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REVIEW

Neuromodulation and antenatal depression: a review

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Background: Depression during pregnancy affects 5%–8% of women. While the percentage of women in the US taking serotonin reuptake inhibitors during pregnancy has risen over the last decade, pregnant women continue to report that they prefer non-pharmacologic interventions.

Objective: We review the literature regarding neuromodulation techniques for major depressive disorder during pregnancy. The rationale for their use in this population, new developments, and future directions are discussed.

Methods: A literature search was conducted in PubMed Plus, Ovid Medline, and Embase to collect all articles on neuromodulation for the treatment of depression during pregnancy. Key search words included electroconvulsive therapy, transcranial magnetic stimulation, deep brain stimulation, transcranial direct current stimulation, neuromodulation, depression, and pregnancy. Given the sparse literature, all articles from 1960 to 2014 that addressed the use of neuromodulation in pregnancy were included.

Conclusion: The data support the use of electroconvulsive therapy in all trimesters of pregnancy for major depressive disorder. New data are emerging for the use of transcranial magnetic stimulation in pregnancy, which is likely safe, but more data are needed before it can be recommended as a primary treatment modality during pregnancy. Other neuromodulation techniques have not been well studied in this population.

Keywords: electroconvulsive therapy, transcranial magnetic stimulation, pregnancy, depression, antenatal depression, perinatal

Introduction

In psychiatry, the term neuromodulation refers to the therapeutic electrical stimulation of a network of neurons in the central nervous system. It is modulation in the sense that the network may be excited, for example, by the stimulation of excitatory neurons or can conversely be inhibited by the stimulation of inhibitory neurons.[1,2] In most cases, neuromodulation is not used as a first-line treatment for depression in the nonpregnant population but rather in treatment-resistant patients or in those who cannot tolerate pharmacologic interventions.[3] However, the treatment of major depressive disorder during pregnancy (antenatal depression, AD) may present an exception to this generality because there is a preference to avoid psychotropics. There are a variety of neuromodulatory modalities that can serve as alternative treatment options. Some of these techniques require surgical intervention or anesthesia (electroconvulsive therapy [ECT], vagus nerve stimulation [VNS], deep brain stimulation [DBS]), while others can be done in an outpatient setting (transcranial magnetic stimulation [TMS], transcranial direct current stimulation [tDCS]). Specialized equipment and training are required to administer all neuromodulation treatments, limiting the possibility of their use in nonacademic settings, especially early in development or when surgical equipment and personnel are required.

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Depressive symptoms affect up to 20% of pregnant women with 5%–8% meeting criteria for major depressive disorder at some point in their pregnancy.[4–6] No psychotropic has been shown to be completely without risk during pregnancy. Likewise, depression is not risk-free and has been shown to be associated with preterm birth (PTB), preeclampsia, and low birth weight,[7,8] as well as undesirable maternal health behaviors such as tobacco, alcohol, and illicit drug use, decreased prenatal vitamin use, and decreased prenatal physician visits.[9–11]

Many pregnant women report moderate-to-high decisional conflict regarding antidepressant use during pregnancy,[12] and find non-medication treatments such as psychotherapy more acceptable than the use of psychotropics.[13,14] Accordingly, the use of antidepressants drops significantly during pregnancy in many women.[15,16] Although there is preliminary evidence that psychotherapies, particularly cognitive behavioral therapy and interpersonal psychotherapy,[17–19] are efficacious for AD, barriers include difficulty finding qualified providers, cost, and significant time necessary to induce improvement. Therefore, neuromodulation is an appealing alternative for the treatment of psychiatric illness in pregnant women. Here, we review the most common neuromodulation options and their applicability to pregnant women with major depressive disorder.

Methods

A literature search was conducted in PubMed Plus, Ovid Medline, and Embase to collect all articles on neuromodulation for the treatment of depression during pregnancy. Key search words included electroconvulsive therapy, transcranial magnetic stimulation, deep brain stimulation, transcranial direct current stimulation, neuromodulation, depression, and pregnancy. Given the sparse literature, all articles from 1960 to 2014 that addressed the use of neuromodulation were included.

Electroconvulsive therapy

ECT is the earliest form (approximately 1938) of neuromodulation still in use today, although its mechanism of action is still not completely understood. It is usually administered in cases of medication-resistant illness, high suicide risk, and psychosis, or when there are serious physical complications such as dehydration or malnutrition.[20] Pregnancy is not a contraindication to ECT, but international-specific guidelines regarding its use do not exist.[21] It has been suggested that ECT is not considered often enough in pregnant women with severe mental illness,[22] and the American Psychiatric Association Task Force on ECT approves of its use in all three trimesters.[21] However, ECT requires the use of anesthesia and muscle relaxants, so it is not a completely medication-free form of neuromodulation.

Two seminal reviews of ECT in pregnancy reviewed cases from 1941 to 1992[23] and 1941 to 2007,[24] respectively. Out of the 339 cases reviewed, one fetal death was attributed to ECT from status epilepticus. The rate of maternal and fetal complications appears to be approximately 10%, but most are transient and not life threatening including vaginal bleeding, uterine contractions, abdominal pain, and fetal arrhythmias. An updated review that used more stringent inclusion criteria than past reviews only included cases where a significant amount of data were available and where primary cases were reported by the authors.[25] This updated review reported on 169 women who received a total of 1,187 ECT sessions, and a mean number of 9.4 ECT sessions per person. Women were treated throughout pregnancy from 4 weeks to 40 weeks of gestation. Anesthetic agents (thiopental was the most common anesthetic agent reported), muscle relaxants, positioning (tilt vs non-tilt), and type of fetal monitoring varied greatly. No maternal deaths were reported, but the stillbirth/neonatal mortality rate was 4.7% (eight out of 169 cases), and the major congenital malformation rate was 4.1% (seven out of 169 cases). The most common adverse obstetric outcome was preterm labor at 11% (19 out of 169 cases), and other common adverse events included vaginal bleeding, uterine contractions, and cesarean sections. A reduced fetal heart rate (FHR) was the most common fetal adverse event reported during ECT at 8.8% (15 out of 169 cases). It is unknown whether the reduced FHR is due to anesthesia or ECT.

A recent case report describes a young pregnant woman who had a prolonged seizure associated with fetal bradycardia that was not repeated when the anesthetic agent was subsequently changed from methohexital to propofol.[26] The author attributed the fetal cardiac deceleration to the prolonged seizure, and the change in anesthetic was made to shorten seizure duration. Unlike previous authors, the authors of this updated review[25] advised significant cautions in using ECT during pregnancy due to the high rate of adverse outcomes observed. However, this advice is based on conflated percentages reported in the paper, which are not reported here. Unlike the percentages reported here, the percentages the authors reported in the review were derived from taking the number of a particular adverse event and dividing it by the total number of adverse events, instead of the total number of ECT cases. Here, we have divided the number of a particular adverse event by the total number of cases. The percentages we report are similar to those reported in other reviews on ECT in pregnancy.

Although reduced FHR was the most common adverse fetal event, in our experience, most FHR tracings are category 1. Category 1 FHR tracings are normal and defined as follows: baseline FHR of 110–160 beats per minute, moderate baseline FHR variability, and absent late or variable decelerations. Early decelerations and accelerations may be present or absent.[27] Category 1 FHR tracings require no intervention as they are not associated with long-term complications (particularly fetal acidemia).[27] Bradycardia is considered abnormal, and increased monitoring by and consultation with an obstetrician is indicated before ECT should be resumed.

A recent retrospective chart review of 33 women treated with ECT during pregnancy (19 had AD) reported that 25% were experiencing a first episode, while 75% had illness prior to pregnancy.[28] Clinically, it is more common for us to see continuing, worsening, or relapse of depressive episodes in women with a mood disorder history rather than de novo illness during pregnancy. The remission rate was high, achieved in 16 out of the 19 women treated for MDD. Two of the women with a partial remission had comorbid obsessive–compulsive disorder. There were no episodes of PTB. The infant complications were one congenital hip dysplasia, one temporary heart failure, and one stillbirth, none of which were attributed to ECT. All trimesters of pregnancy were represented in this study, although the majority of women were in their second trimester when treatment was initiated, a trend seen in many of the reviewed cases. Other reports confirm that ECT is generally administered during the second trimester,[25] although it is not known whether this is due to an increase in symptoms during this trimester or whether this is when most practitioners feel that it is safest to prescribe ECT.

Another recent report, not included in the chart review by Leiknes et al retrospectively reported on 12 women with AD or bipolar depression treated with ECT during pregnancy.[28] Most were on psychotropic medications in addition to ECT. All had prepregnancy psychiatric diagnosis with eleven out of the 12 women reporting worsening during the index pregnancy. Treatment was started during all three trimesters as needed. One woman with previous risk factors for PTB delivered preterm. However, all infants were born healthy.

There are no absolute contraindications to ECT in pregnancy, although special care should be taken in cases where a patient is at increased risk for vaginal bleeding or PTB. In these cases, an obstetrician should be readily available, and the ability to urgently deliver the baby is essential. After week 24 of pregnancy, the patient should be tilted slightly to her right or have her right hip elevated 30° to decrease the risk of supine hypotension which results from uterine pressure on the inferior vena cava. Due to prolonged gastric emptying, the anesthesiologist should take extra precautions to avoid aspiration. For example, oral sodium, citrate, intravenous (IV) odansetron, and IV metoclopramide have been used.[29] The uterus does not generally contract during a tonic–clonic seizure,[24] but a prolonged seizure can decrease blood supply to the fetus, so the muscle relaxant, succinylcholine, is safe to administer during pregnancy to decrease this risk.[30] All of the most common anesthetics used cross the placental barrier but are not teratogenic.[24] Pretreatment with IV hydration has also been recommended to decrease the risk of supine hypotension,[31] but the necessity of this is unclear if the pelvic tilt is employed.

Long-term follow-up of children exposed to ECT is lacking. Of the three earlier reports of the effects of ECT on long-term child outcomes (past 6 months of age), two did not find any developmental delays in 16 and 15 children, respectively,[32,33] and one reported that at 19-year follow-up, two of the eight children in the report were "mentally deficient".[34] A case report of a child exposed to 18 bilateral ECT treatments during the second and third trimesters of pregnancy showed normal postnatal development at 18 months of age.[29] In a recent report of three pregnant women with primary psychotic disorders who were treated with ECT, fetal tachycardia and fetal spasms were observed.[35] However, during follow-up at 1–3.5 years, all children were developing normally. Another report of a 48-year-old female with treatment-resistant bipolar disorder who received nine ECT treatments stated that at 9 months of age, the infant was developing normally.[36]

O'Reardon et al suggested guidelines for the use of ECT during pregnancy (Table 1).[29] The only new data are that the use of acetaminophen has recently become controversial based on data suggesting that it may increase the risk of attention deficit and hyperactivity disorder.[37–39] Formerly, acetaminophen has been recommended for post-ECT headaches and muscle soreness in pregnant women, as aspirin and nonsteroidal inflammatory agents have been linked to premature closure of the fetus ductus arteriosus.[29] Large, frequent doses of acetaminophen should be avoided, but occasional use is likely of low risk.

While there are no randomized controlled trials (RCTs) of ECT for the treatment of depression during pregnancy, this is common in the field of perinatal psychiatry, and data are often extrapolated from case reports and case series as well as retrospective database reviews. Evidence to date for the

Table 1 Recommendations for ECT during pregnancy

General measures
Obstetric consult to assess risk factors for spontaneous abortion, preterm, and abruptio and uteroplacental insufficiency before starting an ECT course
Treatment should be performed in a facility with immediate access to obstetric care in the event of an emergency
Monitoring of fetal heart rate before and after treatments (gestational age >14–16 weeks)
Additional monitoring (nonstress test with tocometry or continuous fetal heart monitoring)* should be done before and after treatment in high-risk pregnancy or close to term
Perform a level 2 ultrasonogram between 18 weeks and 22 weeks of gestational age
For post-ECT headache and muscle soreness, acetaminophen is the drug of choice
Avoid aspirin and nonsteroidal anti-inflammatory medications because they might lead to early closure of the fetal ductus arteriosus
Metoclopramide, prochlorperazine, or meclizine can be used tor nausea
Routine anesthetic measures to
Avoid gastric reflux
Premedication with nonparticulate antacid, gastric motility enhancer, or H_2 blocker (cimetidine, ranitidine, and metoclopramide can be safely used during pregnancy)
Consider intubation in the third trimester
Withhold nonessential anticholinergic agents (because they decrease the tone of the lower esophageal sphincter. If necessary, glycopyrrolate is usually preferable)
Avoid aortocaval compression (>20 weeks of gestation)
Pre-ECT IV hydration (avoid glucose solution to prevent diuresis)
Ensure adequate oxygenation but not hyperventilation (hyperventilation reduces fetal oxygenation by decreasing placental blood flow and by reducing the dissociation of oxygen from hemoglobin)
Place a wedge to elevate patient's right hip to displace uterus to the left

Notes: Reprinted with permission from Acute and maintenance electroconvulsive therapy for treatment of severe major depression during the second and third trimesters of pregnancy with infant follow-up to 18 months: Case report and review of the literature. O'Reardon JP. *Journal of Electroconvulsive Therapy*. 2011;27(1):25. Copyright [2011] by Lippincott, Williams & Wilkins. *This measure might be implemented in cases where obstetric management is likely to be modified by monitoring.
Abbreviations: ECT, electroconvulsive therapy; IV, intravenous.

use of ECT in pregnancy suggests that it is of low risk to both the mother and the fetus and should be used when indicated by the mother's psychiatric status. Vaginal bleeding, uterine contractions, abdominal pain, and fetal arrhythmias are the most commonly reported adverse events, but fetal death, major congenital malformations, and PTB occur at rates similar to the psychiatric population not receiving ECT.[8,40–42] The exact risk of each event – vaginal bleeding, uterine contractions, abdominal pain, and fetal arrhythmias – is difficult to estimate based on the literature, but there is approximately a 10% chance of a transient, nonlife-threatening adverse event to occur. It is important to remember that the correct comparison group when evaluating the risk of adverse outcomes with ECT is not a completely healthy pregnant population but a significantly psychiatrically ill population not receiving ECT. The long-term effects of ECT on child health and development are not well studied, and more data are needed before a conclusion can be drawn. However, given the degree of illness in patients who are prescribed ECT, in most pregnant women, the benefit will outweigh the risk.

Deep brain stimulation

DBS involves implanting electrodes into the brain that can be calibrated through an implanted pulse generator, sometimes referred to as a "brain pacemaker". Electrical impulses are generated and sent through the electrodes to specific brain regions to modulate neuronal activity. DBS is FDA approved for Parkinson's disease, dystonia, and obsessive–compulsive disorder but is not currently FDA approved for depression. Although there are three cases in the literature of DBS in women with dystonia who had healthy pregnancies, all of whom had the stimulator placed prior to pregnancy,[43] there are no published reports of DBS in pregnancy in women with AD. DBS would require anesthesia if it were placed during pregnancy, so ideally, it would be in place prior to pregnancy. The risk of placing and starting DBS during pregnancy is unknown at this time.

Vagus nerve stimulation

VNS is another technique that requires surgical intervention. VNS uses a small pulse generator, implanted in the left thoracic region to stimulate the left vagus nerve. In 2005, VNS was FDA approved for treatment-resistant depression.[44] There is one case report of VNS in a woman with AD. She was a 28-year-old woman who was obese and had mild bronchoconstriction, hypertension, sleep apnea, and arthritis. She had been diagnosed with unipolar depression and had been receiving VNS for approximately 3 years prior to her pregnancy.[45] She continued to receive VNS throughout her pregnancy at her regular parameters, and no adverse perinatal

events were reported for this case. She was also on a relatively high dose of citalopram and bupropion throughout the pregnancy. Currently, no research studies have attempted to validate the efficacy of VNS in AD. A report of a 19-year-old woman with generalized seizure disorder started treatment with VNS 1 month prior to conception. While receiving VNS, the woman averaged one seizure per month throughout her pregnancy. She developed "mild" preeclampsia at term and was subsequently inducted for labor. Her child's APGAR scores were 6 (1 minute) and 8 (5 minutes), and there was no mention of an adverse outcome for her child.[46] This is another modality that would be an alternative to medication for women with AD. As with DBS, VNS would require anesthesia if placed during pregnancy.

Transcranial magnetic stimulation

TMS is another form of neuromodulation that uses strong, focal magnetic pulses to the dorsolateral prefrontal cortex (DLPFC) to depolarize neuronal circuits.[47] In pregnancy, unlike ECT, no pharmacologic agents are necessary for its administration. Typically, during right-sided low-frequency (≤1 Hz) TMS, the stimulus is applied in a continuous train for 10–15 minutes.[48] Left-sided, high-frequency (>1 Hz) TMS has shorter periods of stimulation that are separated by intervals of no stimulation to reduce the risk of seizure induction (called intertrain intervals). High-frequency TMS sessions last between 30 minutes and 45 minutes.[48] An acute course of TMS is usually 20–30 treatments given Monday to Friday for 4–6 weeks. It is well tolerated with headache and scalp pain being the most common side effects.[49] As with ECT, a 30° pelvic tilt should be employed for women at or beyond 24 weeks of pregnancy to prevent supine hypotension.[50] Based on a small cohort of subjects, low-frequency, right-sided TMS does not appear to impose a risk of causing uterine contractions or fetal arrthymias. This was explored in an open-label pilot study of TMS in ten depressed women with major depressive disorder in which antenatal tocodynamometry for uterine contractions and FHR were monitored 20 minutes before, during, and 20 minutes after treatments 1, 10, and 20.[51]

The earliest case report in pregnancy was published in 1999.[52] A 36-year-old Gravida 1 Para 0 female with no psychiatric history refused antidepressants and was not responsive to psychotherapy. TMS treatment to the DLPFC for AD with prominent anxiety was initiated at 22 weeks of gestation (14 sessions of left-sided, 5 Hz, 5 seconds on, 25 seconds off) at 100% motor threshold (MT). She improved rapidly and delivered a healthy term infant. The next two cases were reported nearly a decade later in 2008.[53] The first patient received 15 sessions of high-frequency left-sided TMS to the DLPFC starting at 16 weeks of pregnancy. It was reported that the patient delivered a healthy, full-term baby boy. The second patient, who was also receiving 225 mg of venlafaxine per day, was treated with 15 sessions of low-frequency right-sided TMS starting at 31 weeks of pregnancy (300 pulses per session, 60-second trains, 60-second intertrain intervals) at 100% MT. The patient delivered preterm at 36 weeks. It was reported that the infant, who was exposed to venlafaxine, appeared irritable for approximately 1 week but was otherwise in "good health". A fourth case was reported in 2010 in which a 28-year-old woman received three courses of treatment with low-frequency left-sided TMS (1 Hz, MT =90%, 1,200 pulses with a 20-second intertrain interval).[54] The first course began at 14 weeks, another was initiated at 22 weeks, and another around 32 weeks. After each of the first two treatments, the woman's Hamilton Depressing Rating Scale (HDRS)[55] score was reduced by at least half. After her third treatment, her HDRS score decreased to an 8, scoring just above what would be considered the normal range, which is generally accepted to be between 0 and 7. Throughout all three treatments, no adverse events were reported, and she gave birth to a "healthy boy".

The first study of TMS in pregnant women with AD was an open-label pilot study of ten women treated with low-frequency right-sided TMS to the DLPFC.[51] In this study, the mean HDRS-17 score decreased by 60% (P=0.005). Seven out of ten (70%) subjects had ≥50% improvement in HDRS-17 scores. Three participants (30%) had a post-TMS HDRS-17 score <8 and Clinical Global Impression Severity[56] score of ≤1, indicating remission. Interestingly, there was little change in the self-rated anxiety scores on the Beck Anxiety Inventory[57] (P=0.10). This suggests that TMS to the right DLPFC may be able to improve depression symptoms while having little effect on antenatal anxiety. Four participants were on antidepressants in conjunction with receiving TMS. There were no PTBs, and all infants were admitted to the well-baby nursery and were discharged with the mother.

Another open-label trial was recently published that reported on high-frequency, left-sided TMS of DLPFC in 30 pregnant women with AD.[58] Women received 3 weeks of six sessions per week (25 Hz, 1,000 pulses per session) at 100% of MT. Forty-one percent had a reduction in HDRS score of ≥50%, and 21% achieved remission (HDRS score <8). At the time of publication, 23 women had delivered healthy infants without complications. Subsequently, the same

group published follow-up data on the children who were between 18 months and 62 months of age and compared them to a group of children who were exposed to AD without treatment.[59] No differences in cognitive or motor development were seen (all were within normal limits), although the mothers treated with TMS perceived a language delay in their offspring.

A recent case report on the maintenance of sequential bilateral TMS every 2 weeks during pregnancy did not result in any adverse neonatal effects.[60] Our group is currently conducting an RCT evaluating the efficacy of TMS for AD.

Transcranial direct current stimulation

tDCS involves applying a direct current to the DLPFC through an anode and a cathode. It alters the excitability of the neurons through weak electrical signals. It does not require medications or anesthesia as required for ECT and does not require the patient to be still for an extended period of time as required for TMS. Because it is a newer treatment, it is not yet FDA approved for any population.[61] The most common side effects reported are tingling sensations on the scalp near the site of treatment, itching at the site of treatment, and fatigue. Less frequently, nausea, headaches, and insomnia have also been reported. A recent meta-analysis assessed the effectiveness of active tDCS and sham tDCS in treating MDD.[62] In seven studies, active tDCS was found to be significantly better than sham tDCS in decreasing major depressive symptoms (Hedges' g=0.37; 95% confidence interval 0.04–0.7). tDCS is currently being assessed as a treatment for AD in a pilot RCT of 30 pregnant women who began enrolling in July 2014.[63]

Conclusion

Advice for clinicians

AD is a common complication of pregnancy, and women prefer non-medication alternatives for treatment. Traditionally, pregnancy is an exclusion criterion for most studies of somatic treatments for fear of causing fetal harm. However, this has left pregnant women without evidence-based choices regarding treatment of their AD. Psychotherapy is a possible option for milder symptoms, but antidepressants should still be considered as the best studied option for pregnant women with AD that is moderate to severe.[64] Currently, in nonpregnant populations, TMS is as effective as antidepressant medications, and ECT is still considered the most effective treatment for depression. The developing field of neuromodulation is an appealing area of research for the treatment of mental illness during pregnancy because of the minimization of fetal exposure to medications. However, there are other potential risks if neuromodulation causes systemic changes that affect the pregnancy. ECT has a clear role in cases of severe psychiatric symptoms that are life threatening. It has been used with minimal serious risk in all trimesters, but special precautions must be taken. In addition, there is fetal exposure to anesthetics, muscle relaxants, and maternal seizures. However, the benefit when the psychiatric illness is severe will usually outweigh the risks. Importantly, PTB and fetal demise are not major risks with ECT. FHR monitoring is essential before and after treatments. As TMS has evolved and we have learned more about dosing and targeting with neuro-navigation, the benefit has been shown in numerous meta-analyses.[2,65,66] TMS would be a possible first-line option for outpatients with AD who refuse or cannot tolerate antidepressants, but more data are needed before it can be definitively recommended.

In addition, the growing availability of different neuromodulation techniques gives pregnant women access to more flexible and accommodating treatment plans. For instance, a woman who had been stable on fluoxetine (20 mg/day) for 2 years began to suffer from severe depression around the seventh week of her pregnancy. She received left-sided TMS to the DLPFC (MT =110%, 15 Hz, 2,970 pulses) in conjunction with fluoxetine. No improvement was seen after 5 weeks (25 sessions) of TMS. At 14 weeks of gestational age, ECT was initiated. She underwent 15 sessions of ECT with significant improvement in her mood, motivation, and appetite. She no longer reported sleep disturbance, suicidal thoughts, or anxiety. No maternal or fetal adverse events were reported throughout her course of TMS and ECT treatments. However, the authors did not provide any data about the outcome of her child.[67]

Future directions

Newer modalities of TMS such as deep TMS (now FDA approved) along with those in development such as EEG-synchronized TMS and theta burst TMS (iTMS and cTMS) offer the potential of a widening range of neuromodulation approaches to treatment. No data on these techniques have been established in pregnancy, but as the field becomes more sophisticated, new options may arise. It should be noted that for all cases of VNS and DBS, the devices were placed prior to pregnancy. Placing these devices during pregnancy involves unknown risk, while treatments such as TMS or tDCS do not require surgery or anesthesia. Currently, DBS and tDCS do not have any published data for AD, but this is

an important future research direction. A pilot study of tDCS in pregnancy is currently underway, although it is still not an FDA-approved treatment for depression. Although research on tDCS is in its infancy, if efficacious, researchers may find it appealing due to its convenience, ease of use, and mild side effect profile. Ultimately, continued research is needed to further assess the place for TMS and other neuromodulation modalities in the treatment hierarchy for women suffering with depression during pregnancy.

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