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When solving dyspareunia is not enough to restore sexual function in women with deep infiltrating endometriosis treated with dienogest

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Contribution to Authorship

JPL-P, CLB-P and DAY conceived and designed the study. JPL-P collects data. All authors were involved in data analysis, interpretation, and writing. All authors approved the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interests.

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Abstract:

Objective: The aim of the study was evaluated dyspareunia and sexual function (SF) in women with deep endometriosis treated with Dienogest for 12 months. **Methods:** Prospective cohort study set in University of Campinas, Brazil, including thirty women with sonographic diagnosis of deep endometriosis and sexual dysfunction treated with 2mg/daily Dienogest for 12 months. SF parameters were assessed by Female Sexual

Function Index (FSFI) before and after the treatment and dyspareunia was quantified through Visual Analogic Scale(VAS) during the follow ups performed every 3 months. Statistical analysis was performed by ANOVA test as well as Statistical Analysis System version 9.4. **Results:** Women were on average 36.13 ± 6.24 years old and all of them showed sexual dysfunction (FSFI = 17.6 ± 5.7) before Dienogest; 88.3% had dyspareunia as main symptom related to deep endometriosis (VAS before $5,3 \pm 3,1$). At the end of the treatment, dyspareunia showed a decrease of intensity (VAS after 3.7 ± 3.3 ; $p=0.0093$) and an improvement on FSFI index was accomplished ($p=0.0023$) however, it did not restore SF completely, considering FSFI cut-off <26.55 . **Conclusion:** Long-term treatment for DIE with Dienogest has provided a decreasing in dyspareunia and also an enhancement on SF, although SF has not been restored to normal levels.

Keywords:

Deep infiltrating endometriosis – Dyspareunia – Female sexual disorder – Dienogest

Introduction:

Deep infiltrating endometriosis (DIE) is an estrogen-dependent inflammatory disease caused by presence of endometrial-like tissue implanted below the peritoneum affecting structures such as recto sigmoid colon, recto-vaginal septum, utero-sacral ligament, bladder and ureters causing pain symptoms such as dysmenorrhea, dyspareunia and chronic pelvic pain.[1]

Dyspareunia is one of the most common symptoms associated with DIE and, in comparison with female general population, there are a nine-fold increase risk of this complaint.[2]

Dyspareunia is a disabling condition that severely affects women physically and psychologically and, consequently, triggering sexual dysfunction.(3,4) Recently, thirty two percent of patients with endometriosis correlated sexual dysfunction with pain intensity during or after intercourse, which leads to avoiding sexual interaction. Experiencing this awful situation, women with endometriosis creates negative expectations about their sexual life hazardous their sexuality.[3,5]

Defined as an overlapping of biological, psychological and interpersonal problems, sexual dysfunction occurs during the sexual response cycle preventing satisfaction from sexual activity due to lack of sexual desire, difficulty in arousal,

inability to reach orgasm, pain during/after intercourse, failure to feel pleasure from sex or anxiety about sexual performance.[6,7]

Nevertheless, there is no permanent treatment for endometriosis and many therapies are claimed to be the answer for this painful distress, mainly those with progestogens.[8,9] Among them, Dienogest, a fourth-generation progestin exhibits highly selective binding to the progestogen receptor and in addition, has an immunologic, antiangiogenic and anti-proliferative activities implying to decrease of pain symptoms associated with endometriosis and as last, but no least result, the improvement of quality of life and sexual function.[8,10–12]

The aim of this study was to assess sexual function and dyspareunia after a long-term treatment with dineogest in women with deep infiltrating endometriosis.

Material and methods:

Longitudinal study including 30 women diagnosed with DIE (intestinal and posterior fornix) at the Endometriosis Clinic of the Department of Obstetrics and Gynecology at University of Campinas (UNICAMP). All women also signed an informed consent form before enrollment in this study. The present study was approved by the Research Ethics Committee of the Faculty of Medical Science of State University of Campinas (nº302817).

Inclusion criteria were age, 18 to 45 years old, diagnosis of deep endometriosis and complaint of deep dyspareunia. Women who had undergone a therapeutic surgical procedure in past 6 months, undiagnosed abnormal menstrual bleeding, chronic diseases such as cancer, liver, heart and/or kidney diseases; women with psychological or psychiatric comorbidities, such as anxiety or depressive symptoms as well as pregnant women were excluded.

Those 30 women selected were referred to our clinic as a candidate to surgical treatment due to expressing persistent pain complaints regardless clinical treatment for at least 6 months. A treatment with dienogest was proposed to them prior to surgery. The inclusion was sequential according to standard attendance until statistically determined sample size was achieved.

Diagnosis of DIE, as well as its control after 12 months of treatment, was established by transvaginal sonography performed by the same expert.

Taking a daily dose of 2 mg DNG, participating patients underwent to outpatient visits at the beginning and after 3, 6, 9 and 12 months of treatment. In all inquiries, pain symptoms related to DIE, including dyspareunia, dysmenorrhea, pelvic pain, were evaluated according to Visual Analogic Scale (VAS) on a 0 – 10 score [13]

Assessment of sexual function was performed by Female Sexual Function Index (FSFI) questionnaire before and after 12 months of treatment with DNG. This instrument consists in six domains, which includes desire, arousal, lubrication, orgasm, satisfaction and pain on a 0 – 5 score points, oscillating from 0 (no sexual activity) or 1 (never/very low) to 5 (always/very high). The score is calculated for each domain and the total score is obtained summing all items. Each domain is awarded a score on a scale from 0 to 5, with higher scores indicating better functioning in each domain. A score of zero indicates that woman reported no sexual activity in the prior month. In our study having intercourse in the preceding month was a requirement for inclusion. The total score range between 2 – 36 and a cut-off of <26.55 is commonly accepted as diagnosis of sexual dysfunction, according to the literature.[14]

The sample size calculation was based on prior studies with DNG as treatment for endometriosis[15–17]

Quantitative data analysis was performed by ANOVA test and the software SAS version 9.4. Significance level of 5% was assumed to be valid.

Results:

Thirty women diagnosed with DIE were on average of 36.13 ± 6.24 years and reported inception of symptoms at 29.24 ± 7.82 years old. Dyspareunia was the most related complaint before treatment (88.3%) with initial AVS 5.3 ± 3.1 , followed by dysmenorrhea (73.3% - AVS 5.0 ± 3.8) and pelvic pain (66.7% - AVS 4.0 ± 3.6).

All women included presented, at the beginning, score that indicates sexual dysfunction (FSFI ≤ 26.55) with a mean of total score of 17.4 ± 5.4 and pain during intercourse was the domain with the lowest rank (2.4 ± 1.6), which indicates great harm related to sexual interaction. After treatment with DNG for 12 months, a significant decrease in pain symptoms, considering frequency and intensity was revealed: pelvic pain ($p=0.0007$), dysmenorrhea ($p<0.0001$) and dyspareunia ($p=0.0093$). (Table 1)

Regarding sexual function, there was significant advancement long-term treatment with DNG (FSFI 22.1 ± 6.2 ; $p = 0.0023$) (Figure 1) in spite of FSFI questionnaire shows no statistically significant enhancement in several domains such as desire ($p=0.2629$), lubrication ($p=0.1879$) and satisfaction ($p=0.1523$). (Table 2)

Side effects related to DNG as headache (63.3%), decrease in desire (43.3%) and nausea (23.3%) during the treatment was not a motivation to therapy discontinuation in any of the 30 cases and through 12 months of management with DNG there was no need of surgical procedure in these patients.

Discussion:

Thirty women suffering from dyspareunia and DIE were referred to our clinic for evaluation of surgical treatment after drug treatment failure and we suggest DNG as last option prior surgery. After 12 months of therapy pain symptoms were reduced, including dyspareunia.

DIE is a serious chronic disease that frequently affects quality of life and female sexual function, most of all, due to related pain symptoms such as dyspareunia as we found in our study, validating the current literature.[18,19]

Pain during the intercourse leads to avoidance of sexual interaction and implies to feelings of remorse towards the partner, lower level of desire and satisfaction during sex.[3,20]

DNG is already a well reputable treatment for pain complaints related to endometriosis at any level. A systematic review with nine randomized trials of the use of dienogest versus placebo or GnRH analogue showed dienogest is an effective drug for controlling pain in women with DIE. [21]

In a comparative study using DNG associated to ethinylestradiol in continuous versus 21/7 regimen obtained, in a 6 month follow up, a better improvement of sexual function with the continuous regimen.[9] In our study, we established a 12-month treatment with follow ups every 3 months and, as we see in our results, with 6 months of treatment was accomplished a significant improvement of dyspareunia ($p < 0.001$) however, it had no implication in upgrading of sexual function score ($p = 0.4220$). After 12-month treatment the complaint of dyspareunia in our patients remained satisfactory ($p = 0.0093$) and related to this we had a statistically significant improvement in the FSFI index of these women with deep endometriosis ($p < 0.0023$).

Despite decreasing in pain objections and the improvement in sexual function after 12 months of DNG usage, it was not enough to completely restore sexual function, considering a FSFI index cut-off of < 26.55 that is usually accepted for diagnosis of female sexual dysfunction.

Long-term treatment for endometriosis has generally been beneficial due to causing decrease in pain symptoms and expressing low and well tolerated side effects.

For this reason, treatment with DNG is believed to be a promising therapy which possibly implies in QoL enhancement.[12,16,22]

Regarding sexual function, after 12-month treatment the complaint of dyspareunia in our patients remained satisfactory ($p=0.0093$) and related to this we had a statistically significant improvement in the FSFI index of these women with deep endometriosis ($p<0.0023$).

All women previously participation in our study expressed sexual dysfunction and this situation showed a discrete yet statistically significant improvement in the FSFI index when assessed after long term treatment follow-up, as we see in current literature. [8,23,24]

Considering each domain of FSFI questionnaire only arousal and orgasm had a substantial enhancement ($p=0.0005$ and $p=0.0075$ respectively). These unexpected finding substantiate the concept that sexuality is a complex issue and is influenced by many features and organic dyspareunia is one among several elements of sexual functioning in women with DIE. [25]

As a limitation of our study, there was no comparison with control group using the gold standard treatment already established. Another limitation of the study was the non-use of the questionnaire the Female Sexual Distress Scale (FSDS); an essential element for diagnosis of sexual dysfunction. The small sample was a limitation too. However, were included only women with DIE affecting posterior fornix and alleged dyspareunia as main symptom aiming to evaluate the significance of this complaint to sexual function and the effectiveness of long-term treatment with DNG, which already proved to be a successful therapeutic alternative for DIE, reducing pain symptoms.[12,15,16,26]

Female sexual function is a multifactorial subject that cannot be only related to pain during intercourse. Aspects as marital distress, anxiety, depression are very

important and certainly exert influence on sexuality and should be evaluated by a multidisciplinary team.

To sum up, long-term treatment to deep endometriosis with DNG implied in decreasing in dyspareunia which reflected positively on female sexual function, nevertheless it was not enough to restore sexual function to normal levels.

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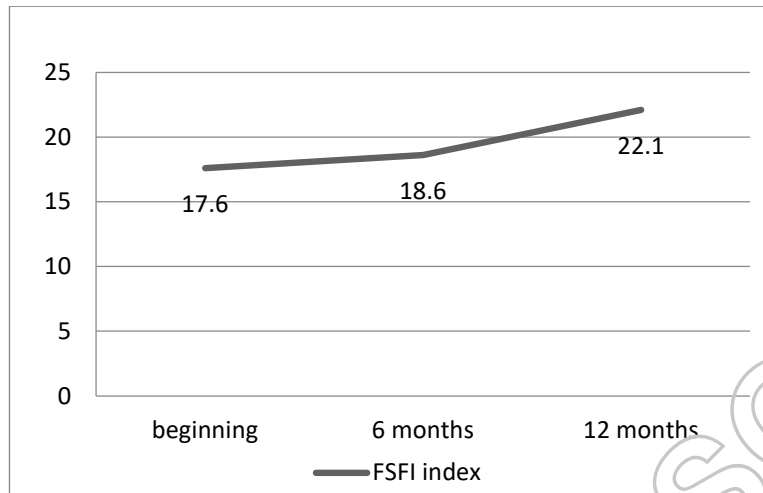
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Figure 1 – Evolution of FSFI index in women with DIE – DNG 12 months



(¹) $p=0.4220$ (²) $p=0.0023$ - ANOVA pairwise comparison

(¹) Comparison 6 months/beginning (²) comparison 12 months/beginning

Table 1- Evaluation of pain symptoms in women with DIE - DNG for 12 months (n = 30)

	Beginning mean±sd	12 months mean±sd	0 – 12 months p-value ¹
VAS – Dysmenorrhea	5.7±3.8	0,7±1.6	<0.0001
VAS – Dyspareunia	5.3±3.1	3.7±3.3	0.0093
VAS – Pelvic Pain	4.0±3.6	1.2±2.1	<0.0001

VAS – visual analog pain scale; sd – standard deviation; ¹Wilcoxon signed-ranktest

Table 2 – FSFI domains in women with DIE -DNG 12 months (n=30)

Domain	Beginning Mean ± sd	6 months Mean ± sd	P-value ⁽¹⁾	12 months Mean ± sd	P-value ⁽²⁾
Desire	3.0 ±1.2	3.1±1.2	0.5692	3.2±1.2	0.5529
Arousal	2.6 ±1.2	2.7±1.3	0.9735	3.5±1.3	0.0005
Lubrication	3.1 ±1.4	3.3±1.3	0.5498	3.8±1.4	0.1225
Orgasm	3.0 ±1.6	3.0±1.5	0.8687	3.8±1.2	0.0075
Satisfaction	3.4 ±1.2	3.6±1.3	0.5692	4.0±1.1	0.1260
Pain	2.7 ±1.7	3.0±1.5	0.2810	3.7±1.5	0.0832

Sd – standard deviation; ANOVA pairwise comparison

⁽¹⁾ comparison 6 months/beginning ⁽²⁾ comparison 12 months/beginning