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Estrogen-Associated Headaches Can Be Treated by Surgery: A Multicenter Retrospective Cohort Study

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Short Running Head: Surgical Treatment of Estrogen-Associated Headaches

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ABSTRACT

Background: Nerve decompression surgery has been successful in treating headaches refractory to traditional medical therapies. Nevertheless, a subset of patients remain unresponsive to surgical treatment.

Methods: We conducted a retrospective chart review of the two senior author's (J.E.J. and W.G.A.) patient data from 2007 to 2020 to investigate differences in surgical outcomes in women reporting estrogen-associated headaches – headaches associated with menstrual period, oral contraceptives, pregnancy, other hormonal drugs – compared to those who did not. For these two groups, we used Migraine Headache Index (MHI) as the metric for headache severity and compared the mean percent change in MHI at 3 months and 1 year.

Results: Of the 99 female patients who underwent nerve decompression surgery and met inclusion criteria, 50 of the patients reported estrogen-associated headaches and were found to have significantly earlier age of onset ($p=0.017$) and initial presentation to clinic ($p=0.046$). At 1-year post-op, the majority of patients improved more than 80% after surgery (67%), but there were a subset of patients who improved less than 5% (12.5%). We did not find a significant difference in percent change in post-op MHI between women with estrogen-associated headaches and those without such headaches.

Conclusion: Women with estrogen-associated headaches have surgical outcomes comparable to women without this association. Nerve decompression surgery should be offered to women experiencing estrogen-associated headaches as an option for treatment.

INTRODUCTION

Primary headache disorders are one of the most common and disabling disorders of the nervous system. In particular, migraines affect 20.7% of females and 9.7% of males in the United States, with similar prevalence worldwide, and have debilitating socioeconomic and health disability consequences resulting in overall lower quality of life.[1–3] Despite advances in therapies for primary headache disorders, there remains no widely accepted permanent cure, and many patients are still refractory to current medical treatments.[4–6] This is due to an incomplete understanding of headache pathophysiology.[6] Clear pathophysiologic data is available for only one type of headache, specifically migraine with aura, but similar information remains elusive for other types of headaches.

Classically, the etiology of migraines is believed to be neurovascular in origin, linked to activation and sensitization of trigeminovascular pathways, which has driven a large majority of therapeutics such as triptans and calcitonin gene-related peptide (CGRP) pathway monoclonal antibodies.[7–9] However, in 2000, Guyuron et al. discovered that patients who underwent corrugator supercilii muscle resection as part of cosmetic browlifting had significant improvement, or in some cases, elimination, of their frontally-based migraine headaches.[10] This has led to an emerging body of evidence suggesting that migraines may be caused by extracranial sources of inflammation along nerve trigger sites, namely at peripheral branches of the trigeminal nerve.[11–14] This theory has been supported by the success of botulinum toxin administration, nerve blocks, and nerve decompression surgery in treating migraine headaches refractory to traditional medical therapies.[11,15–21] Despite demonstrated efficacy of surgery, there are a subset of patients who remain unresponsive. Gfrerer et al. found that patients either improved completely or failed to improve after surgery, in what may be an “all or nothing

phenomenon."[22] It is not yet known why nerve decompression surgery is ineffective in these patients and current screening efforts are unable to recognize poor surgical candidates in at least 14% of cases.[22]

One potential factor that may play a part in triggering these debilitating headaches is estrogen. Changes in estrogen have been found to have a complicated association with migraines, with the prevalence of migraines changing across milestones in a woman's life – puberty, menses, and pregnancy.[23–28] On a pathophysiological level, the decline in estrogen before menstruation has been linked to pro-inflammatory signaling and pain-modulating pathways.[29–33] Furthermore, menstrual-related migraines have been found to be more resistant to medical treatment compared to migraines that occur at other times of the month.[34] Given these associations, estrogen could potentially play a role in inflammation related to or extending beyond nerve compression, as well as nerve decompression outcomes. We hypothesize that patients who experience estrogen-associated migraines may be more refractory to surgical treatment, resulting in a subset of patients who are simply poor surgical candidates.

In this study, we sought to examine estrogen as a factor affecting headache surgery outcomes in hopes of finding an explanation to the "all or nothing phenomenon" to improve surgical screening for appropriate surgical candidates. We propose that headache surgery will be less effective for women who experience estrogen-associated headaches.

METHODS

We performed a retrospective chart review of both senior author's (J.E.J. and W.G.A.) patient data from 2013-2020. Metrics representing aspects of preoperative migraine symptoms were extracted: 1) the number of migraines per month, with a maximum of 30 days, 2) migraine intensity, between 1-10, and 3) migraine duration, recorded as number of hours out of 24 hours.

These three components were multiplied together to determine the migraine headache index (MHI), an overall metric of migraine severity. The maximum possible MHI was 300, representing a 10/10, 24-hour headache that occurs every day of the month. Other baseline information included patient demographics, location of headache, associated symptoms, triggers and reliefs, and whether patients experienced headaches related to menstrual periods, oral contraceptives, pregnancy, and other hormonal drugs. Briefly, the surgical procedures of the two senior authors can be summarized as the following. After the surgical candidate and trigger sites are identified, trigger site deactivation is performed via nerve decompression from muscle, fascia, bone, and/or vessels (Janis et al. 2019). Ligation/ablation of associated vessels is also performed. A portion of W.G.A patients received nerve transection, while no J.E.J. patients received nerve transection.

Data were parsed for female patients who underwent surgery, performed by the senior authors. Next, the control group was defined as patients who did not experience estrogen-associated headaches, and the experimental group was defined as patients who did experience estrogen-related migraines. Baseline quantitative data between groups were compared using the 2-sample t-test, and baseline qualitative data between groups were compared using the Chi-square test. Post-operative MHI data were considered for patients with follow-up at approximately 3 months and 1 year. Patients who did not have follow-up data for these time points were removed from consideration in the analysis; in other words, a patient who only had follow-up data at 3 months would only be considered for analysis at 3 months, while a patient who had follow-up data for 3 months and 1 year would be considered for analyses for both time points. Patients were not grouped or excluded by site of decompression nor number of trigger sites surgically addressed. To elucidate if there was a significant difference in surgical outcome

between control and experimental groups, we calculated the percent change between each patient's baseline MHI and post-op MHI at 3 months and 1 year by subtracting post-op MHI from baseline MHI and dividing over baseline MHI. Percent change was also calculated for MHI components (number of migraines per month, migraine intensity, migraine duration) at 3 months and 1 year.

Hypothesis tests were conducted for each follow-up time point, comparing the percent change in MHI between Control and Experimental groups. The null hypothesis was that there is no difference in means of percent change in MHI between patients who experienced estrogen-associated headaches and those who did not. The MHIs of each sample were examined via histogram; given non-normal distributions, the Mann-Whitney U test ($\alpha = 0.05$) was used. This process was repeated for MHI components (percent change in number of migraines per month, migraine intensity, and migraine duration). The effect of nerve transection on percent change in MHI between Control and Experimental groups was investigated using a two-way ANOVA ($\alpha = 0.05$). Sub-analyses were also conducted specifically for estrogen-associated variables: menstrual cycle, oral contraceptives (OCPs), pregnancy, and other hormonal drugs. Finally, to investigate the isolated effects of these estrogen-associated variables on MHI, multiple linear regression models were generated for 3-months and 1-year follow-up. Each variable was plotted on the x-axes as a binary "yes" or "no." and the MHI was plotted on the y-axis for each patient. All data were processed using RStudio (Boston, MA).

RESULTS

We identified a total of 238 patients who underwent evaluation and workup. Of these, 200 were female, with 106 undergoing surgery. Seven patients were lost to follow-up and removed from consideration, leaving 99 patients overall, 47 of which had nerve transection.

Forty-eight patients did not experience any estrogen-associated headaches (control), while 51 patients did (experimental). Table 1 shows the characteristics of these two samples. The mean age of presentation of the control group was 46.7 years, and the mean age of the experimental group was 40.7 years; patients with estrogen-associated headaches were significantly younger than those who did not ($p < 0.05$). The mean age of migraine onset for the control group vs. the experimental group was 25.6 years old vs. 18.5 years old, respectively. ($p < 0.05$). Forty-five patients reported changes in headaches associated with menstrual cycle, 17 with OCPs, 9 with pregnancy, and 5 with other hormonal drugs. These estrogen-associated variables were not mutually exclusive, so one patient could experience one or more of these variables. Patients in both groups experienced similar baseline headaches, with no statistically significant differences (Table 2).

To investigate the effect of nerve decompression surgery in each group, we calculated the percent change in MHI (Figure 1). Using 50% reduction in MHI as the traditional threshold for success, we determined that, at 3 months, 86.7% of all patients demonstrated greater than or equal to 50% change in MHI. At 1 year, 78.7% of all patients demonstrated greater than or equal to 50% change in MHI. More detailed analysis showed that change in MHI tended to fall in two extremes. At 3 months, 7.2% of all patients demonstrated less than 5% change in MHI, while 75.9% of all patients demonstrated greater than or equal to 80% change. At 1 year, these values were 12.4% and 67.4%, respectively. The remaining 20.2% were distributed across 5% to 80% change in MHI but were observed to fall approximately in two groups that leaned toward the two extremes, rather than being evenly distributed. There were no statistically significant differences in MHI improvement between control and experimental groups. Overall, percent change in MHI components also tended to improve, although there were a few outliers (Figure 2). There was no

significant difference in percent change of MHI between the two groups at both time points (Table 3). Nerve transection had no significant independent or additive effect to percent change in MHI at either follow-up time point ($p > 0.05$).

Estrogen-associated variables were also sub-analyzed to better understand the isolated effect of these estrogen-associated variables on postsurgical outcomes. A multiple linear regression model demonstrated that patients significantly improved after nerve decompression surgery, as the intercept showed a positive slope of 77.8 with $p < 0.001$ at 3 months and a positive slope of 72.4 with $p < 0.001$ at 1 year. However, none of the other estrogen-associated variables showed a significant association to percent change in MHI (Table 4).

DISCUSSION

This study aimed to understand why headache surgery is less effective for some patients compared to others. We postulated that estrogen was a factor in explaining the "all or nothing phenomenon", as demonstrated by Gfrerer et al.[22] In our study, we found that women with estrogen-associated headaches had significantly earlier age of onset and age of presentation compared to women who did not. Otherwise, baseline migraine symptomatology did not differ significantly between the two groups. While the majority of patients improved more than 80% after nerve decompression surgery, there were a subset of patients who failed to improve; specifically, at 1-year follow-up, 67.4% of patients had greater than 80% change in MHI, while 12.4% of patients had less than 5% change in MHI. This was similar to rates found by Gfrerer et al., who reported 69% of patients with greater than 80% change and 14% patients with less than 5% change, at 1 year follow-up.[22] However, there were no significant differences in post-operative outcomes between women who did not experience estrogen-associated headaches and

women who did, nor could we identify a specific estrogen-associated variable responsible for any significant differences in outcomes between the two groups.

Migraine headaches have a high prevalence rate worldwide and a serious impact on quality of life. Many studies have attempted to uncover the etiology of migraines in search of new therapies, but neither medical nor surgical pathways have come to a decisive conclusion that drives a definite cure, and a subset of patients remain refractory to both medical and surgical treatment. There are few studies that seek to elucidate why some patients do not respond well to surgical treatment. Given that migraine headaches predominantly affect females, we initially hypothesized that surgical treatment may not be as effective for some female patients because their headaches may be driven by additional hormonal factors not addressed through surgery. Sex hormones have been found to play an important role in anatomical and functional differences in migraine patients.[35,36] Maleki et al. show that certain areas of the cerebral cortex of female migraineurs were thicker, more sensitive to activation, and had different connections to the rest of the brain, resulting in a "sex phenotype" of these migraines.[37] Yet, in our study, estrogen-related effects did not have a significant impact on post-operative outcomes; nerve decompression/deactivation surgery was still effective in patients with estrogen-associated headaches.

What role might estrogen play in these patients' headaches? Current literature implicates estrogen as a direct trigger of inflammation via mechanisms such as activating endothelial cells to promoting pro-inflammatory cytokines.[29–33] Estrogen has been found to alter gene expression of glial cells in a rat model, leading to release of factors that affect neurogenic inflammation.[38] The decline in estrogen before menstruation is thought to inactivate neuroinhibitory systems and enhance excitatory glutamatergic tone.[23,29,39] Interestingly, these theories correlate with the

pathophysiology of entrapment neuropathy. For instance, glutamate has a prominent role in the development of hyperalgesia and allodynia.[14,40,41] Chronic constriction injury of the infraorbital nerve is found to increase proliferation of satellite glial cells, and changes in these cells are thought to affect nociception.[42,43] Thus, we postulate that estrogen may "biologically prime" nerve inflammation, which combined with extrinsic nerve compression, may lead to the development of migraines. This combined effect is akin to the "double crush hypothesis."[44,45] First described by Upton and McComas in 1973, this theory suggests that compressed axons are susceptible to damage at a secondary site.[44] Serial sites of impingement, which may be clinically silent alone, are compounded, leading to severe dysfunction of the nerve. Studies have found that non-physical factors, such as diabetic neuropathy, can also lead to increased susceptibility to chronic nerve compression, for which nerve decompression surgery has been used as treatment.[46] We suspect that estrogen-related effects work similarly to "prime the nerve", leading to headaches, though it is unclear if one must occur before the other. Regardless, we found that nerve decompression/deactivation surgery is successful even in estrogen-associated migraines; estrogen-related effects on the nerve may be clinically silent without extrinsic compression, so deactivation would lead to alleviation of symptoms.

We also do not yet understand why some women of reproductive age experience estrogen-associated migraines, while others do not. It is possible that women have variations in gene expression that increase their risk of "biological priming" by estrogen. This may explain why our patients with estrogen-associated headaches had significantly earlier onset of migraines. Variability in the response to changes in estrogen through life events such as puberty may impact when women first experience migraines, and those more at risk of "biological priming" may have earlier onset of their headaches. Women with menstrual-related headaches have been found

to have certain patterns of rapid estrogen decline in the late luteal phase that predispose them to environmental triggers of migraine, such as stress or lack of sleep.[26] Some post-menopausal women develop headaches after depo-estradiol injection, indicating a potential biological predilection for estrogen-triggered migraines.[47] In contrast, there are inconsistencies in the effects of exogenous sources of estrogen, such as oral contraceptives and hormone replacement therapy, on migraine headache.[48–51] The variability in women who experience estrogen-associated migraines may be a reflection of underlying genetics that affect how women respond to estrogen, and consequently, if estrogen compounds the pathophysiology of nerve compression.

There are several limitations to this study. One limitation of this study is that patients were only analyzed to 1-year follow-up. This makes it difficult to ascertain if benefits of surgery are maintained over time or require more time to take effect for patients more resistant to treatment; however, Guyuron et al. have shown that patients retained benefits from surgery at 5 years post-op, which was not significantly different from results at 1-year post-op.[52] This study is also challenged by a patient's self-reported metrics of headache symptomatology. We chose not to use other validated assessment tools, such as the Global Assessment of Migraine Severity (GAMS) or the Migraine Disability Assessment (MIDAS), because these metrics are also limited by strongly subjective responses. However, it would be useful to assess surgical outcomes based on these other tools to paint a more comprehensive picture. These tools will be utilized in future studies. We also did not analyze or control for specific trigger sites or number of trigger sites decompressed due to inadequate sample sizes to power a hypothesis test analyzing such variables. These variables may have an effect on surgical outcome, related to or independent of estrogen-related effects. Patients who develop new trigger sites after surgery would likely continue to report headache symptomatology, even if surgery did have a benefit at addressed

trigger sites. Detailed analysis on a larger sample size would have to be performed to tease apart the nuances related to trigger sites. Lastly, all of the patients in this study were Caucasian, leading to poor generalizability. Ultimately, there are myriad factors that could be investigated to better understand surgical outcomes in these patients, and long-term, large sample prospective studies are required to build upon the findings in this analysis.

CONCLUSION

Nerve decompression surgery is a growing area of interest for treatment of migraine headaches refractory to traditional medical therapies. Estrogen may act as a biological primer that increases nerve susceptibility to compression, but this process does not affect surgical outcomes. Patients with estrogen-associated migraines are viable surgical candidates and should be offered nerve decompression surgery, while further investigation is required to elucidate why some patients fail to improve after surgery.

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TABLES AND FIGURES LEGEND

Table 1. Characteristics of the Patient Sample

Table 2. MHI Descriptive Statistics for Control and Experimental Groups

Figure 1. Distributions of Percent Change in MHI at Post-Op Follow-Up**.** Percent change in MHI at 3 months and 1 year post-op follow-up for All Subjects (Left Column), No Estrogen-Associated Migraines (Control; center column), and Estrogen-Associated Migraines (Experimental; right column). Subjects with percent change < 5% and ≥ 80% are shown in green and blue, respectively, with subjects in between shown in red. At 3 months, 7.2% of All Subjects (7.5% Control vs. 7.0% Experimental, p=1) < 5% change; 75.9% of All Subjects (72.5% Control vs. 79.1% Experimental, p=0.61) had ≥ 80% change. At 1 year, 12.4% of All Subjects (16.3% Control vs. 8.7% Experimental, p=0.34) had < 5% change; 67.4% of All Subjects (69.8% Control vs. 65.2% Experimental, p=0.66) had ≥ 80% change. Asterisks (*) indicate distributions with outliers not visible in the plots; these may be seen in Figure 2. P-values were obtained using Fisher's Exact Test.

Figure 2: Percent Change in MHI Metrics at Post-Op Follow-Up. Boxplots comparing the percent change in (above, left) MHI, (above, right) number of migraines per month, (below, left) migraine intensity, and (below, right) migraine duration for 3-months and 1-year post-op between patients who did not experience estrogen-associated migraines (Control) to those who did (Experimental). Means of distributions are marked by diamonds. (above, left) Control 3 mo μ: 77.3, SD: 52.0; Experimental 3 mo μ: 82.6, SD: 29.1; Control 1 yr μ: 74.4, SD: 39.4; Experimental 1 yr μ: 60.8, SD: 101. (above, right) Control 3 mo μ: 54.7, SD: 84.7; Experimental 3 mo μ: 73.7, SD: 34.4; Control 1 yr μ: 61.7, SD: 44.7; Experimental 1 yr μ: 62.4, SD: 48.6. (below, left) Control 3 mo μ: 49.7, SD: 43.3; Experimental 3 mo μ: 42.9, SD: 40.4; Control 1 yr

μ: 43.3, SD: 41.9; Experimental 1 yr μ: 52.6, SD: 85.0. (below, right) Control 3 mo μ: 52.6; SD: 85.0; Experimental 3 mo μ: 30.6, SD: 96.3; Control 1 yr μ: 40.6, SD: 71.6; Experimental 1 yr μ: 31.3, SD: 126.

Table 3. Mann-Whitney U Tests Comparing Percent Change in MHI Metrics for Patients With and Without Estrogen-Associated Migraines.

Table 4. Multiple Linear Regression Analyzing Isolated Effects of Different Estrogen-Associated Variables on Percent Change in MHI.

Table 1. Characteristics of the patient sample

	No Estrogen-Associated Migraines (Control)	Estrogen-Associated Migraines (Experimental)	P
Number of patients	48	51	
Mean age at presentation, years (SE)	46.7 (1.91)	40.7 (1.77)	**0.024**
Age Range	18-73	17-65	
Race/Ethnicity			
White	48	51	
Aura			0.105
Yes	43	50	
No	5	1	
Mean onset of migraines, years (SE)*	25.6 (2.38)	18.5 (1.36)	**0.012**
Age Range	5-62	1-49	
Estrogen-Associated Variables			
Menstrual Period	-	45	

Oral Contraceptives (OCPs)	-	17
Pregnancy	-	9
Other Hormonal Drugs	-	5

Note: Comparison between mean age of groups was tested with the 2-sample t-test (α=0.05).

Comparison of auras was tested with Fisher's Exact Test (α=0.05).

*Patients who did not report a specific age of onset were excluded from this statistic.

Table 2. MHI descriptive statistics for Control and Experimental groups, for each time point

	No Estrogen-Associated Migraines		Estrogen-Associated Migraines	
	μ (SD)	**Median (Q1, Q3)**	**μ (SD)**	**Median (Q1, Q3)**
Baseline (all patients)*	N=48		N=51	
MHI	125 (93.3)	112 (40.6, 193)	120 (97.2)	96 (35, 210)
# per month	19.5 (9.41)	20 (10, 30)	20.5 (8.11)	20 (15, 30)
Intensity	7.55 (1.85)	8 (6, 9)	7.75 (1.23)	8 (7, 8)
Duration	0.93 (0.80)	1 (0.41, 1.00)	0.77 (0.62)	0.58 (0.29, 1.00)
Post-op MHI (3-mo FU)	N=40		N=43	
MHI	29.7 (69.6)	0.86 (0, 15.6)	15.3 (38.3)	3.5 (0, 15)
# per month	7.41 (9.99)	3 (0, 10.5)	4.44 (5.65)	2.5 (0, 6.5)
Intensity	3.86 (3.41)	4 (0, 7)	4.25 (3.07)	5 (0, 7)
Duration	0.29 (0.51)	0.052 (0, 0.29)	0.37 (0.66)	0.17 (0, 0.25)
Post-op MHI (1-yr FU)	N=43		N=46	
MHI	32.0 (68.6)	4 (0.13, 18.0)	38.3 (69.3)	2.13 (0, 46.9)
# per month	7.65 (10.6)	2 (0, 12)	7.20 (9.54)	4 (0, 10)
Intensity	4.30 (3.28)	4 (0, 7)	4.59 (3.36)	5 (1, 7)
Duration	0.46 (0.75)	0.17 (0, 0.56)	0.51 (0.84)	0.13 (0, 0.59)

**Note:* Baseline statistics for all patients are not representative of baseline statistics used in analyses for each follow-up time point. Only patients with follow-up data at each time point have their baseline data compared to post-op data at the chosen time point. Sample sizes for these analyses are provided in this table.

Table 3. Mann-Whitney U tests comparing percent change in MHI metrics for patients with and without estrogen-associated migraines.

	MHI (% change)			# per month (% change)			Intensity (% change)			Duration (% change)		
	Control Median (IQR)	Exp Median (IQR)	P	Control Median (IQR)	Exp Median (IQR)	P	Control Median (IQR)	Exp Median (IQR)	P	Control Median (IQR)	Exp Median (IQR)	P
All Estrogen-Associated Variables (Exp N=51)												
3 mo	99.4 (22.8)	93.3 (18.5)	0.41	82.3 (57.5)	86.7 (38.8)	0.70	50.0 (100)	35.4 (92.5)	0.52	93.7 (53.1)	59.2 (100)	0.086
1 yr	96.7 (33.9)	97.3 (38.8)	0.85	86.7 (98.3)	80.0 (66.7)	0.91	40.0 (94.4)	93.7 (53.1)	0.062	66.7 (100)	78.1 (100)	0.67
Menstrual Period (Exp N=45)												
3 mo	99.4 (19.4)	94.3 (19.3)	0.30	87.8 (50.0)	84.2 (37.4)	0.75	50.0 (96.9)	35.4 (58.7)	0.30	93.7 (59.4)	59.2 (93.4)	0.054
1 yr	96.8 (31.1)	97.2 (38.9)	0.96	87.1 (64.3)	76.9 (66.7)	0.67	36.7 (100)	33.3 (87.5)	0.71	70.8 (100)	75.0 (100)	0.81
OCPs (Exp N=17)												
3 mo	97.4 (18.1)	85.0 (19.4)	0.38	87.1 (50.0)	82.9 (37.5)	0.95	44.4 (100)	33.9 (58.0)	0.84	76.8 (75.0)	50.0 (96.9)	0.32
1 yr	95.8 (38.4)	97.8 (40.1)	0.59	83.3 (80.0)	80.0 (33.3)	0.53	33.3 (100	35.4 (50.0)	0.82	70.0 (100)	82.3 (100)	0.62
Pregnancy (Exp N=9)												
3 mo	96.9 (20.2)	93.3 (15.3)	0.91	83.3 (50.0)	90.0 (27.5)	0.51	44.4 (90.0)	33.3 (100)	0.84	75.0 (100)	66.7 (100)	0.93
1 yr	95.6 (40.0)	99.1 (2.65)	0.20	80.0 (70.0)	88.3 (21.3)	0.34	33.3 (88.9)	35.4 (80.2)	0.50	66.7 (100)	91.7 (18.8)	0.13
Other Hormonal Drugs (Exp N=5)												
3 mo	96.4 (20.6)	100 (4.81)	0.14	83.3 (50.0)	100 (6.67)	0.086	42.9 (100)	100 (50.0)	0.20	75.0 (100)	100 (50.0)	0.36
1 yr	96.3 (40.8)	100 (0.00)	**0.039**	80.0 (70.0)	100 (0.00)	**0.022**	33.3 (87.8)	100 (50.0)	0.15	72.5 (100)	100 (0.00)	**0.041**

Note: Only patients with follow-up data at each time point have their data analyzed at the chosen time point; provided sample sizes reflect total number of experimental patients in each group.

Table 4. Multiple linear regression analyzing isolated effects of different estrogen-associated variables on percent change in MHI.

	3 months			1 year		
	Estimate	SE	P	Estimate	SE	P
(Intercept)	77.8	6.45	**<2E-16**	72.4	11.4	**1.16E-8**
Menstrual Period	1.40	10.2	0.891	-25.1	18.7	0.183
OCPs	6.00	15.3	0.696	17.6	25.3	0.488
Pregnancy	-3.72	17.6	0.833	22.2	31.2	0.480
Other Hormonal Drugs	17.7	20.1	0.382	24.1	36.4	0.510

Figure 1

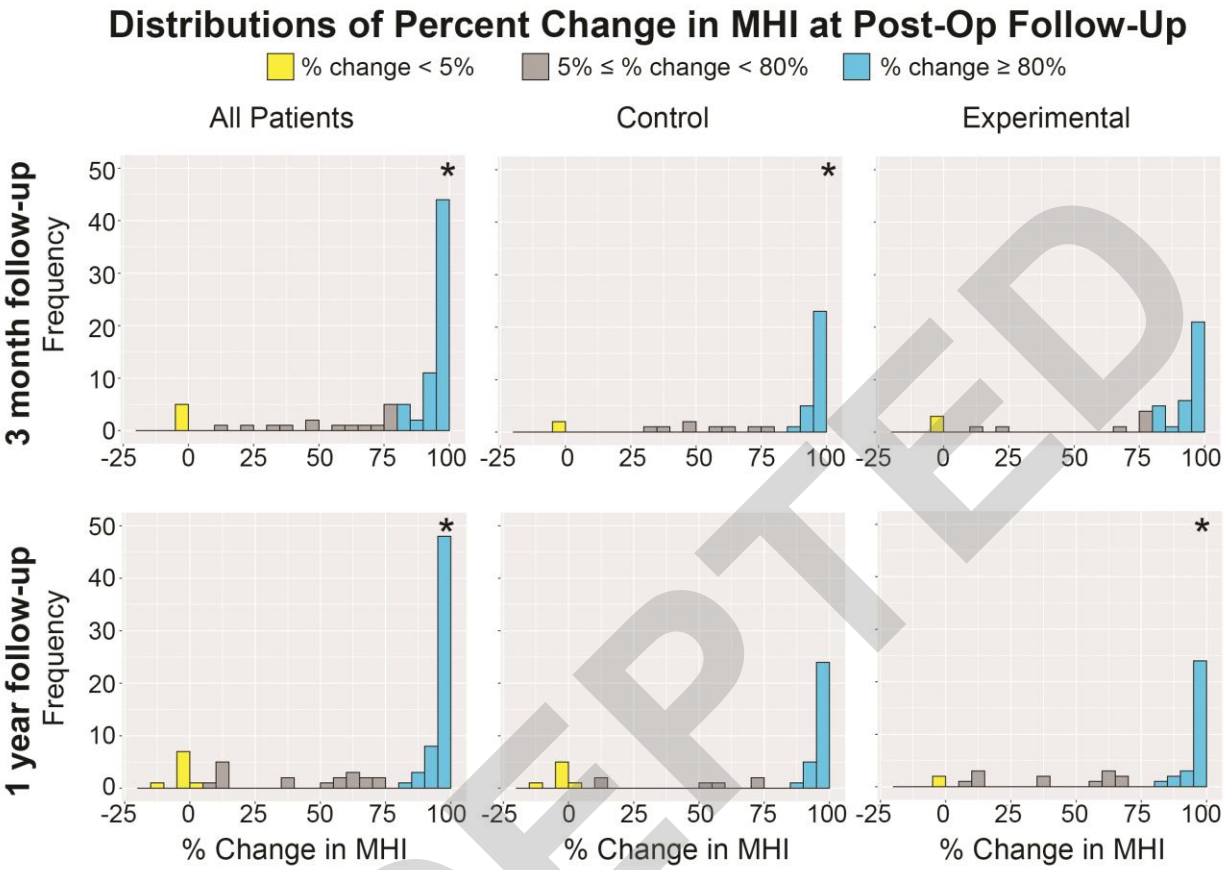

Figure 2