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Beneficial Effects of Tibolone on Sexual Dysfunction in Women with Premature Ovarian Failure (POF)

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Abstract

Introduction: Premature Ovarian Failure (POF) is cessation of ovarian functions before the age of 40 years old with consequent cessation of menstruation. Objective of study: The aim of this study was to evaluate the association between Premature Ovarian Failure and sexual dysfunctions and outcome of management with tibolone. Patients and Methods: Thirty-one women with Premature Ovarian Failure seen at the outpatient clinic of Maternity Hospital were enrolled into the study with 31 healthy women as control group. The instrument of data collection included two types of questionnaires to assess the effect of Premature Ovarian Failure on sexuality. All the women with POF had oral tibolone 2.5 mg for at least one year and the second questionnaire and the profiles were repeated. Results: Of the 31 women with POF that presented with sexual dysfunction (SD), 27 (87.1%) complained of one or more SD domains such as reduced frequency of coitus, dyspareunia, vaginal dryness, reduced libido and general sexual satisfaction ($P < 0.01$), amenorrhea ($P < 0.01$) and hot flashes compared to 5 (16.1%) control women ($P < 0.01$). Administration of tibolone was associated with significant increase in frequency of coitus, reduced dyspareunia and vaginal dryness, increase libido and general satisfaction and happiness. Reduction of sexual dysfunction was predicated on the estrogenic, progestogenic and androgenic metabolite of tibolone through the reduction of serum level of FSH and LH and increased levels of estrogen and testosterone ($P < 0.01$). Tibolone had no adverse effect on serum lipid profile. Conclusion: Premature Ovarian Failure is associated with sexual dysfunction. Tibolone provides an effective means of treating sexual dysfunction caused by Premature Ovarian Failure.

Keywords

Premature Ovarian Failure, Sexual Dysfunction, Tibolone, Replacement Therapy

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1. Introduction

Premature Ovarian Failure is defined as reduced function of the ovaries with cessation of menstruation and increased serum levels of gonadotropins and decreased levels of estrogen before the age of 40 years old. It is also called Primary Ovarian Insufficiency and Premature Menopause [1]. It may occur as a result of genetic, autoimmunity, gonadotoxicity from chemotherapy and radiotherapy in cancer patients and surgery. It affects about 1 percent of women and as a result of estrogen deficiency, it leads to severe long-term health consequences [2].

Although sexual function in women with normal menopause has been extensively dealt with in specialized literature worldwide [3] [4], very few and specific studies have been reported on this subject in women with premature ovarian failure [5]-[7]. The paucity of biological data on sexual dysfunction in women with POF may be attributed to lack of reliable experimental models and tools for the investigation of female sexual function [8]. Six domains of sexual dysfunction have been identified, including desire, arousal, orgasm, satisfaction, pain and vaginal lubrication [8] [9]. In a national survey, about 25 percent of women reported sexual dysfunction [10]. The parasympathetic and sympathetic nervous systems are two parts of the autonomic system that keeps sexuality in balance. A number of side-effects from an imbalance of the two systems as a result of peripheral nervous disorders can result in sexual dysfunction [11] and manifest loss of erotic sensation, dyspareunia, loss of lubrication, loss of feeling during vaginal intercourse, difficulties in achieving orgasm, and changes in the feeling of orgasm [12]-[14].

In a recent cross-sectional study, the use of systemic estrogen among women with POF was not enough to improve complaints of lubrication and pain despite conferring similar tropism and vaginal flora. Progestins usually combined with estrogen to prevent endometrial hyperplasia are less effective when used alone for hot flushes [15]. Recent reviews have supported the addition of testosterone to HRT to improve sexual function and wellbeing [16]. Testosterone therapy may be needed to restore sexual arousability. Tibolone is a synthetic steroid derived from 19-nortestosterone, structurally similar to norestinone and noretinodrel. It is a selective tissue estrogenic activity regulator (STEAR) because it has specific effects in different tissues after conversion to three active metabolites following oral ingestion, with estrogenic, progestogenic and androgenic effects. Estrogenic metabolites act centrally, on the vagina and other tissues and, together with androgenic metabolites, relieve hot flushes and improve energy and sexual well-being. In a well-designed trial comparing tibolone to estrogen/progestin therapy, tibolone was similar or superior in the treatment of sexual dysfunction [17]. On bone, tibolone has estrogenic effect acting on the estrogenic receptor [18]. Tibolone is a well-established treatment for climacteric complaints and prevention of osteoporosis in post-menopausal women and improve sexuality [18]-[20]. Concerns and caution have been expressed about the side-effects of tibolone such as breast cancer, stroke and cardiovascular disease [21].

Objective of the study

The aim of this study was to evaluate.

1) The pattern of sexual dysfunction in women with POF in the community.

2) Factors that could contribute to sexual dysfunction and,

3) The effect of hormone replacement therapy using Tibolone among women with premature ovarian failure in Kuwait.

2. Patients and Methods

Patients: Between June 2000, and May 2014, details of sexual history were compiled from 31 women that attended the Menopause Clinic at the Maternity Hospital, Kuwait, with premature ovarian failure (Primary Ovarian Insufficiency or Premature menopause).

1) During the five year study period, there were 52 women with features of premature ovarian failure, who were below the age of 40 years, who attended our menopause clinic, but only 31 who were married and perceived to be sexually active were included in the study.

2) Control group matched for Age was chosen from the clinic, staff and students.

3. Ethical Consideration

The study was approved by the Institutional Review Board of the Maternity Hospital. Kuwait. Verbal informed consent was received from all women and to obtain the participants' informed consent, the objectives and general procedures of the research were explained to them as well as their right to drop out at any given moment

with no ensuing change in the quality of the medical care they would continue to receive.

3.1. Study Design

3.1.1. The Study Was in Two Parts

1) This was a cross-sectional study with 31 study patients and 31 control healthy women with normal menstruation, with regards to the pattern of sexual dysfunction and hormone and lipid profile.

2) Comparison of pre and post tibolone therapy with regards to attenuation of the different domains of sexual dysfunction.

3.1.2. Inclusion Criteria for Study Women

1) The woman should be less than 40 years.
2) Amenorrhea for at least 4 - 6 months.
3) Serum FSH ≥ 40 IU/L and LH ≥ 28 IU/L and Estradiol ≤ 12 pmol/L.
4) Should be married

3.1.3. Inclusion Criteria for Control Healthy Women

1) All below 40 years.
2) Regular menstrual periods, bleeding for 3 to 7 days, with cyclicity of 22 to 35 days regularly.
3) With no medical disorder and not on any medication.

3.1.4. Exclusion Criteria

1) All those with medical disorders like diabetes mellitus and genital surgeries.
2) Those currently on radiotherapy or Chemotherapy.
3) All women who are not sexually active on cultural and religious grounds.

3.1.5. Clinical Evaluation

At the first clinic consultation a full history including coital history was taken and a physical examination carried out for each patient, including weight in kilograms and height in metres for Body mass index (BMI). For cultural and religious sensitivities, only married women were investigated in issues pertaining to sexuality in POF women and non POF controls matched with age (±2 years). In order to confirm POF, serum hormone profile-FSH, LH and estradiol were estimated. Estimation of Androstenedione Prolactin and Testosterone and lipid profile were also carried out.

4. Interviews

4.1. Two Types of Questionnaires Were Used for Data Collection

1) Personal data of the women (both study and healthy controls) through history, investigations and investigations.

2) Sexual index Scores. More of the existing instruments like the self-administered Derogatis Interview for Self (DISF-SR) [22], the Female Sexual Function Index (FSFI) [23] and 8 other descriptive and psychometric contemporary measures of quality of sexual function [22] was completely suitable for assessment of sexual dysfunction in our community because of cultural and religious sensitivities. We therefore developed an acceptable home-based, original and simple instrument for data collection consisting of six domains: Coital frequency, Desire, Dyspareunia, Vaginal dryness, Satisfaction and General well-being, in a scale of 1 to 5 in an ascendancy of favorability.

For Example

1) Coital frequency, scores are 1 = no coitus, 2 = once, 3 = twice, 4 = 3 and 5 = ≥4 sexual contact per week.
2) Dyspareunia: 1 = Regularly, 2 = Almost always, 3 = Sometimes, 4 = Occasionally, 5 = Never.

4.2. Hormone Measurements

10 ml of blood was taken from each patient and centrifuged at 1000 g and serum separated and stored at −20˚C until assayed. Each blood sample was assayed for Follicle Stimulating Hormone, Luteinizing Hormone, Estradiol, Testosterone and androstenedione. Sex Hormone Binding Globulin was estimated with ELIZA technique.

4.3. Administration of Tibolone

All the women with POF had oral tibolone 2.5 mg for at least one year and the second questionnaire and the profiles were repeated.

The second clinical and laboratory evaluations were carried out after one year. However, the patients were seen in the clinic every 3 months mainly to evaluate their well-being, sexual satisfaction and side-effects of tibolone.

4.4. Statistical Analysis

We analyzed fully completed questionnaires only. We report results as mean (SD) or median (range) and tested comparisons with the Wilcoxon Rank Sum. To examine the relationship between sexual functioning and possible factors, multiple regression analysis were performed and logistic regression analysis for dichotomous outcomes. The correlation among variables and sexual dysfunction domain in each set of emotional reaction to POF was calculated using the Spearman and Pearson lineal correlation coefficients, respectively. For calculation and elaboration of graphs, SPSS (version 22) was used. Significant correlation was considered at significance level $P = 0.05$.

5. Results

There were no significant differences between age, ethnic background, marital status and body mass index (BMI) between women with POF and control group. As shown in **Table 1**, Of the 31 women with POF, 27 (87.1%) had sexual dysfunction compared to 5 (16.1%) of the control women ($P < 0.01$). Fewer women with POF were University graduates than the control group ($P < 0.05$). Women with POF had more hot flashes (77 percent) ($P < 0.01$) and night sweats (52 percent) ($P < 0.05$) compared to healthy ovulatory controls.

As shown in **Table 2**, all the women with POF had high gonadotropins FSH and LH and low Estrogen in the postmenopausal range with high positive correlation with hot flushes ($r = 0.628$, $P < 0.01$) and night sweat ($r = 0.448$, $P < 0.05$) and inverse relationship with Estrogen ($r = -0.542$ $P < 0.05$). Nine women (29 percent) with POF had serum Testosterone level below the lower quartile range of ≤ 0.5 nmol/L. In lipid profile, the LDL-C was significantly higher in the POF group ($p < 0.05$). Conversely, vitamin D3 was much higher in the control group than in women with POF ($P < 0.01$).

Table 1. Comparison of socio-demographic and clinical characteristics between with premature ovarian failure and control.

Variables	Women with POF number = 31	Control group number = 31	P value
Age (years)	28.8 ± 6.4	29.2 ± 6.8	NS
BMI (Kg/m)	27.8 ± 4.8	28.2 ± 4.4	NS
Ethnic groups			
Arabs	18 (58.7)	15 (48.4)	NS
Asians	7 (22.6)	9 (29.0)	NS
Africans	4 (12.9)	5 (16.1)	NS
others	2 (6.5)	2 (6.5)	NS
Marital Status			
Married	31 (100)	(80.6)	NS
Highest Education			
Primary School	3 (9.7)	2 (6.5)	NS
Secondary	17 (54.8)	15 (48.4)	NS
College/Graduate School	11 (35.5)	14 (45.2)	0.05
Vasomotor Symptoms			
Hot flashes	24 (77.4)	2 (6.5)	0.01
Night Sweats	16 (51.6)	3 (9.7)	0.01
Insomnia	12 (38.7)	11 (35.5)	NS

Table 2. Comparison of hormone and lipid profiles in women with POF and healthy controls.

1.	Hormone Profile	Women with POF N = 31	Healthy women N = 31	P value
	LH (1U/L)	28 ± 6	6.4 ± 2.2	0.01
	FSH (1U/L)	52 ± 4	8.8 ± 2.8	0.001
	Testosterone (nmol/L)	1.2 ± 0.4	2.2 ± 0.6	0.05
	Androstenedione (nmol/L)	4.8 ± 2.2	5.2 ± 2.2	NS
	Prolactin (mlu/L)	31.5 ± 7.5	34.8 ± 8.2	NS
	Estrogen (pmol/L)	80.4 ± 6.4	258.4 ± 12.4	0.01
	Sex Hormone Binding Globulin (SHBG) (nmol/L)	216 ± 64	234 ± 6.8	NS
	FT4	4.8 ± 2.2	5.2 ± 1.8	NS
	TSH (mIU/L)	4.4 ± 2.8	3.8 ± 3.2	NS
2.	Lipids			
	T. Cholesterol (mmol/L)	4.2 ± 1.2	4.4 ± 2.4	NS
	HDL-C (g/dl)	2.6 ± 0.8	2.8 ± 1.2	NS
	LDL-C (mmol/L)	4.1 ± 1.1	2.8 ± 0.6	0.05
	Triglyceride (mIU/L)	1.9 ± 0.8	1.8 ± 1.2	NS
3.	Vitamin D3 ng/ml	11.4 ± 4.23	54.8 ± 8.2	0.01

NS: Not significant.

Table 3 compared the 6 sexual dysfunction domains in women with POF and controls. The actual frequency of sexual contact with the husband was significantly lower in women with POF than control women ($P < 0.01$). Women with POF experienced problems of impaired sexual desire, dyspareunia, and increased vaginal dryness during sexual contact more often than control women ($P < 0.01$). With respect to satisfaction with their sexual life, women with POF tended to be less satisfied than the control women. The satisfaction rating frequencies in women with POF was significantly lower than those for the control women ($P < 0.05$), When questioned about the sense of well-being, they scored this item significantly less often as compared with control women ($P < 0.05$).

Understanding of the contributing factors to sexual dysfunction will certainly help in any therapeutic intervention strategy. Climacteric Symptom is a risk factor for effect of POF on sexuality. Multiple regression analysis and Spearman and Pearson correlation coefficients identified age, hot flashes and night sweats (vasomotor symptoms), low estrogen, low testosterone as having differential contributions to sexual dysfunction as shown in **Table 4**. Low androgen levels had a significant influence on sexual desire and satisfaction; higher total testosterone levels were associated with increased frequency of desire for sexual contact, and higher androstenedione levels were associated with elevated frequency of sexual contact.

Table 5 summarizes the attenuation of different domains of sexual dysfunction by tibolone. In order to gauge the degree of improvement, the mean composite scores of the healthy controls were included for comparison between pre-thaerapy and post-therapy of tibolone. For coital frequency, there was 71 percent improvement over the pretherapy mean composite score. As to effect of tibolone on dyspareunia and vaginal dryness, there was improvement of 90 percent and 83 percent respectively. The analysis for sexual satisfaction and well-being revealed improvement of 83 percent and 50 percent respectively in the two domains.

In **Figure 1**, the effects of tibolone on hormone profile are outlined. There is highly significant ($P < 0.01$) reduction of serum FSH and LH with positive correlation with reduction of hot flushes ($r = 0.624$, $P < 0.01$). Conversely, tibolone was associated with significant increase with serum testosterone ($P < 0.01$) and estradiol ($P < 0.05$ and inverse correlation with vasomotor symptoms ($r = -0.425$, $P < 0.05$). There ws no significant change in the serum level of androstenedione with tibolone. However, there was significant increase in SHBG, which was inversely correlated with Serum testosterone ($r = -0.542$, $P < 0.01$).

Table 3. Comparison of mean composite sexual scores between women with POF and healthy controls.

Variables	Women with POF number = 31	Healthy controls number = 31	P value
Coital Frequency.	2.8 ± 1.6	4.8 ± 2.2	0.01
Desire (Libido)	1.9 ± 1.2	4.2 ± 1.8	0.01
Dyspareunia	2.4 ± 2.1	4.4 ± 2.3	0.05
Vaginal Dryness	1.4 ± 0.8	4.8 ± 2.2	0.01
Satisfaction/Happiness	1.2 ± 0.8	4.4 ± 2.8	0.01
Sense of well being	1.6 ± 1.2	4.4 ± 2.6	0.05

Table 4. Factors contributing to sexual dysfunction in patients with premature ovarian failure.

Variables	Coital frequency	Sexual desire	Dyspareunia	Vaginal dryness	Sexual satisfaction	General well-being
Age	0.324	0.456*	0.242	0.244	0.642**	0.554**
Childlessness	0.234	0.224	0.312	0.462*	0.544**	0.228
Hot flushes	0.122	0..222	0.412*	0.424*	0.216	0.322
Night Sweats	0.482*	0.423*	0.221	0.116	0.112	0.442*
Low Estrogen	0.540**	0.547**	0.842**	0.824**	0.236	0.224
Low Testosterone	0.488**	0.464*	0..268	0.122	0.624**	0.564**

*P < 0.05, **P < 0. 01.

Table 5. Effect on tibolone on sexual dysfunction.

Variable	Pre Tibolone (a)	Healthy Controls (x)	Post Tibolone (b)	P value a vs. b
Coital Frequency	2.8 ± 1.6	4.8 ± 2.2	4.2 ± 1.2	0.05
Desire (libido)	1.9 ± 1.2	4.2 ± 1.8	3.6 ± 2.2	0.01
Dyspareunia	2.4 ± 2.1	4.4 ± 2.3	4.4 ± 2.3	0.05
Vaginal Dryness	1.4 ± 0.8	4.8 ± 2.2	2.6 ± 2.0	0.05
Satisfaction/Happiness	1.2 ± 0.8	4.4 ± 2.8	2.2 ± 2.4	0.05
Sense of well being	1.6 ± 1.2	4.4 ± 2.6	2.44 ± 2.2	0.01

A vs. b: pre tibolone versus post tibolone. X = composie sexual scores for healthy controls (not on Tibolone).

5.1. Safety of Tibolone

There were six patients (19.4 percent) that reported very few and mild side-effects such as slight breakthrough vaginal bleeding. As shown in **Figure 2**, tibolone use was associated with a slight increase in total Cholesterol, LDL-C and triglyceride but the differences did not reach level of significance

5.2. Discussion

This is the first study aimed to explore the prevalence and the different domains of sexual dysfunction among women with premature ovarian failure in the community. There is general perception of taboos surrounding discussion of issues of sexuality [24]. Cultural and religious beliefs certainly play a key role in the perception and attitude to issues pertaining to sexual dysfunction. This is why a locally developed in-house and acceptable scale was used in this study instead of validated scales [22] [23] that may be offensive to women in the community.

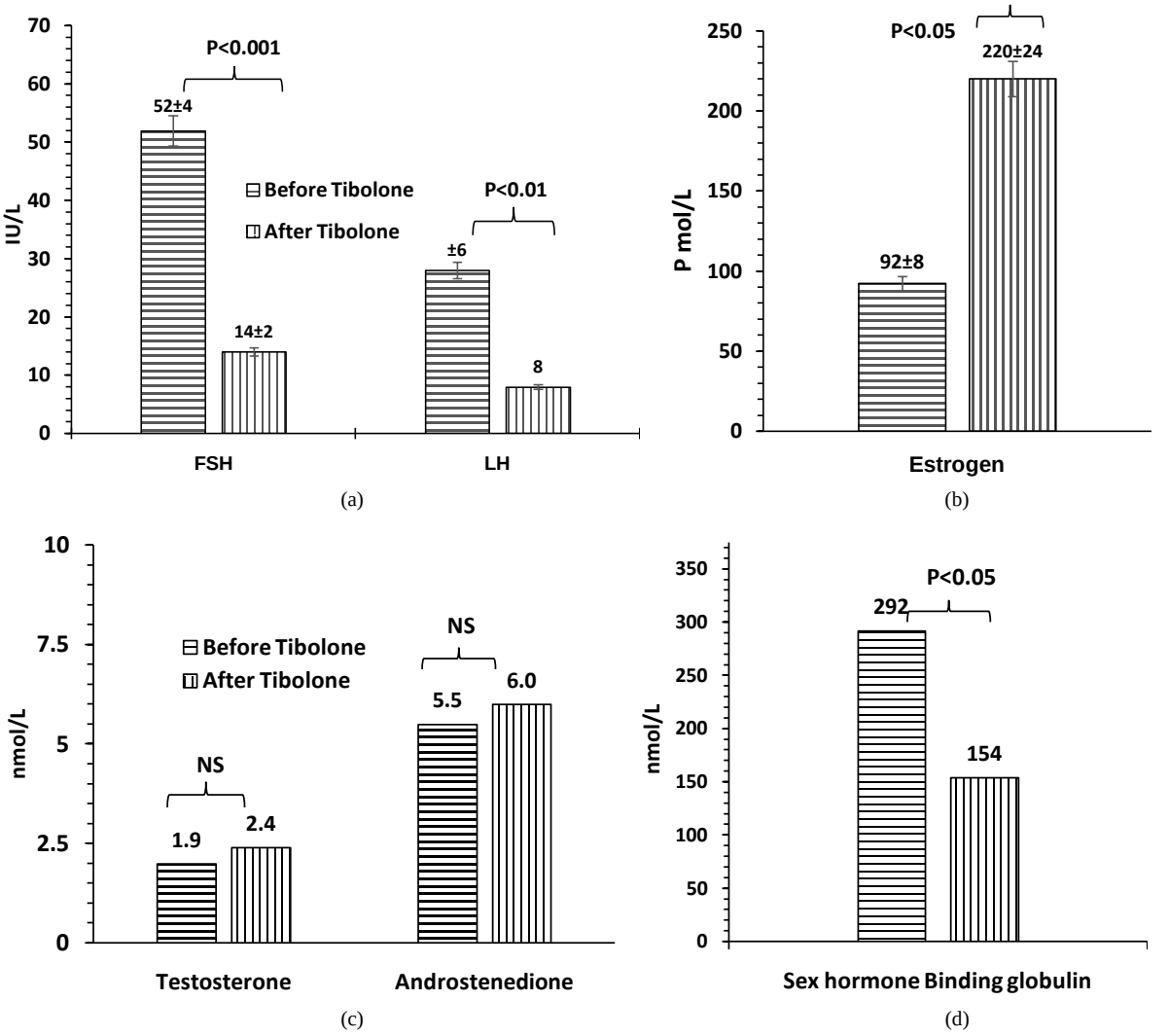

Figure 1. Effect of tibolone on hormone profile. (a) FSH and LH, (b) Estrogen, (c) Testosterone/androstenedione, (d) Sex Hormone Binding Globulin (SHBG).

The present study has shown that there is high prevalence of POF of 87.1 percent occurs in Kuwait as in other parts of the world with the usual multifactorial origin [25] and it is associated with a highly associated with vasomotor symptoms and sexual dysfunction determined by changes in frequency of sexual contact, dyspareunia and vaginal dryness. During the postmenopausal period, sexual interest and activity seem to decline, as part of the menopausal effect of oestrogen deficiency. Vasomotor Symptoms and Sexual dysfunction occur frequently in women who have an abrupt menopause from chemotherapy or ovarian suppression. Hormone replacement was advocated in our previous study [26]. Problem with oestrogen replacement is the stimulation of breast and endometrial cells. Recent studies have also shown that use of systemic estrogen among women with POF is not enough to improve complaints of lubrication and pain [1]. Oestrogens have been shown to have some beneficial effect on sexual desire, but oestrogen alone may be ineffective in completely ameliorating dyspareunia. The addition of testosterone is usually beneficial and improves quality of life [27] and restores sexual arousability [5]. Although a woman's motivation or desire might change as a result of HRT, on its own this will not influence the frequency of intercourse or response during intercourse. Non-menopausal aspects of the sexual relationship must be considered too. These aspects include the quality of the relationship, the sexual performance of the partner (since sexual desire decreases in both sexes with age), and age-related changes in self-image [27]. In the present study, tibolone significantly ameliorated vasomotor symptoms such as hot flushes and night sweats, and different domains of sexual dysfunction, without significant short term side-effects. Women with POF have impaired

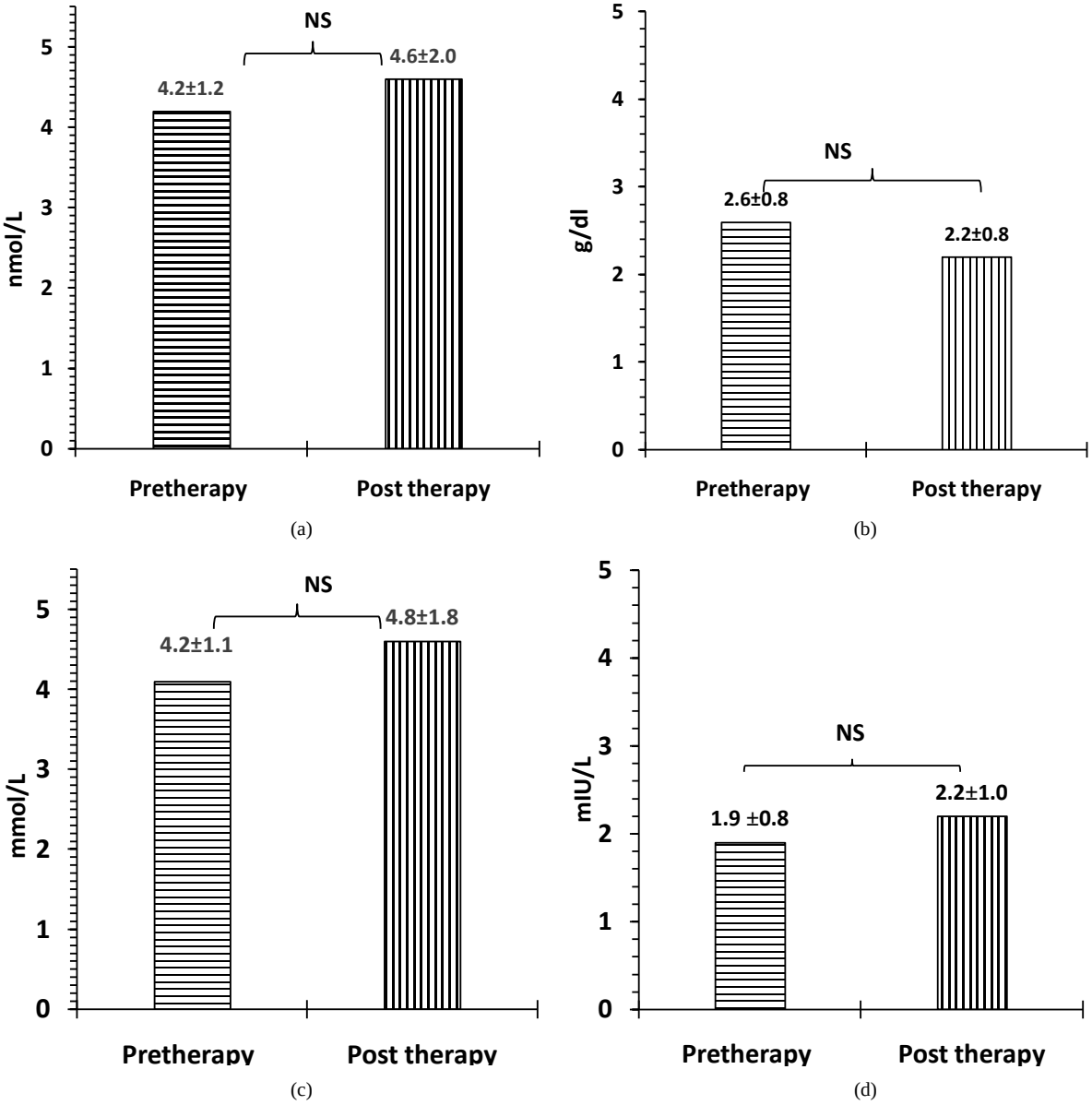

Figure 2. Effects of Tibolone on lipid profile. (a) Total cholesterol, (b) HDL-C, (c) LDL-C, (d) Triglycerides.

sexual function, determined mainly by changes in arousal and desire. Aspects related to lubrication and dyspareunia complaints have lower determination coefficient in SF. These results are important in adapting the approach of sexual disorders in this group of women.

Tibolone undergoes differential tissue-selective metabolic transformation and may exert estrogenic, progestogenic and androgenic activity [20]. There is abundant evidence that each of these three metabolites has its effects in the body and contributes to the overall remedial action of tibolone in ameliorating sexual dysfunction in women with POF [18] [28] [29]. Some randomized controlled studies [20] [30] have suggested that tibolone decreases vasomotor symptoms and ameliorates vaginal dryness and dyspareunia as demonstrated in the present study. This is probably through the estrogenic metabolite. This estrogenic metabolite effects are mainly evident in the brain, bone and vaginal tissue [18] [20] [21], This effect is weak or absent in the endometrium because it is transformed into progestogen and increase the progestogenic metabolite and robustly counteract the stimulating effects of estrogen on the endometrium to prevent endometrial hyperplasia [28] [29].

There is abundant evidence that androgens are necessary for sexual arousability, libido and sexual satisfaction

[5] [16] [27]-[31]. The present study has demonstrated a positive effect of tibolone on sexual frequency, desire, satisfaction and general wellbeing and this may be due to the androgenic metabolites of tibolone.

Tibolone has been shown to be generally safe throughout the present study period and well tolerated, with mild side-effects like headache, dizziness, nausea, abdominal pain, swollen feet and itching and breast tenderness and vaginal bleeding [20]. Recent research suggests that tibolone may increase the risk of stroke in vulnerable women [21]. This risk is mainly seen in women over 60 years of age with an extra 13 cases per 1000 women [30].

High level of stressors like past traumas such as sexual abuse and rape often seem to have effect on different domains of sexual dysfunction [32]. Many women complained of being given inadequate information about their problem by their physicians [33]. These issues should be addressed at health education level and specific counselling to women who present with premature ovarian failure [34] [35].

5.3. Limitations of the Study

1) A significant limitation of this study is the small sample size. In the future it is hoped that a large sample size will be used.

2) A standard well tested scale of evaluation of sexuality could not be used, before and intervention with tibolone because of cultural and religious sensitivities. We have in fact identified this as a rich and veritable area of future research.

3) The women in the present study were followed up for one year. For the evaluation of side-effects of tibolone, a longer period of more than a year may be needed.

6. Conclusion

POF is multifactorial in origin. There is a decline in sexual response and activity in women with POF in Kuwait with diminished general and sexual well-being and is less satisfaction with their sexual lives than control women. There is an important independent role for androgens in various aspects of sexual functioning. Clinicians have an important role in encouraging women to report and discuss their sexual complaints. Giving women the opportunity to talk about sexual problems is a fundamental part of health care and may improve their quality of life. Research into optimal management of sexual dysfunction with POF is urgently needed. The long-term side-effects of Toulon should be of concern. The use of tibolone should be monitored with lipid profile as is done in the present study.

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Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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