ISSN: 0976-3376

Available Online at http://www.journalajst.com

ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

Asian Journal of Science and Technology
Vol. 14, Issue, 09, pp. 12680-12683, September, 2023

RESEARCH ARTICLE

BIOIDENTICAL HORMONE REPLACEMENT THERAPY (BHRT) IN THE PERIMENOPAUSE

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ARTICLE INFO

Article History:
Received 11th June, 2023
Received in revised form
28th July, 2023
Accepted 09th August, 2023
Published online 30th September, 2023

Keywords:

Perimenopause, Bioidentical Hormone replacement therapy (BHRT), case report, menopause, hormone profile.

ABSTRACT

Aim & background: Bioidentical hormone replacement therapy has completely altered the therapeutic concerns of Endocrinologists and gynecologists. The case discussed below is a prime example of their success. **Case description:** A 46-year-old woman suffering from perimenopausal conditions presents in the clinic. Her vitals and hormone profile were not at optimum levels. Ultrasound shows proliferative endometrium and ovarian cysts. She had been described with BHRT, including Estradiol, Progesterone, testosterone, and melatonin. She had been monitored regularly on her follow-ups and gradually improved. She had an improved lifestyle, which positively affected her mental and physical health. **Conclusion :** Eventually, it is concluded from this case that bioidentical hormones would play an important role in regulating normal body functions, even rebuild it after the patient lose it due to the fall in her hormone level. **Clinical significance**: Hormones have a huge impact on mental health as well.

Citation: ***Dr. Leila Soudah.*** **2023.** "Bioidentical hormone replacement therapy (BHRT) in the perimenopause", *Asian Journal of Science and Technology*, 14, (09), 12680-12683.

INTRODUCTION

Perimenopause marks the end of the reproductive capability of a woman. According to Delamater, L., & Santoro, N. (2018), fertility characteristics gradually disrupt and result in menopause almost after 10 to 12 months (Delamater & Santoro, 2018). Menopause attains after two transition periods in the hormonal cycle. The first is due to the fluctuating Follicle Stimulating Hormone (FSH) level. The menstruation would be reduced to one in a few months (Burger, 2006). The later stage includes the depletion of Estrogen production along with the reduction of reduced ovarian follicles (Burger *et al*., 2008). Menopause is a physiological phenomenon with variability in reproductive hormones since the beginning of the perimenopause period (Santoro *et al*., 2021). The present case concerns a woman experiencing perimenopause conditions and anxiety disorder, making her a suitable patient for bioidentical hormone therapy.

CASE DESCRIPTION

A 46-year-old female patient presented to Dr. Leila 'Soudah's clinic for the first time on 9th February 2022 with extreme fatigue, mood swings, emotional stress, and premenstrual bleeding elaborating premenstrual syndrome (PMS). Apart from these symptoms, she was also experiencing a disruption in menstruation, tinnitus, insomnia, hypoglycemia, constipation, muscle atrophy, arthralgia, palpitations, and decreased libido. Thyroid disorders were prevalent in her family. She was a vegetarian woman with a history of smoking and non-alcoholic background.

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According to her vital signs, she was hypotensive, hada blood pressure of 95/63 mmHg with 92 beats per minute, a body mass index was 19.0, with Weight of 50.70 kg, and a height of 163 cm, and an average body temperature was 36.4 ℃. She had conceived six times, with only one successful delivery in four years of her marriage. She had been going through serious anxiety attacks due to her perimenopause condition leading toward menopause. These symptoms have been presented four to six years earlier in her body. She was not financially stable. She has been converted into a different person after appearing of these symptoms. She was also going through insomnia, causing disruptions in her daily routine. Based on the presented symptoms, a liver function renal function test, and Gyne ultrasound has been prescribed after the first appointment. As per ultrasound (Figures. 1, 2a & 2b), there was a proliferation in the endometrium with the anteverted uterus. Cyst in both of the ovaries was also seen. Laboratory findings were non-significant, although the total protein level was below normal. On the second appointment on 10th march 2022, the patient presented with a complaint of amenorrhea for 5 weeks, with the same anxiety and disturbances in daily routine. She was then prescribed for conducting a hormone profile test. According to Laboratory findings, estradiol levels were below the normal range showing the perimenopause stage. The Prolactin level was normal (<25 ng/ml), considering the patient's condition. Testosterone and progesterone levels were below the normal range, while increased Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) indicated the perimenopause condition. Levels of Dehydroepiandrosterone (DHEA) show an increased fluctuation in sex hormones. Diagnostic features included hormone imbalance, low pregnenolone, nocturia, and fatigue. The most significant finding was the decreased level of hydroxypregnenolone, which defines the cause of depression as it is anxiolytic.

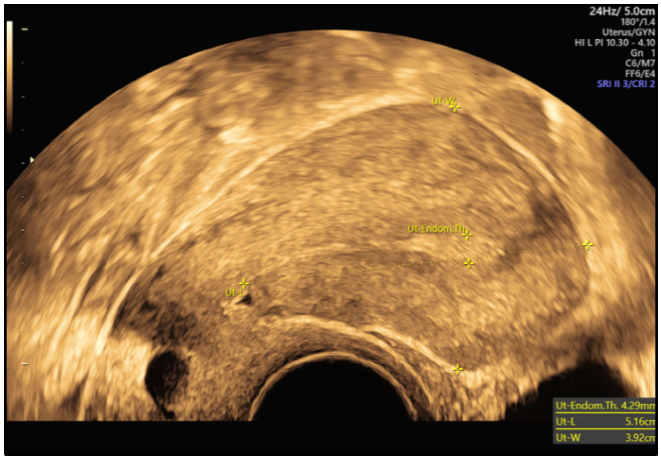


Figure 1. Proliferation of endometrium

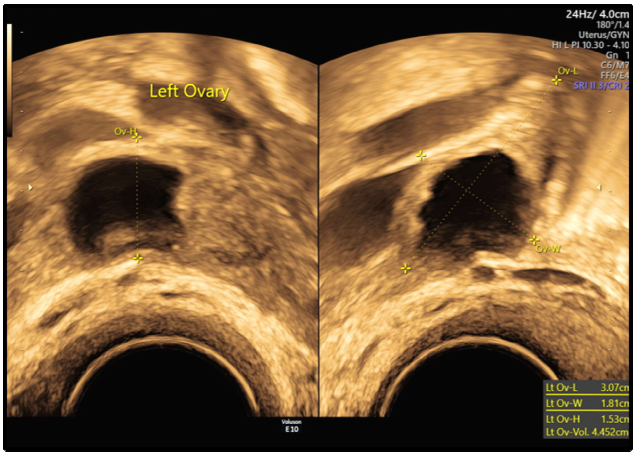


Figure 2a. Ovarian cyst in left ovary

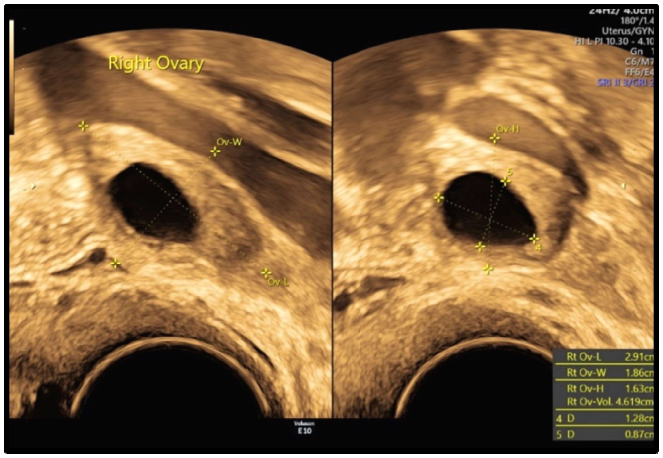


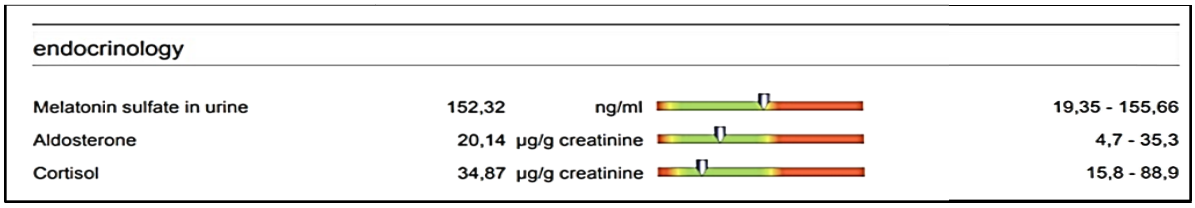
Figure 2b. Ovarian cyst in right ovary

Table 1. Initial regimenfor 1 month, including Biodentical Hormones

Medication/ Supplement	Dosage	Frequency
Cream Estradiol E2	1.5 mg/ml	once a day, morning
Cream Testosterone	0.25 mg/ml	once a day, morning
Cap Progesterone SR	200 mg	1 capsule once a day, evening
Cap DHEA-7-Keto	10 mg	*1 capsule once a day, morning*
Cap Pregnenolone	10 mg	1 capsule twice a day, morning
Inhal. Oxytocin intranasal spray	40 IU	1 puff once a day

Treatment had not been related to secondary symptoms caused due to anxiety. The practitioner had to focus on the root cause for a good prognosis. In the above-discussed case, prescribing antidepressants and hypnotic drugs were insufficient to eliminate the fundamental cause. The treatment plan aims to reverse the sypmtoms caused by aging and reduce symptoms of menopause. There was no evidence that antidepressants could treat the psychological effects of perimenopause. Anxiolytics must be coupled with hormone therapy to offer the best therapeutic strategy (Graziottin & Serafini, 2009). Treatment includes Estradiol E2, Testosterone, Progesterone, DHEA-7-Keto, Pregnenolone, and Oxytocin (Table 1). Treatment includes Bioidentical hormones for one month and a review of its effects. Effects of estrogen and testosterone include improved human behavior. After one month, the patient felt comfortable, symptoms decreased significantly, and the patient's anxiety level decreased by 60%. The lifestyle has been improved, and symptoms of menopause started to reverse. She also felt active and developed an interest in activities.The risk of estrogen-dependent diseases and the significance of methylation activity have been outlined in (Figure. 4). The hormone profile showed a normal level of melatonin and a lower normal level of aldosterone in urine (Figure 3).

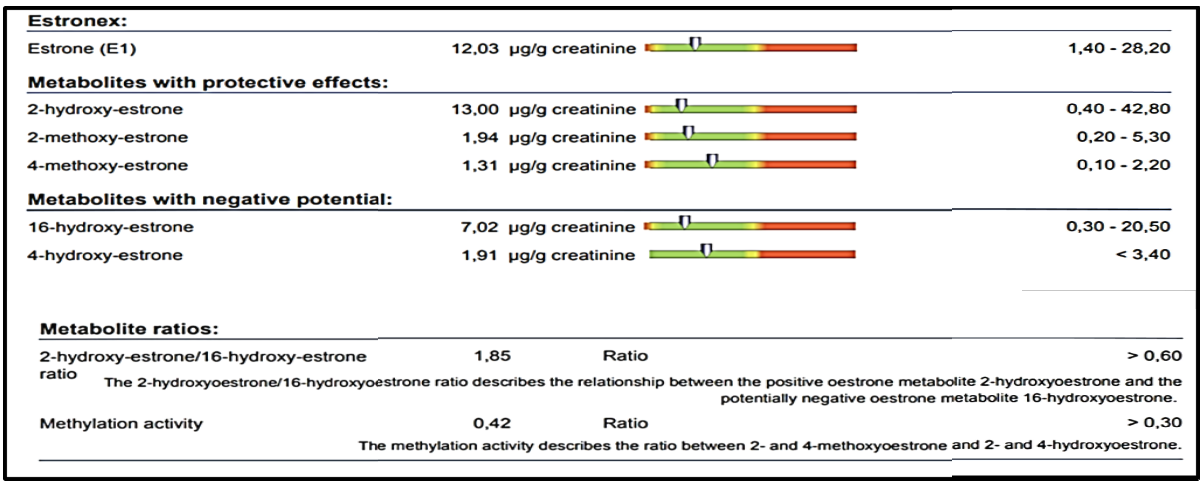
After the second follow-up session on 14th April 2022, the patient has advisedof the same regimen with the same doses, including a higher estrogen dose of 2mg/ml. This time the duration increases, and the patient is advised to visit after two months. The results after this dose have balanced the patient's life near perfection. Her anxiety level has been reduced, and she has become a good listener. After her third follow-up, she was prescribed corticosteroids and melatonin (Table 2). Cortisol has been prescribed twice daily to activate her body for routine work. These were given as the patient's body has not produced optimal corticosteroids. Melatonin is given sublingually to enhance its effects and for a rapid response. The responses to this three-step approach toward treating a premenopausal patient have been significantly positive. There was a decrease in exhausted feelings and insomnia. Medications related to decreasing depression and anxiolytics had worked efficiently. Reduced muscle size and joint also contributed to enhancing the patient's attitude. Treatment also responds to the evening fatigue and flexibility of the patient. There have also been improvements in urinary flow, stress management, hair dryness, hypertension issues, tinnitus, and headaches. Most of these conditions gradually respond to the given treatment. The patient's main complaint was resolved due to the induction of Bioidentical hormone treatment, which shares a significant



endocrinology

Melatonin sulfate in urine	152,32	ng/ml	19,35 - 155,66
Aldosterone	20,14	µg/g creatinine	4,7 - 35,3
Cortisol	34,87	µg/g creatinine	15,8 - 88,9

Figure 3. Hormones present in Urine



Estronex:

Estrone (E1)	12,03	µg/g creatinine	1,40 - 28,20

Metabolites with protective effects:

2-hydroxy-estrone	13,00	µg/g creatinine	0,40 - 42,80
2-methoxy-estrone	1,94	µg/g creatinine	0,20 - 5,30
4-methoxy-estrone	1,31	µg/g creatinine	0,10 - 2,20

Metabolites with negative potential:

16-hydroxy-estrone	7,02	µg/g creatinine	0,30 - 20,50
4-hydroxy-estrone	1,91	µg/g creatinine	< 3,40

Metabolite ratios:

2-hydroxy-estrone/16-hydroxy-estrone ratio	1,85	Ratio	> 0,60

The 2-hydroxyoestrone/16-hydroxyoestrone ratio describes the relationship between the positive oestrone metabolite 2-hydroxyoestrone and the potentially negative oestrone metabolite 16-hydroxyoestrone.

Methylation activity	0,42	Ratio	> 0,30

The methylation activity describes the ratio between 2- and 4-methoxyoestrone and 2- and 4-hydroxyoestrone.

Figure 4. Hormone profile showing estrogen metabolism

Table 2. Second regimen, including corticosteroids & hormone

Medication/ Supplement	Dosage	Frequency
Cap Hydrocortisone	10 mg	1 tablet once a day, 8:00 AM
Cap Hydrocortisone	5 mg	1 tablet once a day, 12:00 PM
Cap Fludrocortisone	50 mcg	1 capsule once a day, morning
Tab Melatonin Sublingual	0.25 mg	1 tablet once a day, night

contribution. The related symptoms, including anxiety, depression, hypertension, and decreased libido, had also reduced due to these regimens. The last hormone screening was done on 11th January, suggesting a normal testosterone, estradiol, and progesterone level compared to the values before the start of treatment (Table 3). The patient has started doing her regular tasks and responding appropriately. She is pleased with her condition. These results mark the success of the BHRT treatment.

DISCUSSION

Bioidentical hormone therapy has a similar composition as the hormones produced in the human body. These hormones included progesterone, androgens, and testosterone (Tsushima & Mikhael, 2021).According to most physicians and patients, it is assumed that these hormones originate from plants (Fishman *et al*., 2015). Perimenopause condition leads to complete menopause, having the same sign and symptoms, often declared as a transition period (White, 2015). According to research, the use of bioidentical hormones has increased in past years, and practitioners prefer Bioidentical hormone therapy over conventional hormone therapy. As mentioned above, estrogen and progesterone have a major therapeutic effect on the mental as well as on the physical health of the person. However, treating perimenopausal women with Bioidentical Hormone therapy would produce the desired results (Conaway, 2011). Irritability is one of the prominent features of a patient transitioning from lactating to the menopause phase. Irritability could be caused due to any underlying chronic medical condition, including heart disease, diabetes mellitus, thyroid disorder, or hypertension (Hanna, 2021). Bioidentical Estrogen and progesterone have a significant effect on the treatment process.

They also aid in treating osteoporosis in aged women and slow vaginal atrophy Medicine, 2020). FDA also indicates using estradiol to prevent bone loss (Jackson *et al*., 2020). Induction of Bioidentical hormone replacement therapy (BHRT) should ideally initiate with proper consultation and advising blood profile test. The patient should be regularly monitored at different intervals during her treatment for a better prognosis. The present case demonstrates the BHRT administration to treat a patient with signs and symptoms of perimenopause. The main symptoms had depression, decreased libido, disruption of the menstrual cycle, mental and physical tiredness, and cardiac issues. These are the secondary signs caused due to perimenopause. She had been treated with estradiol, progesterone, testosterone, and melatonin. Specific roles of melatonin and estrogen include reducing body weight, working as an antidepressant, and regulating body metabolism (Parandavar *et al*., 2014; Rubinow *et al*., 2015).The final results concluded that the adverse symptoms of the patient had been resolved. According to most recent research, these hormones have occupied an important place in the pharmaceutical market. They have produced successful outcomes and are generally available in all parts of the world.Bioidentical hormone replacement treatment positively impactsa patient's life (Santoro & Liss, 2021). The effects of BHRT treatment are more beneficial than their side effects(Ruiz *et al*., 2011). It has a better general perspective among practitioners and patients and is more popular than conventional hormone therapy. High levels of follicle-stimulating hormone and Luteinizing hormone has been observed in the body. The menstrual cycle is disturbed without hormones and may be delayed for a few months. This condition has developed anxiety symptoms and imbalanced body metabolism(Lee *et al*., 2012). It can also affect the body's metabolism, leading to weight gain. The FDA-approved bio-identical hormones, including progesterone, estrogen, and DHEA, were tested and monitored before its launch.

Table 3. Hormone Profile indicating improvement

Hormones	Level (before)	Level (after)	Referencevalues
Testosterone (ELFA) serum	0.09 ng/ml	0.62 ng/ml	Cyclic women 0.1 – 0.9 ng/ml Men 3.0 – 10.6 ng/ml
Estradiol (ELFA)-D	39.83 pg/ml	178.89 pg/ml	Follicularphase18 – 147 pg/ml Preovulatorypeak93 – 575 pg/ml Lutealphase 43 – 214 pg/ml Menopause<58
Progesterone (ELFA)-D	0.78 ng/ml	5.70 mg/ml	Follicularphase< - 0.54 ng/ml Luteal phase1.5 - 20 pg/ml Ovulation 0.12 – 6.2 pg/ml Post Menopausal< 0.41 ng/ml First trimester 26 – 133 ng/ml Second trimester 48 – 410 ng/ml Third trimester 156 – 722 ng/ml Men < 0.25 – 0.56 ng/ml

Compounded hormones used for the treatment have been manufactured by compounding pharmacies (Santoro & Liss, 2021). So their standard is not equal to the FDA-approved ones. As elaborated by this case report, they also have the least side effects and could be used according to symptoms. The quantity of compounded hormones variates along different pharmacies and manufacturers, which justifies the risks of variability (Stanczyk *et al*., 2021; Stanczyk *et al*., 2019).

CONCLUSION

Health practitioners are responsible for providing comprehensive and accepted treatment to our patients. Perimenopause is a degrading disorder in which the human body starts deteriorating and ends at complete menopause. Bioidentical hormone replacement therapy is an advanced way to cure these patients. These mainly include hormones extracted from plants which are more easily accepted by the human body. In the present case, Bioidentical hormone therapy has positively impacted the patient's lifestyle.

Clinical significance: BHRT is one of the best treatment option for perimenopausal women. It has limited side effects with accurate and rapid symptoms relief. It is manufactured from

Abbreviations

BHRT: Bioidentical hormone replacement Therapy; FDA: Food and Drug Administration; ELFA: enzyme-linked immunofluorescence assay; DHEA: Dehydroepiandrosterone; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone.

Acknowledgments: None.

Conflict of Interests: None.

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