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Correspondence

Reply to "Letter to the Editor" by Moran et al. "Comment on 'Potentized estrogen in homeopathic treatment of endometriosis associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study'"

To the Editor,

We would like to thank Moran et al. [1] for the attention they paid to our study [2] probably awakened for its reporting on a homeopathic treatment, a therapy seen with mistrust and prejudice by many researchers. While many of Moran et al.'s major concerns might be elucidated by a careful reading of the original manuscript, their comments provide us an occasion to dispel other possible doubts and reaffirm the efficacy of potentized estrogen in the homeopathic treatment of endometriosis-associated pelvic pain (EAPP).

In regard to the calculation of the sample size (statistical power), agreeing with Bayoglu et al.'s study [3], our trial sought to assess changes in the VAS score "between groups (control and treatment)" and not "intragroup", as Moran et al. observe; this outcome is clearly stated in the "Data analysis" section [2]: "Comparison between groups and time points was performed by means of generalized estimating equations with first-order autoregressive structure, normal marginal distribution and identity link function. Outcome measures that showed statistical significance were subjected to the Bonferroni test to establish between which groups and time-points differences in symptoms and scales occurred".

Consequently, as described in the "Sample size" section [2], the sample size was calculated so as to obtain a difference of 2.16 in the VAS score between the groups (placebo and treatment). This difference was actually overestimated, because we used a 0–50 points VAS (EAPP global score), i.e. half the one used by Bayoglu et al. (0–100 points). Even so we detected higher significant differences between the groups at the end of the study. It is worth to stress once again the lack of similar studies in the literature, which made the sample size difficult to calculate.

As concerns the initial randomization (1:1 ratio), the final groups were not homogeneous (placebo, n = 27; treatment, n = 23), because we prepared a randomization model for 60 patients (i.e., larger than the minimum estimated of 23 participants per group) to compensate for eventual losses to follow up. However, in accordance with the previously stipulated schedule, we had interrupt the recruitment period when it reached 50 participants, which favored imbalance between the groups at the end of this study. However, this situation does not influence the results, because the minimum sample size was attained also in the smallest group.

Regarding the assessment of normality at baseline described in "Table 2" [2], the analyzed characteristics were assessed by means of the Kolmogorov-Smirnov test and then by parametric or non-parametric tests as per need. Age, EAPP modalities score (global and partial) and anxiety, depression and quality of life scales were described per group by means of summary measures (mean, standard deviation and median), and compared between groups (placebo and treatment) using Student's *t*-test or the Mann-Whitney test. In the final analysis ("Table 2") the scores on the dysmenorrhea (P = 0.044), acyclic pelvic pain (P = 0.027) and depression (P = 0.025) were significantly higher in group treatment compared to the placebo group. The remainder of the variables did not exhibit significant difference between the groups. It is worth to notice that although the condition of the participants in group treatment was more severe regarding the three just mentioned variables, they exhibited significant improvement after homeopathic treatment, which was not the case of the ones in group placebo, which fact represents an additional evidence for the efficacy of potentized estrogen.

In the analysis of the data after intervention (outcomes), EAPP modalities score (global and partial), anxiety, depression and quality of life scales were described per group and along follow up by means of summary measures (mean, standard deviation and median) and compared between groups (placebo and treatment) and time-points (baseline-24 weeks) using generalized estimating equations with first-order autoregressive structure between time-points, normal marginal distribution and identity link function (logarithmic link function for quality of life scores). For the outcomes that exhibited statistical significance (<0.05), analysis was complemented with the Bonferroni multiple comparison test [mean difference, standard error, p-value and (95%) CI]. This included per protocol (PP) and intention-to-treat (ITT) analysis and is summarily described in subsections "Primary outcome measures" and "Secondary outcome measures" of the "Results" section [2].

As concerns the representation of those results (primary and secondary outcome measures) in the "Figures 2, 3, 4 and 5" [2] the represented data are 'mean scores' and 'standard error', which information lacks in the captions of figures, as Moran et al. observed. The mean difference (MD) of the scores, mentioned in the captions of figures and in the description of the results, was calculated by subtracting the value at baseline from the final value (24 weeks), as is clearly visualized in the graphs.

To help visualize the analyses that led to the study results and corresponding figures (since the estimated results are not always clear in graphs) we made a table (Table 1. Multiple Comparisons of Bonferroni) in which the outcomes of the Bonferroni comparison test is associated with the corresponding figures. In the analysis of depression symptoms, "it is worth stressing that treatment group presented significantly higher score on BDI at baseline compared

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Table 1
Multiple Comparisons of Bonferroni (Outcome/Figure).

Outcome	Moment or Group	Comparisons	Mean difference	Standard error	p-value	IC (95%)	
						Lower	Upper
EAPP global	Baseline	Placebo/Treatment	−4.33	2.79	>0.999	−13.05	4.39
(ITT analysis)	Placebo	Baseline-24 weeks	−0.94	1.69	>0.999	−6.20	4.33
(Fig. 2)	Treatment	Baseline-24 weeks	12.82	1.95	<**0.001**	6.74	18.89
Dysmenorrhea	Baseline	Placebo/Treatment	−0,65	0.76	>0.999	−3.02	1.72
(ITT analysis)	Placebo	Baseline-24 weeks	−0.11	0.63	>0.999	−2.07	1.85
(Fig. 3)	Treatment	Baseline-24 weeks	3.28	0.72	<**0.001**	1.04	5.52
Non-cyclic pelvic pain	Baseline	Placebo/Treatment	−0.94	0.76	>0.999	−3.30	1.42
(ITT analysis)	Placebo	Baseline-24 weeks	0.07	0.66	>0.999	−1.98	2.11
(Fig. 3)	Treatment	Baseline-24 weeks	2.71	0.75	**0.009**	0.36	5.05
Cyclic bowel pain	Baseline	Placebo/Treatment	−1.83	0.95	>0.999	−4.79	1.13
(ITT analysis)	Placebo	Baseline-24 weeks	−0.16	0.63	>0.999	−2.14	1.82
(Fig. 3)	Treatment	Baseline-24 weeks	3.40	0.73	<**0.001**	1.12	5.68
Bodily pain	Baseline	Placebo/Treatment	7.53	4.79	0.698	−5.12	20.18
(SF-36)	Placebo	Baseline-24 weeks	−5.04	3.76	>0.999	−14.96	4.87
(PP analysis)	Treatment	Baseline-24 weeks	−13.71	4.47	**0.013**	−25.49	−1.92
(Fig. 4)							
Vitality	Baseline	Placebo/Treatment	1.26	5.56	>0.999	−13.41	15.94
(SF-36)	Placebo	Baseline-24 weeks	−2.50	4.01	>0.999	−13.07	8.07
(PP analysis)	Treatment	Baseline-24 weeks	−13.82	4.76	**0.022**	−26.38	−1.27
(Fig. 4)							
Mental health	Baseline	Placebo/Treatment	10.75	5.95	0.427	−4.96	26.45
(SF-36)	Placebo	Baseline-24 weeks	−3.00	4.22	>0.999	−14.13	8.13
(PP analysis)	Treatment	Baseline-24 weeks	−14.35	5.01	**0.025**	−27.58	−1.12
(Fig. 4)							
Depression	Baseline	Placebo/Treatment	−10.13	3.00	**0.004**	−18.04	−2.21
(BDI)	Placebo	Baseline-24 weeks	3.21	2.35	>0.999	−2.99	9.41
(PP analysis)	Treatment	Baseline-24 weeks	11.53	2.79	<**0.001**	4.16	18.90
(Fig. 5)							

Bold values: <0.05 (level of statistical significance).

to placebo group (MD 10.13; 95% CI −18.04 to −2.21; P = 0.004)" [2]. The significant improvement in this regard exhibited by group treatment, and lacking in the placebo group, might be considered a further evidence for the efficacy of potentized estrogen.

We would like to thank *European Journal of Obstetrics & Gynecology and Reproductive Biology* the opportunity to make our work known, and also to congratulate its Editorial Board for its lack of prejudice as concerns to studies reporting on therapies complementary to conventional treatment.

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Marcus Zulian Teixeira*
Department of Obstetrics and Gynecology, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil

Sérgio Podgaec[a,b]
[a]*Department of Obstetrics and Gynecology, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil*

[b]*Jewish Teaching and Research Institute, Albert Einstein Hospital, Sao Paulo, Brazil*

Edmund Chada Baracat
Department of Obstetrics and Gynecology, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil

* Corresponding author at: Hospital das Clínicas da FMUSP, Departamento de Ginecologia e Obstetrícia, Av. Dr. Enéas de Carvalho Aguiar, 255, 10° andar, sala 10.166, 05403-000 São Paulo, SP, Brazil.
E-mail address: mzulian@usp.br (M. Teixeira).

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