Despite the role of anxiety in these previous studies, in our analysis, we found that agitation, less retardation, less depressed mood, less somatic symptoms, and more weight loss seem to characterize the caregivers of symptomatic versus asymptomatic children. When comparing only caregivers of symptomatic children, those caring for children with impact presented higher levels of anxiety, which is in line with the existing literature. Greater knowledge of mechanisms underlying caregiver-offspring interactions is needed to improve treatment strategies.

Camila T. Matsuzaka,[1] Milton L. Wainberg,[2,3] Andrea Norcini Pala,[3,4] Marcelo F. Mello[1]
[1]*Departamento de Psiquiatria, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.* [2]*Division of Epidemiology, New York State Psychiatric Institute, New York, NY, USA.* [3]*Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA.* [4]*HIV Center for Clinical and Behavioral Studies, New York State Psychiatric Institute, New York, NY, USA.*

Submitted Sep 20 2017, accepted Nov 07 2017.

### Disclosure

The authors report no conflicts of interest.

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# Repetitive transcranial magnetic stimulation for the treatment of major depression during pregnancy

Rev Bras Psiquiatr. 2018;40:227–228
Brazilian Journal of Psychiatry
doi:10.1590/1516-4446-2017-2522

The prevalence of mental disorders is high among pregnant women.[1] Major depression during pregnancy is a risk factor for negative outcomes for both mother and child.[2] Psychotherapy and pharmacotherapy are well-established conventional treatments for depression. However, some cases fail to respond, and the safety of some psychopharmaceuticals during pregnancy is unclear. Within this context, certain neuromodulation techniques, including repetitive transcranial magnetic stimulation (rTMS), have been studied in pregnant women with depression.

A review of the recent literature[3] suggested that rTMS is an effective alternative for the treatment of depression in pregnant women, and there have been no reports of malformations or other relevant negative fetal outcomes.[4] However, use of the rTMS technique in pregnant women has only been evaluated in one open study[5] and a few case reports; there have been no randomized clinical trials evaluating its use in this setting. Here, we report the cases of four nulliparous pregnant women (one with a twin pregnancy) diagnosed with major depressive disorder and treated with rTMS.

Sociodemographic and clinical features are summarized in Table 1. In three patients, rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC) at 3,000 pulses/session (120% of the motor threshold; frequency 10 Hz; figure-eight coil). In the remaining patient, rTMS was applied to the right DLPFC at 1,800 pulses/session (120% of the motor threshold; frequency 1 Hz; figure-eight coil). To evaluate symptoms of depression and anxiety, the 21-item Hamilton Depression Rating Scale (HDRS-21), the 14-item Hamilton Anxiety Rating Scale (HARS-14), and the Clinical Global Impression-Severity (CGI-S) scale were applied before and after rTMS. Three of the patients were medicated, two with sertraline and one with fluoxetine, and the prescribed dosages were maintained throughout rTMS treatment.

According to the HDRS-21 and HARS-14, all patients presented a response, with a 65% mean reduction in depressive and anxiety symptoms. CGI-S scores also showed a 66% reduction in depressive symptoms. All patients tolerated the treatment, although all but one reported some side effects. None of the patients had complications at delivery. All infants had 5-minute Apgar scores of 9, except for the twins born to patient 2, who were preterm (36 weeks) and had Apgar scores of 6 and 8.

Our results are in agreement with existing experience regarding the responses obtained with rTMS in pregnant women with depression. Our choice of the prefrontal cortex as the rTMS target was based on previous reports.[5,6] The frequency of stimulation varies according to the side of application. Studies of rTMS in pregnant women with depression have employed 10-25 Hz and 1 Hz in the left and right DLPFC, respectively, quite similar to the frequencies used in the general population of adults with depression.[2] Despite these promising findings, there is a need for controlled, double-blind studies involving larger samples, with well-designed rTMS parameters, and even for prospective studies (following pregnant women and their offspring) to assess the long-term safety of rTMS in children exposed *in utero*.

Ygor Arzeno Ferrão,[1] Renata de Melo Felipe da Silva[2]
[1]*Departamento de Psiquiatria, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.* [2]*Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil.*

Submitted Oct 21 2017, accepted Dec 17 2017.

**Table 1** Sociodemographic and clinical features of four pregnant women who received rTMS for major depression, and 5-minute Apgar scores for their children

| Variable | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Total sample Mean (SD) |
|---|---|---|---|---|---|
| Age at rTMS (years) | 38 | 33 | 34 | 36 | 35.2 (2.2) |
| Week of gestation at symptom onset | 4 | 4 | 6 | 6 | 5 (1.2) |
| Week of gestation at rTMS initiation | 4 | 6 | 10 | 8 | 7 (2.6) |
| Antidepressant use before rTMS (weeks) | 52 | 32 | 12 | N/A | 32 (20) |
| Previous major depressive episodes (n) | 2 | 1 | 1 | 1 | 1.25 (0.5) |
| HDRS-21 score | | | | | |
| Before rTMS | 29 | 27 | 12 | 17 | 21.2 (8.1) |
| After rTMS | 13 | 4 | 6 | 5 | 7.0 (4.1) |
| Relative change (%) | -55.2 | -85.2 | 50.0 | -70.6 | -65.3 (15.9) |
| HARS-14 score | | | | | |
| Before rTMS | 42 | 15 | 28 | 20 | 26.3 (11.8) |
| After rTMS | 19 | 3 | 12 | 6 | 10.0 (7.1) |
| Relative change (%) | -54.8 | -80.0 | -57.1 | -70.0 | -65.5 (11.8) |
| CGI-S score | | | | | |
| Before rTMS | 5 | 6 | 5 | 5 | 5.3 (0.5) |
| After rTMS | 2 | 1 | 2 | 2 | 1.8 (0.5) |
| Relative change (%) | -60.0 | -83.3 | -60.0 | -60.0 | -65.8 (11.7) |
| Characteristics of rTMS treatment | | | | | |
| DLPFC side | Left | Left | Right | Left | |
| Sessions (n) | 50 | 38 | 20 | 40 | 37.0 (12.5) |
| Pulses ( × 1,000) | 150 | 114 | 36 | 120 | 105.0 (48.6) |
| % of motor threshold | 120 | 120 | 120 | 120 | |
| Concomitant pharmacotherapy | Yes | Yes | Yes | No | 3.0 (75.0) |
| Antidepressant | Sertraline | Sertraline | Fluoxetine | | |
| Daily dosage | 150 mg | 150 mg | 40 mg | | |
| Concomitant psychotherapy | No | Yes | Yes | No | 2.0 (50.0) |
| Technique | | CBT | PP | | |
| Duration of therapy before rTMS (weeks) | | 12 | 36 | | |
| Family history of depression | Yes | No | Yes | Yes | 3.0 (75.0) |
| Current psychiatric comorbidity | None | OCPD | None | None | 1.0 (25.0) |
| Previous psychiatric comorbidity | None | None | Alcohol abuse and BD-II | None | 1.0 (25.0) |
| Side effects of rTMS | | | | | |
| Pain/discomfort at the application site | No | Yes | Yes | Yes | 3.0 (75.0) |
| Transient difficulty in concentration | Yes | No | No | No | 1.0 (25.0) |
| Sore throat | No | No | Yes | No | 1.0 (25.0) |

BD-II = bipolar disorder type II; CBT = cognitive behavioral therapy; CGI-S = Clinical Global Impression-Severity; DLPFC = dorsolateral prefrontal cortex; HARS-14 = 14-item Hamilton Anxiety Rating Scale; HDRS-21 = 21-item Hamilton Depression Rating Scale; N/A = not applicable; OCPD = obsessive-compulsive personality disorder; PP = psychodynamic psychotherapy; rTMS = repetitive transcranial magnetic stimulation.

## Disclosure

The authors report no conflicts of interest.

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