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CLINICAL RESEARCH ARTICLE

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Pregnancy planning may impact maternal and neonatal outcomes in people with myasthenia gravis

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Abstract

Introduction: Myasthenia Gravis (MG) is an acquired autoimmune condition commonly diagnosed in young people of reproductive age resulting in neuromuscular junction dysfunction. The course of MG during pregnancy and its impact on maternal and neonatal outcomes is vary in the literature. Pregnancy planning is a known strategy and modifiable risk factor in obstetric practice to decrease maternal and neonatal morbidity. We aim to assess if planning a pregnancy impacts maternal and neonatal outcomes, MG exacerbation, and pregnancy-related complications.

Methods: This study utilized data from an online, North American survey entitled "A Patient Centered study on Pregnancy in People with Myasthenia Gravis", distributed with the assistance of MG advocacy groups in the United States and Canada. It included individuals with MG who had at least one pregnancy in the last 10-years. Key maternal and neonatal outcomes were compared between planned and unplanned pregnancies.

Results: Out of 156 survey participants, 58 had a pregnancy following MG diagnosis, totaling 90 reported pregnancies. Of these, 56 (62.2%) were planned and 34 (37.8%) were unplanned pregnancies.

The unplanned pregnancies were associated with more MG exacerbations, hospitalizations, and intensive care unit admission (37.7% vs. 13.7%, 26.5% vs. 11%, and 17.6% vs. 8.9%, respectively, $p \leq .05$). The neonatal outcomes did not significantly differ between the groups.

Discussion: Planned pregnancies in people with MG may be associated with a reduced gestational and post-partum risk of MG exacerbation, hospitalizations, and ICU admissions. Larger studies are required to confirm this association and account for potential contributing variables.

Abbreviations: BMI, body mass index; ICU, intensive care unit; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MGSC, Myasthenia Gravis Society of Canada; MuSK, muscle-specific kinase; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes; SLE, systemic lupus erythematosus; T1DM, Type 1 diabetes mellitus.

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KEYWORDS
myasthenia gravis, pre pregnancy consult, neonatal myasthenia gravis, planning pregnancy, pregnancy

1 | INTRODUCTION

Myasthenia gravis (MG) commonly affects people of childbearing age.[1,2] Managing this population necessitates considering pregnancy's impact on disease activity, along with the potential risks posed by MG and its treatment to pregnancy, the fetus, and the newborn.

The course of MG is variable in pregnancy, and exacerbations may be more common in the first trimester and postpartum period.[3] Medications such as pyridostigmine and prednisone are safe options for controlling MG symptoms during pregnancy, while methotrexate should be avoided.[4] Recent evidence has suggested that stopping immunosuppressive therapy is associated with exacerbation of MG in pregnancy.[5]

There are also several potential effects that MG may have on the pregnancy and the fetus. Pregnant people with MG have an increased risk of complications at delivery, including preterm rupture of amniotic membranes.[6] There are more frequent interventions during birth, and in particular a 2-fold increase in Cesarean section. Potential risks to the fetus and newborn include polyhydramnios, decreased fetal movements, arthrogryposis, and transient neonatal MG.[7]

Despite the complexity of managing MG during pregnancy, there is relatively limited literature on this topic. Several retrospective case series have been reported over the past several decades, though the majority include a limited number of participants[8–10] and provide variable and conflicting information about the course of MG during pregnancy, and the timing of expected exacerbation, if any.[10–14]

MG also can impact fertility choices, as demonstrated by a survey reporting that 80% of the people with MG made reproductive decisions based on their disease, including the choice to not have children.[15]

This study aims to assess if planning a pregnancy impacts maternal and neonatal outcomes, including changes in MG clinical status, adverse pregnancy outcome, and neonatal-associated risks in people with MG.

2 | METHODS

This was an online North American survey examining MG history and reproductive health outcomes of people with female reproductive organs diagnosed with MG, designed with input from people with MG.

People who indicated in the survey that they currently have, or ever have had a uterus, cervix, vagina, and/or ovaries, were over 18 years old at the time of the survey, who have MG and are members of Myasthenia Gravis Foundation of America (MGFA) and the Myasthenia Gravis Society of Canada (MGSC), were considered eligible to complete the online survey.

Individuals were contacted directly by the respective MG organizations via an email with a link to the online survey three times at 2-week intervals starting in July 2018. The research team members themselves did not have access to the organizations' email databases or any identifying information.

The survey was available in English only, and included 124 detailed questions (a sample of the questions is provided in Supporting Information Appendix S1) about the participant's demographic data, course and diagnosis of MG in general, course and management of MG in pregnancy, pregnancy complications, and fetal and neonatal outcomes. Not all participants were exposed to all parts of the survey due to branching of the survey depending on pregnancy history.

Each question of the survey had a different set of responses from which to choose and a free text field. People had to choose for each pregnancy whether it was planned or unplanned. "A planned pregnancy" refers to a pregnancy that was intentionally conceived by the individual involved. It typically involves preconception discussions, family planning, and taking deliberate steps to conceive at an optimal time, considering various factors such as health, readiness, and personal circumstances. On the other hand, "an unplanned pregnancy" refers to a pregnancy that occurs without prior intention or planning, however, can include wanted but mis-timed pregnancies. This study included only pregnancies that occurred since the diagnosis of MG.

This study was approved by the ethical committee of Sunnybrook Health Science Center, and a consent form was embedded at the beginning of the survey and completed by participants.

Data analysis was performed using SPSS version 25 (IBM, Armonk, NY). Descriptive statistics for continuous variables included mean, standard deviation, median and percentiles. Differences in the continuous variables were assessed using the Student's *t*-test and the Mann–Whitney *U* test. Differences in the categorical variables were analyzed using the chi-square test and the Fisher exact test. A $p \leq .05$ was considered statistically significant.

3 | RESULTS

Of all people who opened the survey (Figure 1), 58 individuals, who reported a total of 90 pregnancies, were eligible for analysis. Thirty-four people reported one pregnancy, 16 reported two pregnancies, and 8 reported three pregnancies. Eight people had at least one planned and one unplanned pregnancy, whereas the other 50 people had all pregnancies in one category.

Table 1 presents the demographic data of the individuals in both groups. The planned group had people who were older at the time of their first pregnancy, had higher body mass index (BMI), and were less likely to be smokers.

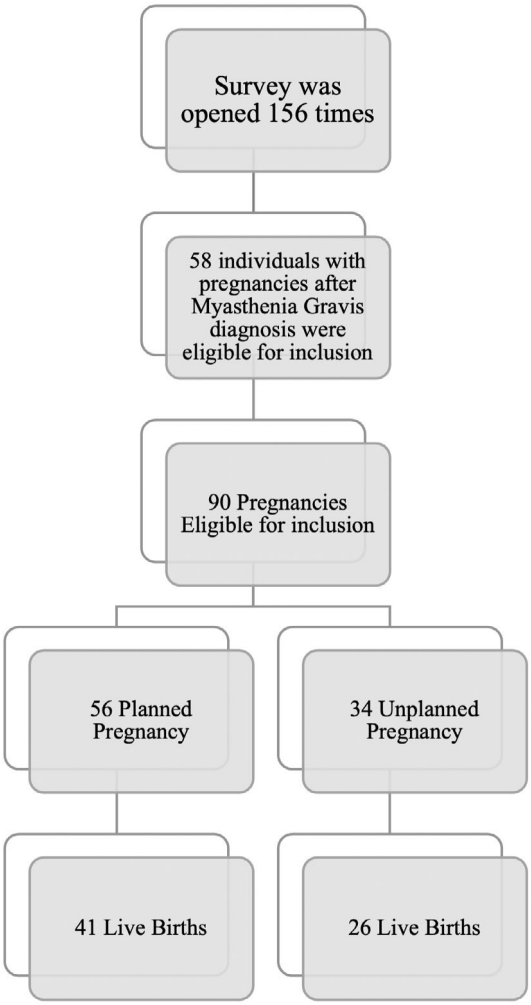

FIGURE 1 Study flow chart.

Individuals in the planned and unplanned groups reported similar baseline MG characteristics (Table 2), including age of diagnosis, MG type, antibody status, and history of intubation for MG. As shown in Table 3, patients in the planned pregnancy group underwent fertility treatments more frequently, but planned and unplanned pregnancies were found to have similar pregnancy-associated, obstetrical, and fetal/neonatal complications. The composite delivery complications included advanced vaginal tears, uterine rupture, perianal infection and chorioamnionitis. Pregnancy outcomes did not differ between the groups (Figure 2). There were 41 and 26 live births in the planned and unplanned pregnancy groups, respectively.

There was no difference in the proportion of people treated for MG with one or more medications at the beginning of the pregnancy (Table 4). The most common treatments among people in both groups were pyridostigmine or prednisone, alone or in combination. Other treatments included azathioprine, intravenous immunoglobulin, and plasma exchange. A comprehensive distribution of treatment regimens among the groups at the beginning of the pregnancy is available in Supporting Information Appendix S2. Importantly, people with planned pregnancies were less likely to experience worsening of symptoms of MG (Table 4). In addition, planning the pregnancy significantly reduced the risk of admission to the hospital and intensive care unit (ICU) during pregnancy compared to the unplanned group (Table 4).

Composite postpartum complications were similar between the groups, including postpartum depression or blues, but there was a significantly reduced risk of post-partum ICU admission in the planned group (Table 5). There was no different in the neonatal complications between the groups (Table 6). The composite neonatal complications included transient neonatal MG, neonatal intensive care unit (NICU) admission, jaundice, and breathing difficulties at birth requiring assistance.

Interestingly, two patients who had two pregnancies in both groups were admitted to the hospital during their pregnancy. One of them was admitted during the unplanned pregnancy due to an exacerbation of MG. The second was admitted in both the planned and unplanned pregnancy; however, during the planned pregnancy, they were admitted due to respiratory syncytial virus causing MG crisis, while in the unplanned pregnancy, they were admitted twice due to MG exacerbation without clear reason.

4 | DISCUSSION

In this study, we found that planned pregnancies were associated with a decreased risk of worsening of MG symptoms during pregnancy, a decreased risk of hospitalization and ICU admission during pregnancy, and a decreased risk of ICU admission in the post-partum period. In addition, the planned group had a greater number of people with improved or unchanged MG symptoms of MG than the unplanned group. Planning a pregnancy did not appear to impact obstetrical, fetal, or neonatal outcomes.

The literature is inconsistent regarding the course of MG during pregnancy. Ducci et al.[14] retrospectively assessed 34 pregnancies in 21 people with established MG, and noted that, out of the 30 pregnancies that concluded in live births, 50% of the mothers experienced a worsening of their MG symptoms, while 30% had an improvement of their symptoms and 20% noticed no change. The worsening of MG symptoms was most frequently noticed in the second trimester.

Importantly, people in the planned and unplanned groups had similar baseline MG disease associated demographics, and although this information is limited by sample size and the retrospective nature of this study, it does not appear to explain this difference in MG associated outcomes.

Interestingly, when examining other baseline demographics that may impact pregnancy-related outcomes, people in the planned pregnancy group were older at the time of their first pregnancy and had higher BMI. These demographics are associated with an increased risk for obstetrical complications such as pre-eclampsia, preterm delivery, and gestational diabetes; however this anticipated increased risk was not seen. Again, although there are the known limitations to this data, it is possible that the planned nature of these pregnancies decreased these risks resulting in both groups having similar obstetrical outcomes.

TABLE 1 Demographic data and comorbidities per individual.

	Planned $n = 32$[a]	Unplanned $n = 18$[a]	p Values
Maternal age at time of first pregnancy (years, mean ± SD)	30.2 ± 7.1	25.7 ± 7.6	0.04*
Maternal age at time of survey (years, mean ± SD)	37.6 ± 8.7	43 ± 15.4	0.1
Nulliparity (*n*,%)	11 (34.3%)	7 (77.7%)	0.8
Race			
White (*n*, %)	23 (72%)	13 (72.2%)	0.9
Black (*n*, %)	3 (9.3%)	2 (11%)	
Other (*n*, %)	5 (15.6%)	3 (16.6%)	
Unknown (*n*, %)	1 (3.1%)	0 (0%)	
Education			
High school (*n*, %)	2 (6.2%)	1 (5.5%)	0.2
University or college Postsecondary level education (*n*, %)	29 (90%)	14 (77.7%)	
Did not finish high school (*n*, %)	1 (3.1%)	3 (16.6%)	
Employment status (full or part time job) (*n*, %)	16 (50%)	5 (27.7%)	0.15
Married or common law marriage (*n*, %)	27 (79.4%)	11 (61.1%)	0.09
Need assistance at home (*n*, %)	3 (9.3%)	1 (5%)	1
BMI (kg/m^2, mean + SD)	31.3 ± 8.2	26.5 ± 6.2	0.04*
Smoking (*n*, %)	0 (0%)	3 (16.6%)	0.02*
Other comorbidities (*n*, %)[b]	9 (28.1%)	8 (44.4%)	0.24

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Eight people had pregnancies in both groups and were excluded from this analysis.
[b]Other comorbidities included Type 2 diabetes mellitus, hypertension, hyperlipidemia, systemic lupus erythematosus, rheumatoid arthritis, and thyroid disorders.
*$p < 0.05$.

TABLE 2 Myasthenia gravis baseline status per person.

	Planned, $n = 32$[a]	Unplanned, $n = 18$[a]	p values
Maternal age at time of MG diagnosis (years, mean ± SD)	23.7 + 8	20.6 ± 8	.8
Type of MG			
Generalized (*n*, %)	30 (93.7%)	18 (100%)	.4
Ocular (*n*, %)	2 (6.3%)	0 (0%)	
Positive antibody status (*n*, %)	24 (75%)	9 (50%)	.3
Previous intubation for MG (*n*, %)	18 (56%)	13 (72%)	.26
Need for mobility device at the time of survey (*n*, %)[b]	5 (5.6%)	4 (22.2%)	.43

Abbreviations: MG, myasthenia gravis; SD, standard deviation.
[a]Eight people had pregnancies in both groups and were excluded from this analysis.
[b]The devices used were walking stick and/or walker and/or wheelchair.

Pregnancy planning is a known modifiable risk factor in a number of obstetric conditions due to timing a pregnancy to correlate with disease stability, health optimization, and timely access to medical care, with specific examples in the management of other autoimmune diseases such as Type 1 diabetes and lupus.[16–19] It is possible that the differences in outcomes demonstrated by this study are due to the planned or unplanned nature and corresponding differences in health and health care access immediately prior to conception.

Exacerbation of MG during the postpartum course has been previously reported in the literature. Braga et al. reported an increased risk for exacerbation of 46%.[20] In this study, we observed an increased risk of MG-associated postpartum ICU admission in the unplanned group. The correlation between planning a pregnancy and its impact on postpartum morbidity in autoimmune conditions in general poorly understood; however, Davis-Porada et al.[19] documented a low frequency of flares in the postpartum period in people with SLE when the disease was well-controlled before and through the pregnancy.

Previous studies have shown that MG does not impact fertility rate.[20,21] In this study, more people had infertility in the planned pregnancy group, which is an expected finding. However, this does not

TABLE 3 Impact of myasthenia gravis on pregnancy.

	Planned pregnancies, $n = 56$	Unplanned pregnancies, $n = 34$	p Values
Fertility treatment (n, %)	9 (16%)	0 (0%)	.01*
Composite obstetrical complications (n, %)[a]	27 (48.2%)	21 (61.7%)	.29
Pre-eclampsia and pregnancy hypertension (n, %)	6 (10.7%)	7 (20.5%)	.13
Composite fetal/neonatal complications[b] (n, %)	8 (14.2%)	6 (17.6%)	.54

[a]Composite obstetrical complication including gestational diabetes, hyperemesis gravidarum, pregnancy-induced hypertension, preeclampsia, antepartum hemorrhage, intrahepatic cholestasis of pregnancy, pulmonary embolism, and deep vein thrombosis.
[b]Fetal growth restriction, preterm birth, premature rupture of membrane, oligohydramnios, fetal anomaly, and placental abruption.
*$p < 0.05$.

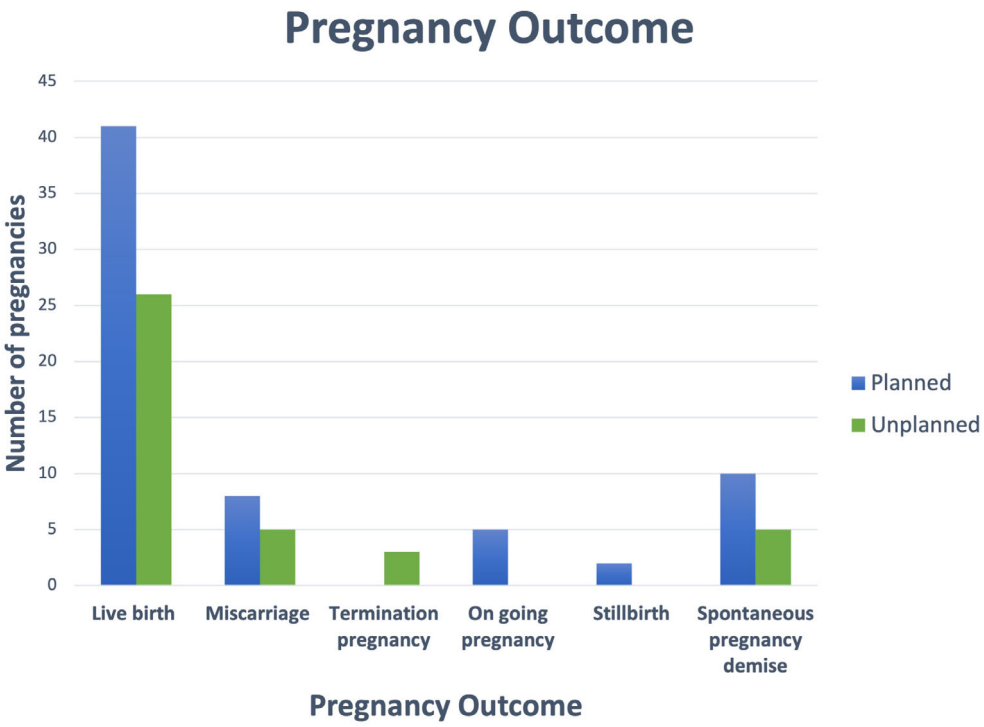

FIGURE 2 Pregnancy outcome. Data are presented as number of pregnancies; the differences were not statistically significant between the groups.

TABLE 4 Impact of pregnancy on myasthenia gravis.

	Planned, $n = 56$	Unplanned, $n = 34$	p value
Treatment for MG			
Treatment for MG at the beginning of pregnancy			
One medication	11 (19.6%)	10 (29.4%)	0.11
Two or more medications	29 (51.7%)	10 (29.4%)	
Symptoms in pregnancy[a]			
Improved or unchanged symptoms (n, %)	44 (86.3%)	17 (62.9%)	0.02*
Worsened symptoms (n, %)	7 (13.7%)	10 (37.1%)	0.04*
Admission to hospital during pregnancy (n, %)	6 (11%)	9 (26.5%)	0.05*
Admission to ICU in pregnancy (n, %)	5 (8.9%)	6 (17.6%)	0.05*
Intubation during pregnancy (n, %)	4 (7%)	5 (14.7%)	0.06*

Abbreviation: ICU, intensive care unit.
[a]Planned group $n = 51$, unplanned $n = 27$—answered the symptoms in pregnancy changes question.
*$p < 0.05$.

TABLE 5 Delivery and postpartum outcome and implications per pregnancy.

	Planned, $n = 41$	Unplanned, $n = 26$	p Value
Composite delivery complications[a] (n, %)	8 (19.5%)	6 (23%)	.7
Preterm delivery (n, %)	0 (24.4%)	8 (30.7%)	.56
Composite postpartum complications[b] (n, %)	15 (36.5%)	12 (46.1%)	.17
Postpartum ICU admission (n, %)	6 (14.6%)	8 (30.7%)	.02*
Gestational age at delivery (n, %)	37.9 ± 2.2	37.85 ± 2.8	.1
Birthweight (n, %)	3080 ± 623	3130 ± 670	.7
Cesarean section (n, %)	14 (34.3%)	12 (46.1%)	.36

Note: Data of the live births of the pregnancy.
Abbreviation: ICU, intensive care unit.
[a]Composite delivery complication included advanced vaginal tears, uterine rupture, perianal infection, and chorioamnionitis.
[b]Composite postpartum complication included postpartum hemorrhage, depression or blues, and preeclampsia.
*$p < 0.05$.

TABLE 6 Neonatal outcome.

	Planned, $n = 41$	Unplanned, $n = 26$	p Value
Composite neonatal complications[a] (n, %)	9 (21.9%)	10 (38.5%)	.14
Admission to NICU	9 (21.9%)	10 (38.5%)	.14
Jaundice	3 (7.3%)	4 (15.4%)	.29
Breathing difficulties requiring assistance	3 (7.3%)	3 (11.5%)	.55
Neonatal MG	1 (2.4%)	1 (3.8%)	.74

Note: For the statistical calculations, we excluded miscarriage and termination in the calculation of stillbirth, and we excluded the ongoing pregnancy on calculating the live birth and stillbirth differences.
Abbreviation: NICU, neonatal intensive care unit.
[a]Composite neonatal complication included transient neonatal myasthenia gravis, neonatal intensive care unit admission, jaundice, and breathing difficulties at birth requiring assistance.

indicate a decrease in the fertility rate among MG patient in general as we did not compare these people to the general population. Furthermore, there were more smokers in the unplanned pregnancy group. Although this finding was statistically significant, our numbers were minimal. None of the three people were admitted to the hospital during pregnancy, and only one was admitted to ICU in the postpartum time.

Our study has some limitations. First, the sample sizes in the planned and unplanned pregnancy groups were small. This could potentially impact the reliability of the results due to the limited number of cases and inability to perform multivariable analysis to better define the impact of planning the pregnancy.

Additionally, the analysis was primarily conducted per pregnancy, which is a common approach in obstetric research. However, some individuals had multiple pregnancies within each group, making it challenging to analyze certain demographic data, such as BMI, on an individual basis. Nevertheless, since the main variable of interest is planned versus unplanned pregnancy, the impact of this limitation is likely to be minimal.

Another limitation is that this study relied on self-reported questionnaires, without professional confirmation and validation, which introduces the possibility of recall bias. This bias might be more notable because of the significant difference between the maternal age at time of survey and the age at the first pregnancy.

Furthermore, there is a possibility of selection bias in this study. The proportion of patients with ocular MG was lower than in the existing literature. Additionally, a significant number of respondents reported undergoing intubation due to MG, which is higher than the reported rate of a 10%–15% lifetime risk.[22] This discrepancy suggests that individuals with more severe disease might have been more inclined to respond to the questionnaire, potentially introducing a bias that could impact the results. Importantly, we do not have the MGFA class or the exact treatment protocol and dosages prior to each pregnancy, which limits our understanding of the disease state before conception. Planning a pregnancy has been shown to improve the state of health prior to conception in a number of medical conditions.[23] Therefore, although the MGFA class in the immediate preconception timeframe is unknown, it is postulated that it may be improved in people with planned pregnancies, as "planners" may wait until they have optimized their health before becoming pregnant. This would be an important association to assess in future studies.

There could be selection bias related to the demographic characteristics of the population that participated in the survey. Only those who were members of the MGFA and MGSC were able to participate, which may not represent the entire MG population and could affect the generalizability of the findings. Finally, although we have some sociodemographic information such as self-reported race, education

level and marital status, we do not have information on household income that could impact the validity and completeness of the results.

In conclusion, this study identifies pregnancy planning in people with MG as a potentially modifiable risk factor that could decrease the risk of hospitalization and ICU admission during pregnancy and in the postpartum period. It is possible that unplanned pregnancies were in individuals who had not optimized their health prior to pregnancy or had limited contact and health management with their physicians earlier in pregnancy. The results of this study suggest the importance of discussion between physicians who care for people with MG and their patients regarding the possible critical health implications of planning a pregnancy. There may be significant benefit to preconception consultation with neurologists and high-risk obstetricians/maternal–fetal medicine specialists, as well as to access to contraception for those who are not actively seeking to become pregnant. The modifiable risk factor of effective pregnancy planning may decrease the maternal risk of severe MG-related adverse outcomes during pregnancy.

AUTHOR CONTRIBUTIONS

Saja Anabusi: Conceptualization; writing – review and editing; writing – original draft; formal analysis; software; investigation. **Aaron Izenberg:** Validation. **Carolina Barnett:** Validation. **Anne Berndl:** Funding acquisition; investigation; validation; methodology; project administration; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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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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