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RESEARCH LETTER

Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study

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The prevalence of migraine among women is highest during reproductive years.[1] Women with migraine and their offspring face an increased risk for adverse pregnancy outcomes.[1] Both women with migraine[1] and their providers[2,3] share concern regarding the potential effect of migraine treatments on pregnancy outcomes. Expert consensus suggests that devices are relatively safe for use in pregnancy,[3] thus neuromodulation devices are prescribed during pregnancy by headache specialists in clinical practice;[3] however, there are no treatments specifically approved nor investigated for the treatment of migraine in pregnant women, creating a great unmet need.

The remote electrical neuromodulation (REN) device (Nerivio®) is a drug-free, non-invasive, wearable, battery-operated stimulation device, wirelessly controlled by a smartphone application, worn on the upper arm for 45-min treatments. It is Food and Drug Administration–cleared for the acute and/or preventive treatment of migraine with or without aura for episodic and chronic migraine patients aged 12 years and older.[4–6] While REN is not contraindicated in pregnancy, a precaution mentions that it had not been tested during pregnancy. This retrospective controlled survey-study (ClinicalTrial.Gov NCT05464069) evaluated the safety of REN for migraine treatment during pregnancy through 3 months postpartum, relative to other options (medications or no treatment). It compared women with migraine who treated their migraine with at least three REN treatments during pregnancy (REN group) to women with migraine who did not use REN during pregnancy (control group) on critical pregnancy outcomes, with the hypothesis that the groups would not differ on these outcomes. Eligibility included migraine diagnosis with a frequency of ≥4 migraine days per month for at least 6 months prior to their pregnancy, last menstrual period between November 1, 2019 and August 1, 2021, age 18–45 years, and ≥4 migraine attacks during the study pregnancy. An online survey was sent to all females in the specified age range and within the REN device

Abbreviations: REN, remote electrical neuromodulation; SD, standard deviation.

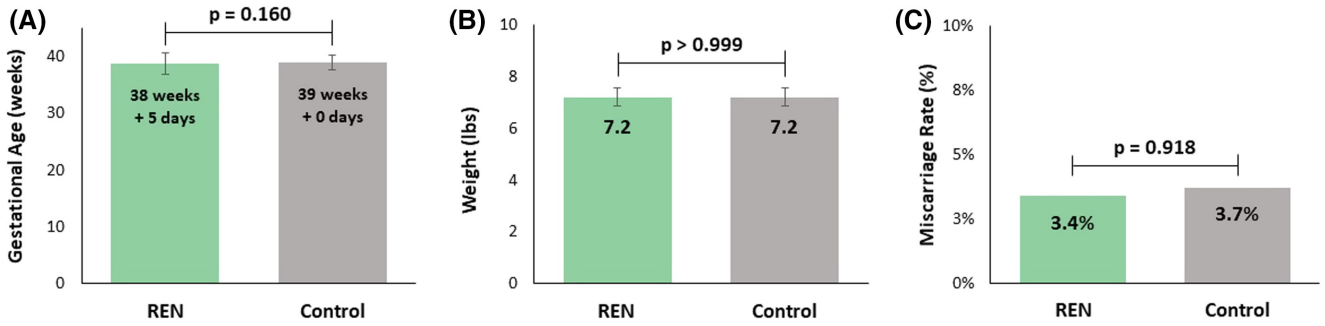

FIGURE 1 Results of the retrospective controlled survey-study evaluating the safety of remote electrical neuromodulation (REN) for the treatment of migraine during pregnancy and 3 months postpartum. (A) Primary endpoint. There was no significant difference between REN (38 weeks and 5 days ± 1 week and 6 days) and control (39 weeks and 0 day ± 1 week and 2 days) groups ($p = 0.160$). Secondary endpoints. All seven secondary endpoints also did not differ between the REN and control groups. (B) First secondary endpoint of newborn weight (REN vs. control: 7.2 ± 1.2 pound vs. 7.2 ± 1.0 pound; $p > 0.999$). (C) Second secondary endpoint of miscarriage rate (3.4% vs. 3.7%; $p = 0.918$). Shown are mean ± standard error.

users' database and to patients in participating headache clinics. The primary endpoint was gestational age at delivery. Secondary endpoints were baby's birth weight, miscarriage rate, preterm birth rate, birth defect rate, stillbirth rate, rate of babies meeting developmental milestones 3 months postnatal, and emergency room visits. The study was approved by Western Institutional Review Board (tracking number 20223515). Participants provided online informed consent. Independent *t*-tests and Fisher exact tests were used to compare continuous endpoints and rates between groups, respectively. Tests were two-tailed, with $p < 0.05$ considered statistically significant.

One hundred seventy-one women completed the study, of which 140 (REN = 59; control = 81) met inclusion criteria for analysis (Figure S1). No statistical difference was found between groups with regard to demographics. There was no statistical difference in the primary endpoint of gestational age between the REN (mean ± standard deviation [SD]: 38 weeks and 5 days ± 1 week and 6 days) and control groups (39 weeks and 0 days ± 1 week and 2 days; mean difference of 3 days; confidence interval: −7 days to 1 day; $p = 0.160$; Figure 1A). All seven secondary endpoints did not differ between REN and control groups: newborn weight (mean ± SD: 7.2 ± 1.2 vs. 7.2 ± 1.0 pound; mean difference of 0 pound; confidence interval: −0.4 to 0.4; $p > 0.999$; Figure 1B), miscarriage rate (3.4% vs. 3.7%, $p = 0.918$; Figure 1C), preterm birth rate (14.0% vs. 6.4%; $p = 0.138$), birth defect rate (14.0% vs. 14.1%, $p = 0.991$), stillbirths rate (0% vs. 0%; $p > 0.999$), rate of newborns meeting developmental milestones at 3 months postnatal (96.5% vs. 94.9%; $p = 0.652$), and rate of participants who visited emergency room during their pregnancy (15.3% vs. 17.3%; $p = 0.749$).

Results indicated that the REN device is a safe treatment of migraine during pregnancy, not increasing the risk for adverse pregnancy outcomes, and therefore offering a much-needed non-pharmacological alternative for women with migraine during pregnancy.

AUTHOR CONTRIBUTIONS

Study concept and design: Alon Ironi, Alit Stark-Inbar, Dagan Harris, Shira Tamir, Addie Peretz, Nina Riggins, Linus Chuang. *Acquisition of data*: Alit Stark-Inbar, Alon Ironi, Dagan Harris, Shira Tamir, Audrey Halpern. *Analysis and interpretation of data*: Alon Ironi, Alit Stark-Inbar, Sharon Shmuely, Shira Tamir. *Drafting of the manuscript*: Alit Stark-Inbar, Alon Ironi. *Revising it for intellectual content*: Addie Peretz, Dagan Harris, Shira Tamir, Sharon Shmuely, Audrey Halpern, Linus Chuang, Nina Riggins. *Final approval of the completed manuscript*: Addie Peretz, Alit Stark-Inbar, Dagan Harris, Shira Tamir, Sharon Shmuely, Alon Ironi, Audrey Halpern, Linus Chuang, Nina Riggins.

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CONFLICT OF INTEREST STATEMENT

Audrey Halperin served as a site-PI (study site) and consulted for Abbvie and Biohaven. **Nina Riggins** served as a consultant for Theranica, Gerson Lehrman Group, Electrocore, Eli Lilly, NeurologyLive, Miles for Migraine, Dolor Technology, and Theraspecs. **Alit Stark-Inbar**, **Dagan Harris**, **Shira Tamir**, **Sharon Shmuely**, and **Alon Ironi** are all employees of Theranica. **Addie Peretz** served as a consultant in this study without financial compensation. **Linus Chuang** declares no conflicts of interest.

CLINICAL TRIALS REGISTRATION NUMBER

ClinicalTrial.Gov NCT05464069.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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