Letter to the editor: Antidepressant effect r TMS during pregnancy in a case of Major Depression Resistant to Pharmacological Treatment

Key words. Repetitive transcranial magnetic stimulation (rTMS); Major depressive disorder (MDD); Treatment resistence; Pregnancy

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ABSTRACT

Major depressive disorder (MDD) is a common complication of pregnancy and the postpartum period. Approximately 5% of women who have MDD during pregnancy or the postpartum period meet criteria for resistant depression, associated with increased morbidity in both the newborn and the pregnant woman. Currently we have different therapeutic options for the treatment of MDD during pregnancy, although in cases of resistance during that period the treatment criteria are not that well established.

We set out the case of a 36-year-old woman who presents an episode of major depression resistant to pharmacotherapy. During the current episode and after four cycles of failed pharmacological treatment she became pregnant. In the 16th week of gestation, she was treated with low-frequency repetitive transcranial magnetic stimulation (rTMS). After 30 treatment sessions, with good tolerance, the patient presented a complete recovery from the depressive symptoms, giving birth to a healthy newborn. rTMS is a good alternative to Electroconvulsive Therapy in some cases of resistant MDD during pregnancy. Despite these promising findings, further double-blind controlled studies with broad samples of pregnant women are required, with well-designed rTMS parameters, and even prospective studies (following pregnant women and their offspring) to confirm the absence of long-term side effects.

Nota clínica: Efecto antidepresivo de la EMTr durante el embarazo en un caso de Depresión Mayor Resistente al Tratamiento Farmacológico

RESUMEN

El trastorno depresivo mayor (TDM) constituye una complicación común del embarazo y el período posparto. Aproximadamente un 5% de mujeres que presentan un TDM durante la gestación o el periodo postparto cumplen criterios para depresión resistente, asociándose con un incremento de la morbilidad tanto en el recién nacido como en la propia gestante. En la actualidad disponemos de diferentes opciones terapéuticas para el tratamiento del TDM durante el embarazo si bien en los casos de resistencia durante el embarazo los criterios de tratamiento no se encuentran tan bien establecidos.

Presentamos el caso de una mujer de 36 años de edad que desarrolló un episodio de depresión mayor resistente al tratamiento farmacológico. Durante el episodio actual y tras cuatro ciclos de tratamiento farmacológico fallido se quedó embarazada. A las 16 semanas de gestación fue tratada con estimulación magnética transcraneal repetitiva (EMTr) de baja frecuencia. Tras 30 sesiones de tratamiento, con buena tolerancia, la paciente presentó una recuperación completa de la sintomatología depresiva, dando a luz a un recién nacido sano. La EMTr constituye una buena alternativa frente a la Terapia Electroconvulsiva en algunos casos de TDM resistente durante la gestación. A pesar de estos hallazgos prometedores, se requiere de un mayor número de estudios controlados, doble ciego que incluyan muestras amplias de pacientes embarazadas, con parámetros EMTr bien diseñados, e incluso estudios prospectivos (siguiendo a mujeres embarazadas y sus descendientes) para confirmar la ausencia de efectos secundarios a largo plazo.

Palabras clave. *Estimulación magnética transcraneal repetitiva (EMTr); Trastorno Depresivo Mayor (TDM); Resistencia al tratamiento; Embarazo.*

Dear Editor,

Depression is a common complication of pregnancy and the postpartum period, with an estimated 10-16% of pregnant women meeting the criteria for Major Depressive Disorder (MDD)[1]. Approximately 5% of women who have MDD during

pregnancy or the postpartum period develop Treatment-Resistant Depression (TRD) and this risk is increased when there is a history of depression[2].

Prenatal depression is associated with high morbidity for both the newborn and the pregnant woman. In addition, it has a long-term impact on the maternal-infant relationship and on the development and behavior of the child.

There is evidence to support the fact that successful treatment of MDD during pregnancy and the postpartum period may lead to an improvement in the psychiatric health of children of pregnant women with MDD[6]. Currently we have different therapeutic options for the treatment of MDD during pregnancy. These include both psychotherapeutic and biological interventions. Among the latter are psychopharmaceuticals and brain neuromodulation techniques [Electroconvulsive Therapy (ECT), rTMS, among others)][7].

The rTMS is a noninvasive brain neuromodulation technique that has been widely shown to be effective in the treatment of MDD[8] with data confirming its efficacy and tolerability in the treatment of MDD in pregnant women.

We present the case of a pregnant woman with MDD who experienced a drug-resistant episode during her third pregnancy, went into complete remission after 30 sessions of rTMS, and gave birth to a healthy baby.

CLINICAL CASE

The subject is a 35-year-old woman from the Dominican Republic who lives with her spouse and two children. She works as a housemaid and is currently on leave.

Her personal history includes hypertension, which is under pharmacological control (Methyldopa 500 mg/12 h), and Graves-Basedow disease, diagnosed when she was 32 (6 months after her second pregnancy), for which a total thyroidectomy was performed. She is currently on hormone replacement treatment (Levothyroxine 88 mg/24 h) and exhibits normal thyroid function.

She presented her first depressive episode at the age of 31, for which she received no treatment. A year later, she had a second episode when she was in the second trimester of her second pregnancy. Her family doctor (FD) prescribed 100 mg of Sertraline/day that she did not take for fear of repercussions on the fetus. After childbirth she continued to suffer depression symptoms so she began treatment with the Sertraline 100 mg/day that had been previously prescribed and reached clinical remission. She continued the treatment for 4-5 months and stopped it on her own initiative.

During the following two years she was in a state of euthymia and then underwent a third depressive episode. The psychopathological exploration carried out at that time highlighted the presence of hypomimia, apathy, anhedonia, hypoproxesia, feelings of guilt, feelings of disability, hyporexia, weight loss, global insomnia and psychic anxiety (Ham-D-17:35). She began treatment with the Sertraline 100 mg/day prescribed by her FD but during 5 months there was no therapeutic response, so the FD referred her for psychiatric assessment. She received treatment from the Psychiatric Service for 9 months, during which her psychiatrist made three changes to the pharmacological treatment (changing the antidepressant taken along with Venlafaxine and optimizing the dose of Venlafaxine) but an adequate clinical response was not maintained (Table 1).

Table 1 Treatments performed prior to rTMS

TREATMENT From the beginning of Psychiatric Service follow-up	Length of treatment	Score HAM-D-17	Response
Sertraline100 mg/day + Venlafaxine R 375/day + Olanzapine 2,5 mg/día	5 months	30	<25%
Venlafaxine R 375/day + Mirtrazapine 30mg/day	2 months	31	<25%
Venlafaxine R 225 /day + Bupropion 300 mg/day	2 months	30	<25%
Pregnancy			
Venlafaxine R 225/day + Fluoxetine 20 mg/day	9 months	40	<25%

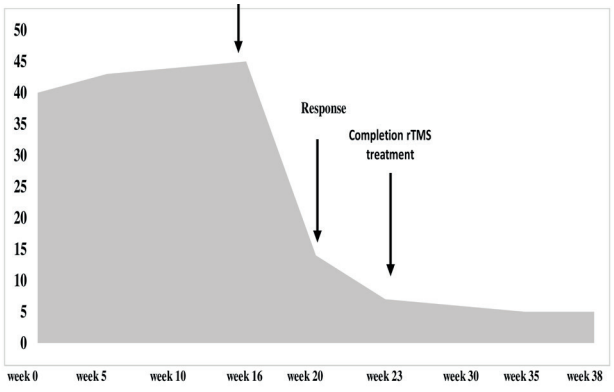
Response: 50% or more decrease in the scale's initial score
Partial response: decrease between 25-49% on the scale's initial score
No response: reduction of less than 25% on the scale's initial score
Remission: score less than or equal to 7

Without prior planning, the patient became pregnant and the depressive symptoms intensified at that time (HAM-D-17:40), showing in addition psychomotor delay, feelings of hopelessness, great psychic agitation and ideation of death. Upon finding out about the pregnancy, her psychiatrist made a change to her medication, replacing 300 mg of Brupropion with 20 mg/day of Fluoxetine and in the absence of a response, in week 16 of the pregnancy referred her to the Neuromodulation Unit for assessment for treatment with rTMS, with a Major Depressive Episode diagnosis according to DSM 5 criteria along with drug resistance. No other pharmacological changes were made during the pregnancy.

For the rTMS treatment we used a magnetic stimulator (Magstim Rapid [2]) with a ventilated focal coil in the form of an 8. We applied a low-frequency inhibitory protocol to reduce the risk of seizures. 3,000 stimuli per session were given at a frequency of 1 Hz and an intensity of 120% of the motor resting threshold. The treatment consisted of a total of 30 five-day rTMS sessions per week, administered to the right dorsolateral prefrontal cortex (R-DLPFC) and we maintained the same pharmacological treatment during the 30 treatment sessions. Beam_F3 Locator 11 was used to locate the R-DLPFC.

Good tolerance with little discomfort on the scalp was observed in the region where the stimulation was applied. We used the Hamilton scale for depression (HAM-D-17) to evaluate the therapeutic effect. At the end of session nº 15 (week 20 of gestation), the patient had already began to exhibit response criteria (HAM-D-17:14) and at the end of session nº 30 (week 23 of gestation), obtained a score in the HAM-D-17 of 7 and was euthymic (Figure 1).

The delivery was normal at 38 weeks and the patient gave birth to a male of 3070 gr, with normal scores in the Apgar test at 1 and 5 minutes (9 and 10). The results of physical and neurological examinations were normal.



No depressed: 0-7; mild/minor depression: 8-13; moderate depression: 14-18; depression evere: 19-22; very severe depression:>22. Autora: Isabel Martínez-Gras

Figure 2 HAM-D-17 scores throughout pregnancy

DISCUSSION

Although the therapeutic options for the treatment of MDD during pregnancy have been established, with regard to treating resistant depression (TRD) cases, the guidelines are not particularly clear. Therefore, clinicians sometimes have to make difficult and complex decisions.

In the clinical case set out here, after five ineffective pharmacological trials, possible therapeutic decisions would include treatment with Electro Convulsive Therapy (ECT) or with r-TMS[7].

TEC is a fast and effective technique suitable for use in cases of pharmacological resistance. Since it can cause adverse effects on the mother and foetus[12,13] we opted for treatment with rTMS. rTMS is a noninvasive brain neuromodulation technique that through the activation or inhibition of the cerebral cortex, modulates the brain circuits that mediate functions related to the pathophysiology of depression, with effects on neurotransmitters and synaptic plasticity[14]. It was approved by the FDA in 2008 for use on adults with depression who failed in a single antidepressant trial during a depressive episode. A recent review supports its efficacy in treating prenatal and postnatal depression, highlighting its favorable safety profile and a side-effects profile that does not significantly differ from that of the general population[16].

However, there are some potential risks and limitations with regard to the use of rTMS for the treatment of a major depressive episode during pregnancy, including: the small number of controlled trials carried out with pregnant women, the lack of long-term data available on the effects of rTMS on children born to women exposed to this technique, and the deterrent effect on pregnant women due to the theoretical risk of seizures, which is very limited in the case of inhibitory protocols. This is why extensive research is still needed to fully elucidate the role of rTMS treatment in this population.

Finally, a further limitation of this work is the fact that we could not ensure the completion of pharmacological treatment by the patient, since up to 20% of TRD cases considered to be resistant stem from therapeutic non-compliance[17].

CONCLUSIONS

This case illustrates the remission of an episode of severe and resistant depression during pregnancy that was achieved through a course of 30 low-frequency rTMD sessions. Although studies in this population are still scarce, it should be considered as a valid alternative for the treatment of TRD in pregnancy.

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest in relation to the material in this article.

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