use antidepressants" *sham*

"Yes, it was better. I am pregnant I was aware of medications and possible side effects. With this treatment, there were no side effects – this meant a lot of me, especially for my child" *active tDCS*

trial of tDCS as a treatment option for antenatal depression. While the trial was not powered to evaluate efficacy, preliminary estimates were promising with a difference between groups on the MADRS corresponding to more than double the minimal clinically important difference on this scale. Positive effects of the treatment distal to the acute treatment course, as evidenced by a significant positive effect of tDCS on PPD risk, further support the argument for a definitive evaluation of this intervention.

The most important consideration of a pilot trial is the applicability of its methods and findings to a future definitive trial. Almost 2 of every 3 eligible women referred to the study consented to participation, a reasonably high proportion of women given that tDCS had never been previously studied in pregnant women. This may speak to a desire of pregnant women to avoid systemic medication treatment, but also supports the feasibility of the education procedures that were implemented to inform providers about the study and ensure appropriate referrals. Women had very positive views of treatment, and the intervention was well-tolerated, as in non-pregnant populations [9]. A relatively high proportion of participants in both groups reported bothersome side effects on the Toronto Side Effects Scale (TSES). The TSES was developed to assess symptoms of antidepressant drug treatment so many of the symptoms are quite non-specific. As such, the high level of symptoms in both groups could be attributable to the somatic symptoms of pregnancy, as well as the high level of depressive symptomatology or expectations about treatment. An alternative method for systematic measurement of side effects might be used in future to complement the TSES measure. The high completion and long-term follow-up rates (88%) also bode well for a future trial.

During over 120 tDCS sessions there was no evidence of negative maternal or fetal physiological impact. Neither were there any adverse events reported in the 3 previously published case studies of tDCS in pregnancy [29–31]. While a definitive safety evaluation would require a much larger sample, an argument could be made to conduct the full clinical trial without the extensive monitoring provided in the pilot phase. Lack of convenience is a barrier to participation in research for pregnant women [32], so offering the tDCS intervention protocol at the clinics where women are already receiving care could increase speed of recruitment. Most eligible women who declined participation did so for practical reasons (e.g. no childcare, long commute times), so we could increase recruitment by using office or home-based treatment protocols. tDCS equipment is portable and inexpensive; home-based treatment protocols are now used in tDCS trials, so this may be a feasible option [33].

The pilot study, by design, was not powered to evaluate the efficacy of tDCS in pregnancy. Yet, the differences in depression symptom scores favouring active tDCS, while not statistically significant, are encouraging. Our findings immediately post-treatment are consistent with reported effect sizes for tDCS in the non-pregnancy literature [15]. The 4 point difference between groups on the MADRS observed in our study is greater than the minimal clinically important difference cited for this scale [27]. Notwithstanding a similar difference between groups compared to prior tDCS studies, it is of interest that the sham response rate is higher than that observed in non-pregnant tDCS studies. Many prior studies were conducted in treatment-resistant populations. Herein, women wanted tDCS so as to avoid systemic fetal medication exposure. So, the reduction in symptoms in the sham group could simply reflect the course of illness over time in non-treatment resistant pregnant populations. Another possibility is that the behavioural activation effect from attending treatment 5 days per week over a 3 week period is greater in pregnant than non-pregnant populations. Further, daily fetal monitoring, representing repeated confirmation that the fetus is viable, could also have lowered symptoms. If a future trial were to be conducted in a home-based setting where the behavioural activation component

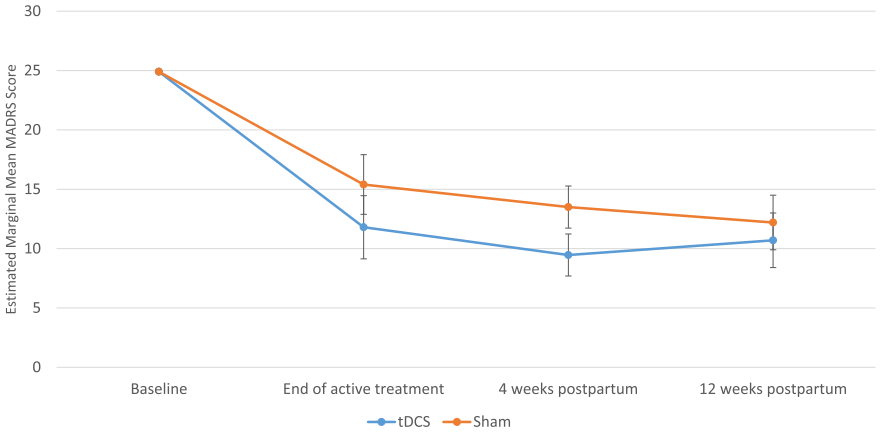

Fig. 2. Intention to treat analysis comparing MADRS scores of active tDCS to sham control at primary (end of active treatment) and secondary endpoints, presented as estimated marginal means (standard error) and analysis of covariance evaluated with baseline MADRS score evaluated at a covariate value of 24.9.
F = 0.97, p = 0.34 at end of active treatment; F = 2.65, p = 0.13 at 4 weeks postpartum; F = 0.22, p = 0.65 at 12 weeks postpartum.

Table 3
Intention to treat analyses of Edinburgh Postnatal Depression Scale (EPDS) and Spielburg State-Trait Anxiety Inventory (STAI), presented as estimated marginal means (standard error, SE) comparing active tDCS to sham control.

	tDCS (n = 8)	Sham (n = 9)	F-statistic	p-value
EPDS				
Primary endpoint	9.9 (1.9)	10.8 (1.8)	0.11	0.75
4 weeks postpartum (n = 8/group)	6.8 (1.7)	9.7 (1.7)	1.31	0.27
12 weeks postpartum (n = 8/group)	6.7 (1.7)	9.0 (1.7)	0.96	0.34
STAI-State				
Primary endpoint	40.9 (4.6)	40.2 (4.3)	0.02	0.90
4 weeks postpartum (n = 8/group)	30.6 (3.6)	39.2 (3.6)	2.81	0.12
12 weeks postpartum (n = 8/group)	39.1 (4.6)	36.8 (4.6)	0.13	0.72
STAI-Trait				
Primary endpoint	49.5 (3.2)	46.3 (3.0)	0.56	0.47
4 weeks postpartum (n = 8/group)	39.5 (4.7)	45.5 (4.7)	0.85	0.37
12 weeks postpartum (n = 8/group)	43.9 (4.9)	49.0 (4.9)	0.54	0.48

is absent, then a lower placebo response rate might be observed. These issues highlight the essential nature of a sham-control group for this type of study, and a sample size calculation for a future study should include a fairly substantive expected response in the sham group.

While the sample was small and the findings would have to be replicated in a larger sample, it is notable that 75% of women in the tDCS group were in remission when assessed at one month postpartum, compared to only 12.5% of women in the sham-control (a statistically significant difference). This finding is consistent with previous findings that tDCS's antidepressant effects are sustained after the acute phase of treatment [13,16,34–37]. Given the rapid hormone shifts from the pregnancy to postpartum state that play a role in the onset of PPD, along with the additive impact of early postpartum sleep deprivation and stress in the transition to parenthood, we would have expected to see postpartum symptom resurgence [38]. If tDCS confers protection to this vulnerability, it may have additional applications as a preventive intervention for women at risk for PPD. A recent randomized trial of 16 women found that one session of active DLPFC tDCS stimulation resulted in reduced amygdala threat reactivity, and increased activity in cortical regions responsible for attentional control in women with high trait anxiety, compared to sham stimulation [39]. PPD (often a clinically anxious state) is associated with altered functional connectivity and activity changes in brain areas implicated in emotion and reward processing, and in executive functioning, including diminished cortical-amygdala connectivity in response to negative emotional faces [40,41]. This therefore suggests a possible target of action for tDCS' treatment effects that could be particularly applicable in the antenatal and/or postnatal period. In a future study, it will be essential to carefully measure possible reasons for any observed immediate and/or distal treatment effects, including the impact of concurrently delivered psychological interventions.

The main limitation to the applicability of this pilot study's results to a future study would be a change of intervention delivery setting to increase recruitment. Our rigorous protocols may have biased the sample in favour of women with support systems that allow for the time-consuming hospital-based intervention protocol (and who are thus more likely to adhere to follow-up protocols). While our completion and follow-up rate might not be generalizable to a larger trial with home or office-based treatment, increased convenience of such a protocol could result in faster recruitment and similar or better retention. Combined with the large body of evidence that tDCS is a non-invasive treatment, our preliminary data support the argument that risk to the developing fetus is unlikely. As such, we believe that proposing a monitoring plan for a future larger trial that continues to include maternal blood pressure and heart rate, and fetal heart rate monitoring around the time of treatment in a clinic or at-home setting is reasonable. A sub-group of consenting participants could receive a more in-depth assessment, not only to better demonstrate safety, but also to explore mechanisms of, or biomarkers for, fetal response to changes in the

maternal depressive state, with similar measures to studies exploring the fetal effects of maternal depression [42]. Additional strategies to increase recruitment in a larger efficacy study could involve promoting convenience by providing on-site childcare supervision, inclusion of women in the first trimester of pregnancy to increase the pool of participants, and expanding the trial to include multiple sites. To our knowledge, there have not been any meaningful changes to recommended tDCS treatment parameters since our original protocol was developed. Given the reassuring safety data and the suggestion of efficacy in our study, we would therefore recommend that a future large study use the same active tDCS parameters as in our pilot. Recommendations for improving the sham in tDCS trials have recently been reported and we would recommend future trials adhere to the recommendations of that report [43]. In a future study, as long as ethical approval is successfully obtained to do so, we will use pre-coded stimulation to blind the delivery agent to the allocation.

In summary, the results of the first known RCT for tDCS among pregnant women with depression provide the basis to proceed to a large confirmatory efficacy trial with procedures that parallel those of this pilot study. If shown definitely to be safe and effective, tDCS could be scaled easily for widespread use to treat depression in pregnant women, and prevent the long-term adverse sequelae of this illness for women and their children.

Declaration of interests

In the past 5 years, Dr. Vigod has received research support from the Canadian Institutes of Health Research, Sick Kids Foundation and the Ontario Ministry of Health. She receives an honorarium from UpToDate for publications related to depression and antidepressant use in pregnancy. Dr. Daskalakis has received research and equipment in-kind support for investigator-initiated studies through Brainsway Inc and Magventure. Dr. Blumberger receives research support from the CIHR, Brain and Behavior Research Foundation, National Institutes of Health, Temerty Family through the Centre for Addiction and Mental Health Foundation and the Campbell Family Research Institute. He receives non-salary operating funds and in-kind equipment support from Brainsway Ltd. for an investigator-initiated study. He is the site principal investigator for a sponsor-initiated clinical trial from Brainsway Ltd. He receives in-kind equipment support from Tonika/Magventure for an investigator-initiated study. No other authors have any competing interests, financial or otherwise, to disclose.

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Author contribution

Concept and design: All authors.
Obtained funding: All authors.
Statistical analysis: Vigod.
Drafting of the manuscript: Vigod.
Critical revision of the manuscript for important intellectual content: All authors.

Data availability

Dr. Vigod had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.06.019.

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