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Research Article

Dienogest Versus Norethindrone In Management of Ovarian Endometrioma Issues

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Abstract

Background: *Endometriosis is considered at molecular, cellular and pathophysiological aspects as an inflammatory disease that is characterized by existence of growing of endometrial-like tissues outside the normal endometrial cavity. A large bulk of gynecologists in infertility clinics prefer usage of progestins, in the form of a first line medical management protocol in cases symptomatizing due to safety, efficacy and tolerability that are considered privilege points in medical management protocols particularly when long term management is required.*

Aim *To compare the therapeutic impacts of Dienogest and Norethindrone acetate in ovarian endometriomas symptomatic cases as regards their effectiveness levels in decreasing the size of endometrioma, symptom relief drug tolerance issues.*

Methodology: *A prospective clinical research trial that recruited 200 cases at reproductive age group, from January 2015 to January 2019 having endometriosis. Cases were categorized into two research equal numbered categorial groups according to the agent used the research first group was administered Dienogest 2 mg/day (research group D), second research group was administered Norethindrone acetate 2.5 mg/day (research group N), starting both from the first menses day after the first outpatient visit.*

Results: *Comparative statistical analysis as regards VAS scoring of dysmenorrheal, chronic pelvic pain and dyspareunia pre, post 3 months and post 6 months in which the VAS scoring levels were statistically significantly lower among the Dienogest research group in comparison to the Norethidrone research group post 3 and 6 months concerning dysmenorrhea, chronic pelvic pain and dyspareunia (p values <0.001).*

Conclusions: *The current study findings reveal that Dienogest is superior in comparison to Norethidrone as regards management of ovarian endometriosis however both are equally effective in reducing the size of endometriomas.*

Introduction

Endometriosis a globally extensively researched disease by infertility specialists throughout the last decades, ovarian endometriosis cases are considered one of the complex infertility case scenarios. Since the gynecologists almost always require balancing between the pros and cons of various management protocols in ovarian endometriomas to achieve the best clinical outcomes as regards pressure, pain and infertility symptoms often patients represent with in every day practice**.** [1,2,3].

Endometriosis is considered at molecular, cellular and pathophysiological aspects as an inflammatory disease that is characterized by existence of growing of endometrial-like tissues outside the normal endometrial cavity having an incidence of around 5-10% of females at reproductive age groups causing pain and infertility issues arising at the everyday gynecological practice clinics, interestingly the ovary was revealed and displayed by various researchers to be the most common affected anatomical zone in a uni- or bilateral manner. Surgical excision of ovarian endometriomas was considered by laparoscopic gynecologists as one of the most definitive lines of management [4,5,6].

On the other hand surgical risks are considered one of the hindering factors for decision making as regards surgical excision arising the issues and concerns around the ovarian reserve after surgical excision completion besides the well-known risks of recurrence [7,8,9].

A large bulk of gynecologists in infertility clinics prefer usage of progestins, in the form of a first line medical management protocol in cases symptomatizing due to safety, efficacy and tolerability that are considered

privilege points in medical management protocols particularly when long term management is required. Various prior research groups of investigators have revealed and displayed that the usage of progestins is a valuable in reducing the endometriomas size and decreasing the pain issues [10,11].

Dienogest and Norethidrone acetate are two types of progestins that have been extensively researched separately as regards their impact on endometrioma size and pain issues and have shown to be effective, however their impact in a comparative manner concerning which agent is most effective is considered an area of research interest [12].

Aim of the work

To compare the therapeutic impacts of Dienogest and Norethindrone acetate in ovarian endometriomas symptomatic cases as regards their effectiveness levels in decreasing the size of endometrioma, symptom relief drug tolerance issues.

Methodology

"The study was conducted at AlZahraa hospital , Jeddah. KSA". A prospective clinical research trial that recruited 200 cases at reproductive age group, from January 2015 to January 2019 having endometriosis. Inclusive research criteria have been as follow: age range from 20 till 45 years old, sonographic diagnosis of mono or bilateral ovarian endometrioma, with a mean diameter = 40 mm or below existence of at least one of the following pain symptom profile e.g. dysmenorrheal issues, chronic pelvic pain syndrome, dyspareunia, progestin medical management using Dienogest or Norethindrone acetate for at least 6 months. Exclusive research criteria were as follows query or definitive diagnosis of deep infiltrating endometriosis on sonographic, clinical or laparoscopic examination, any hormonal agent undertaken within three months before recruitment for the research study.

Cases were categorized into two research categorial groups according to the agent used the research first group was administered Dienogest 2 mg/day (research group D), second research group was administered Norethindrone acetate 2.5 mg/day (research group N), starting both from the first menses day after the first outpatient visit. full clinical and gynecological examination was conducted besides transvaginal and transabdominal sonographic assessment was performed in all research study subjects.

Visual Analogue Scaling system was used to evaluate pain related symptoms of endometriosis disease from 0 (absence of pain) to 10 ("the maximum pain you could imagine") All research study subjects gave a written informed consent, sonographic subjective assessment was conducted by gray-scale mode in conjunction to Doppler evaluation of the lesion ovarian endometrioma was diagnosed by appearance of a unilocular cyst with sonographic characteristics as follows regular wall, 'ground glass appearance' echogenicity of the cyst content and poor capsular vascularization by power Doppler. ovarian endometrioma longitudinal, transverse, and antero-posterior diameters were measured, and the mean diameter have been calculated.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data with parametric distribution were presented as mean and standard deviations and compared between the two groups using Independent t-test while qualitative data were presented as numbers and percentages and compared using Chi-square test. The comparison between more than two paired groups was done by using repeated measures ANOVA followed by post hoc analysis using Bonferoni test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the level of < 0.05.

Results

Table 1 reveals the basic features of the two investigated research groups (Dienogest and Noreethidrone acetate in which there was no statistically significant difference as regards age, BMI, previous deliveries, surgeries for endometriosis, cases with monolateral or bilateral cyst side (p values=0.114, 0.074, 0.727, 0.228, 0.438 consecutively).

Table 2 and figure 1 reveals the comparative statistical analysis between the two investigated research groups as regards diameter of ovarian cysts pre, post 3 months and post 6 months of treatment in which there was no statically significant difference between both research groups at pre, post 3 and 6 months using t-test (p values 0.538,0.522,0.399 consecutively) however using ANOVA there was statistically significant difference among both research groups between pre, post 3 months and post 6 months regarding ovarian cyst diameter (p values <0.001 denoting effectiveness of both agents in reducing the cyst diameter by time in a significant manner although there is no difference between both agents by time.

Table 3 and figure 2 reveals the comparative statistical analysis as regards VAS scoring of dysmenorrheal, chronic pelvic pain and dyspareunia pre, post 3 months and post 6 months in which the VAS scoring levels were statistically significantly lower among the Dienogest research group in comparison to the

Norethidrone research group post 3 and 6 months concerning dysmenorrhea, chronic pelvic pain and dyspareunia (p values <0.001).

Table 4 reveals the comparative statistical analysis between both Dienogest and Norethidrone research groups as regards the side effects after 6 months of treatment in which weight gain , uterine bleeding and loss of libido was statistically significantly higher among the Norethidrone research group (p values =0.002, 0.003, 0.035 consecutively) whereas there was no statistical significant difference between both research groups as regards vaginal dryness mood disorders, breast tenderness ,bloating or swelling ,acne ,headache, hair loss, and nausea (p values =0.346, 0.120, 0.248, 0.756, 1.00, 0.733, 0.650, 0.560 consecutively).

Table 5 reveals the comparative statistical analysis between both Dienogest and Norethidrone research groups as regards the side effects after 6 months of treatment in which weight gain , uterine bleeding and loss of libido was statistically significantly higher among the Norethidrone research group (p values =0.023, 0.014, 0.022 consecutively)whereas there was no statistical significant difference between both research groups as regards vaginal dryness mood disorders, breast tenderness, bloating or swelling, acne, headache, hair loss, and nausea (p values =0.322, 0.088, 0.248, 0.516, 0.561, 0.700, 0.561, 1.000 consecutively).

	Group D No. = 100	**Group N No. = 100**	**Test value**	**P-value**	**Sig.**
Age (years), mean ± SD	35.8 ± 6.27	37.14 ± 5.64	1.589•	0.114	NS
BMI (kg/m^2), mean ± SD	23.25 ± 4.31	24.64 ± 6.42	1.798•	0.074	NS
Previous deliveries	22 (22.0%)	20 (20.0%)	0.121*	0.727	NS
Previous surgery for endometriosis	18 (18.0%)	15 (15.0%)	1.452*	0.228	NS
Patients with cyst side monolateral	73 (73.0%)	68 (68.0%)	0.601*	0.438	NS
Patients with cysts side bilateral	27 (27.0%)	32 (32.0%)			
*BMI: Body mass index *Data were presented as mean and standard deviations or numbers and percentages *Independent t-test *: Chi-square test					

Table 1: Basic features of the two investigated research groups.

Diameter of ovarian cysts (mm)	**Group D No. = 100**	**Group N No. = 100**	**Test value•**	**P-value**	**Sig.**
Pre	21.32 ± 3.69	21.65 ± 3.88	0.616	0.538	NS
Post 3 months	17.53 ± 3.36[a]	17.83 ± 3.25[a]	0.642	0.522	NS
Post 6 months	14.25 ± 2.86[a,b]	14.62 ± 3.32[a,b]	0.844	0.399	NS
Repeated Measures ANOVA (P-value)	< 0.001	< 0.001			
Data were presented as mean and standard deviations •: Independent t-test [a]: Significant difference between pre and 6 months [b]: Significant difference between post 3 months and post 6 months					

Table 2: Comparative analysis between the two investigated research groups as regards diameter of ovarian cysts pre, post 3 months and post 6 months of treatment.

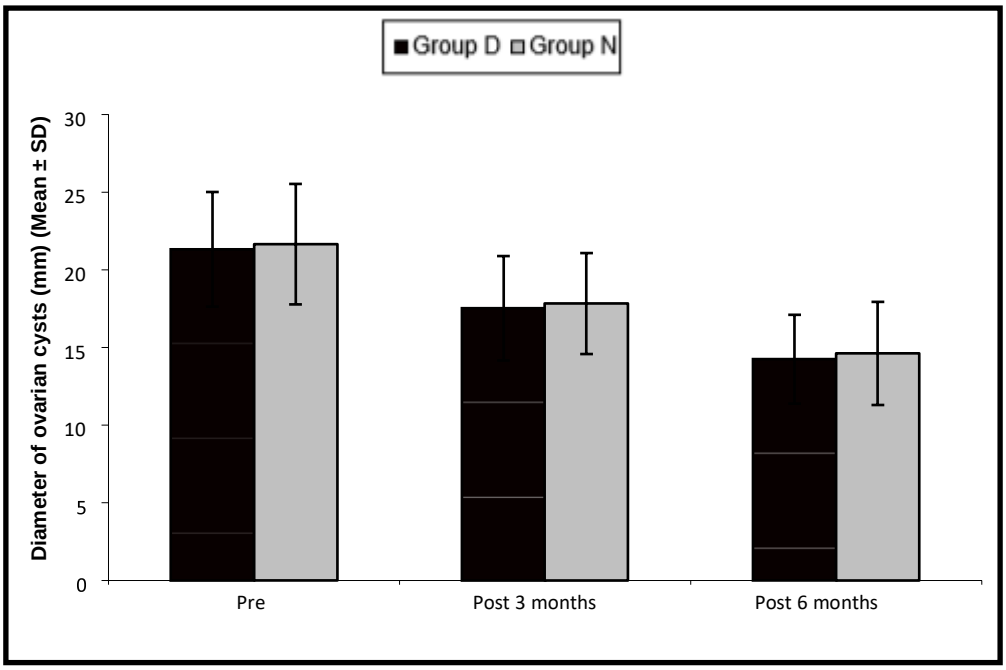

Figure 1: Comparative analysis between the two investigated research groups as regards diameter of ovarian cysts pre, after 3 months and after 6 months of treatment

Visual Analogue Score (VAS)		Group D	Group N	Test value	P-value	Sig.
Dysmenorrhea	Pre	5.22 ± 1.67	5.21 ± 1.8	0.041	0.967	NS
	Post 3 months	2.25 ± 1.12	4.58 ± 1.62	11.831	<0.001	HS
	Post 6 months	1.78 ± 0.56	4.22 ± 0.88	23.392	<0.001	HS
Chronic pelvic pain	Pre	4.98 ± 1.52	5.12 ± 1.63	0.628	0.531	NS
	Post 3 months	2.37 ± 1.25	4.88 ± 1.57	12.507	<0.001	HS
	Post 6 months	1.82 ± 0.95	4.58 ± 1.27	17.402	<0.001	HS
Dyspareunia	Pre	4.82 ± 1.32	4.91 ± 1.33	0.480	0.632	NS
	Post 3 months	3.63 ± 1.10	4.52 ± 1.21	5.443	<0.001	HS
	Post 6 months	2.57 ± 0.95	4.20 ± 1.05	11.511	<0.001	HS

Table 3: Comparative analysis between the two investigated research groups as regards VAS scoring of dysmenorrheal, chronic pelvic pain and dyspareunia pre, post 3 months and post 6 months.

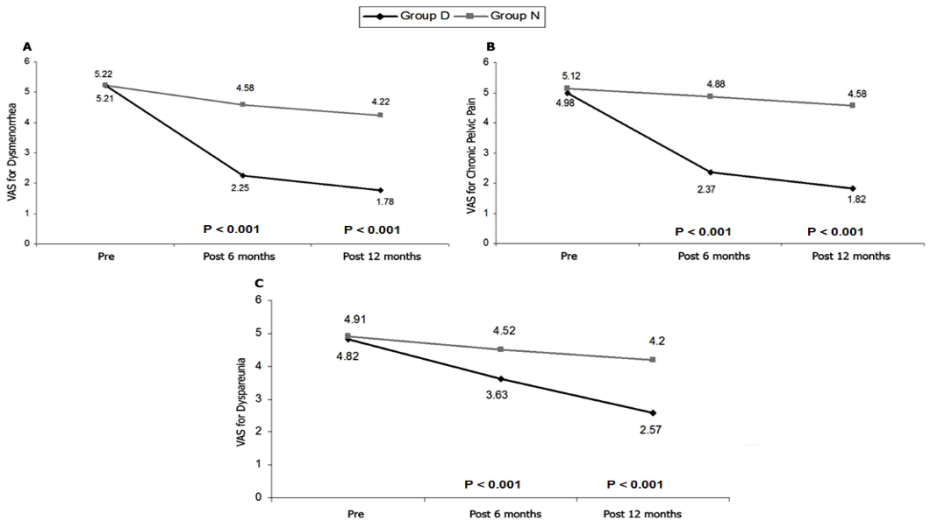

Figure 2: Comparative analysis between the two investigated research groups as regards VAS scoring of dysmenorrheal, chronic pelvic pain and dyspareunia pre, post 3 months and post 6 months.

	Group D No. = 100	Group N No. = 100	Test value*	P-value	Sig.
Weight gain	13 (13.0%)	31 (31.0%)	9.441	0.002	HS
Uterine bleeding	9 (9.0%)	25 (25.0%)	9.072	0.003	HS
Loss of libido	8 (8.0%)	18 (18.0%)	4.421	0.035	S
Vaginal dryness	8 (8.0%)	12 (12.0%)	0.889	0.346	NS
Mood disorders	3 (3.0%)	8 (8.0%)	2.405	0.120	NS
Breast tenderness	2 (2.0%)	5 (5.0%)	1.332	0.248	NS
Bloating or swelling	6 (6.0%)	5 (5.0%)	0.096	0.756	NS
Acne	2 (2.0%)	2 (2.0%)	0.000	1.000	NS
Headache	5 (5.0%)	4 (4.0%)	0.116	0.733	NS
Hair loss	3 (3.0%)	2 (2.0%)	0.205	0.650	NS
Nausea	2 (2.0%)	1 (1.0%)	0.338	0.560	NS
Data were presented as numbers and percentages *: Chi-square test					

Table 4: Comparison between the two studied groups regarding side effects after 6 months of treatment.

	Group D No. = 100	Group N No. = 100	Test value*	P-value	Sig.
Weight gain	11 (11.0%)	23 (31.0%)	5.103	0.023	S
Uterine bleeding	8 (8.0%)	20 (20.0%)	5.980	0.014	S
Loss of libido	8 (8.0%)	19 (19.0%)	5.181	0.022	S
Vaginal dryness	7 (7.0%)	11 (11.0%)	0.977	0.322	NS
Mood disorders	2 (2.0%)	7 (7.0%)	2.909	0.088	NS
Breast tenderness	2 (2.0%)	5 (5.0%)	1.332	0.248	NS
Bloating or swelling	4 (4.0%)	6 (6.0%)	0.421	0.516	NS
Acne	1 (1.0%)	2 (2.0%)	0.338	0.561	NS
Headache	3 (3.0%)	4 (4.0%)	0.148	0.700	NS
Hair loss	2 (2.0%)	1 (2.0%)	0.338	0.561	NS
Nausea	0 (0.0%)	0 (0.0%)	0.000	1.000	NS
Data were presented as numbers and percentages *: Chi-square test					

Table 5: Comparison between the two studied groups regarding side effects after 6 months of treatment.

Discussion

Ovarian endometriomas are considered an issue of concern for infertility practitioners all over the world some gynecologists prefer to avoid surgical excision to avoid possible side effects of surgery that could affect the ovarian reservoir besides the recurrence rates that are well known to cause recurrence of symptoms [13,14].

Dienogest agent has at molecular and cellular level activity an impact on endometriotic lesions via triggering a hypo estrogenic status besides initial decidualization effect with consecutive endometriotic implants atrophy. Similarly, Norethidrone acetate triggers a hypo estrogenic status by inhibiting gonadotropins, ovulation, and consequently causing amenorrhea with consecutive decidualization and endometrial atrophy of endometrial tissue [15].

A prior research group of investigators performed a study similar to the current study in approach and methodology comparing the effectiveness of efficacy of Dienogest and Norethidrone as regards the reduction of ovarian endometrioma size, symptoms relief and tolerability of administering the agents in 6 months their research findings in an interesting manner have shown that both agents can reduce ovarian endometriomas size in a statically significant fashion denoting the effectiveness of both agents those findings are similar and in harmony to the current study results [1,4,9].

On the other hand another research team of investigators have shown that Dienogest is a more effective agent in

comparison to Norethidrone in reducing symptoms related to endometriosis 3 and 6 months period of implementing the medical management protocol besides Dienogest is a more tolerable agent in comparison to Norethidrone agent, furthermore those research findings have revealed a great similarity to the current study findings and statistical analysis [2,8,10].

Prior research groups of investigators have demonstrated that progestins in general particularly both Dienogest and Norethidrone acetate are effective agents when administered as regards reducing the requirement for surgical intervention to excise the endometrioma [3,7].

Both Dienogest and Norethidrone in prior research studies have shown similar effectiveness as regards the relief of finding comparable effects in terms pain, sexual function enhancement .those research findings could be justified by the fact that histopathological assessment of endometriotic lesions in cases managed by Dienogest have reduced proliferation, aromatase expressive activity, angiogenesis and raised levels of apoptosis besides greater rates of decidualization in comparison to control research groups as revealed and displayed by previous research studies [5,12].

The greater improvement in VAS scoring symptoms during management in Dienogest research group could be correlated to the anti-proliferative and anti-inflammatory impacts of Dienogest on endometriotic cells [9,13].

Conclusions and recommendations for future research

The current study findings reveal that Dienogest is superior in comparison to Norethidrone as regards management of ovarian endometriosis however both are equally effective in reducing the size of endometriomas. Future research studies are recommended to consider racial and ethnic differences as those could affect the responsiveness to the agents implemented in management due to differences in genetic background, besides future research is recommended to be multicentric in fashion to verify the current research study results.

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