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CORRELATION BETWEEN OXIDATIVE STRESS AND OXYTOCIN HORMONE IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY

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ABSTRACT : To assess Oxytocin, Inhibin B, myeloperoxidase (MPO) and Superoxide Dismutase (SOD) activity in women with premature ovarian Insufficiency (POI) and to compare them with menopausal women, and healthy fertile women. The current study was done at Bint Al-Huda Hospital in Thi-Qar and in the Biochemistry Laboratory in the College of Science (University of Thi-Qar). This study included ninety women divided into three groups, each of 30 women, group(A) with premature ovarian insufficiency, group (B) menopause women and group (C) healthy women. Oxytocin, Inhibin B, MPO and SOD were measured and comparison were made between three groups. The mean Inhibin B was (95.58± 12.27 pg/ml) in POI group, (79.02±15.02 pg/ml) in MW group and (125.04±28.01 pg/ml) in control group. The mean oxytocin was (97.34± 19.83 pg/ml) in POI group, (134.97± 26.82 pg/ml) in MW group and (192.88 ±31.48 pg/ml) in control group. The mean MPO was (2.67±0.42 ng/ml) in POI group, (3.34±0.30ng/ml) in MW group and (2.35±0.28ng/ml) in control group. The mean SOD was (33.43±5.54ng/ml) in POI group, (26.29±2.32 ng/ml) in MW group and (47.30±7.16 ng/ml) in control group. There was a significant decrease in the concentration of Inhibin B in MW and POI groups in a comparison with the control group. And there was a significant decrease in OT level in groups POI, MW in contrast to control group, which was highly significant. An a significant elevated MPO level was observed in MW, POI groups comparison with control group. Whereas was a significant decrease in SOD level in MW group comparison with POI and control groups. In conclusion, OT and Inhibin B levels in women with premature ovarian insufficiency is so low when compared to normal cycling women and close to the levels in menopause women. While, the MPO level was high in menopausal women, which was close to women with POI compared to healthy women. On the contrary, there was a significant decrease in the level of SOD in the menopausal women group and the POI group. We suggest that oxytocin may have a role in promoting endogenous antioxidant enzymes and reducing oxidative stress associated with aging through its antioxidant capacity.

Key words : Oxidative stress, primary ovarian insufficiency, oxytocin, inhibin B, myeloperoxidase, superoxide dismutase.

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INTRODUCTION

Premature ovarian insufficiency (POI) or premature ovarian failure (POF) is defined as the failure of ovarian function in women under the age of 40 years, clinically, and this condition is characterized by amenorrhea for four months or more with estrogen deficiency and a high level of gonadotropin (Welt, 2008; De Vos *et al*, 2010). The spread of the disease rate among women under the age of 40 years is 1% around the world (Skillern and Rajkovic, 2008; Altuntas *et al*, 2006) and the rate of infection is increasing. The development of POI is related to special, autosomal gene disorder, autoimmune dysfunction, infection and iatrogenic factors. Smoking and dietary factors have been found to influence the age at which POI occurs (De Vos *et al*, 2010). However, about half of the remaining cases of the disease are unknown reasons. The incidence of spontaneous premature ovarian insufficiency reaches 4% of women, and this percentage may vary according to the origin (Golezar *et al*, 2019). Regardless of the cause of premature ovarian insufficiency, according to the above, the lack of estrogen in the blood of women at an early age and not the natural age of menopause is now recognized as causing an increased risk of various diseases and premature death (Ikeme *et al*, 2011). Although, the accurate etiology is not known in 90% of the conditions with POI, genetic factors play a main role,

with family history reported in 10–15% of the conditions (Tokmak *et al*, 2015). One of the most important problems that women suffer from with premature ovarian insufficiency is infertility. Inhibin B is also a good marker to assess ovarian reserve. However, it is measured depends on the stage of the cycle since it is generated by the granulosa cells of the early antral follicles fundamentally in the follicular phase of the menstrual cycle. In the early follicular phase, the levels of inhibin B show the number and quality of follicles in the ovarian. So, patients with POI have decline levels of inhibin B (Jankowska, 2017). Inhibin B is a protein secreted by granulosa (female) and Sertoli (male) cells in response to FSH (Ying, 1988). Gonadal inhibin B is the principal peptide hormone that stimulates the synthesis and releasing of FSH during folliculogenesis, the main role of inhibin B is to selectively suppress the production of FSH by the pituitary gland. Inhibin enhances LH activation of androgen synthesis in theca cells to work as a substrate for estrogen aromatization in granulosa cells (Makanji *et al*, 2014).

Oxytocin (OT) is a cyclic nonapeptide synthesized in the cell bodies of the Paraventricular nuclei of the hypothalamus and transported through the axons of these cells to the posterior pituitary gland. It plays a dual role of neuromodulator/neurotransmitter and hormone. OT is an effective stimulant of uterine contraction and is mainly used to induce or enhance labor in obstetrics (Broekmans *et al*, 2009). In addition, OT plays a crucial role in the ejection of milk from the breasts during lactation and is also produced by different peripheral tissues, such as skin, placenta, ovaries, testes, thymus, pancreas, adipocytes, kidneys, heart and blood vessels. In addition, OT receptors have also been shown in the aforementioned bodies in the literature. In addition to its classic functions, OT plays anti-inflammatory, anti-apoptotic, anti-stress and antioxidant roles in numerous metabolic pathways (Ying, 1988 and Sharief *et al*, 2018).

Oxidative stress is one of the important theories linked with aging. In cells, through aerobic metabolism, reactive oxygen species that involving hydroxyl radicals, hydrogen peroxide, and superoxide anions are produced, Since the high reactive oxygen species levels, renders cells unable to get rid of them through its antioxidant capacity, so they react with nucleic acids, lipids, and proteins, in cells, causing oxidation or peroxide formation. These mechanisms cause the demolition of the cell membrane, differences in permeability, and cytotoxic reactions. Oxidative stress may be another potential contributor to the aging process (Boonekamp *et al*, 2017). We could hypothesize that the hypothalamic neuropeptide oxytocin (OT) may play an important role in this process (Stevenson *et al*, 2019). The current study aims to assess the level of the inhibin B and oxytocin in women with (POI) and menopausal women compared with fertile women with normal cycles. In addition to assessing the oxidative stress status by measuring MPO and SOD enzymes and studying the relationship between inhibin B hormone and oxytocin. On the other hand, the relationship of oxytocin with oxidative stress through the study of the role of OT in reducing oxidative stress in women with POI. The current study aims to assess the level of oxidative stress in women with POI and menopausal women compared with healthy women as a control group, by measuring the level of serum myeloperoxidase (MPO) as a marker of oxidative and inflammation processes, and superoxide dismutase SOD as an endogenous antioxidant. In addition to assessing the level of inhibin B hormones as a marker of ovarian reserve and oxytocin hormone and its relationship to oxidative stress.

METHODS

The total sample size was 90 composed of women and divided as the following: Thirty well-defined premature ovarian insufficiencies (POI) patients were selected by the hormonal analysis and clinical parameters. Thirty menopausal women were selected by the hormonal analysis and clinical parameters. The other thirty healthy women with normal menstrual cycles. Both patient groups' samples were collected at Bint Al-Huda Hospital in Thi-Qar and in the Biochemistry Laboratory in the College of Science (University of Thi-Qar) in the period between (July 2020) until (June 2020), Thi-Qar, Iraq.

The POI group chosen criteria were including females aged between 25 and 42 years, who had no menses or suffer from irregular menses through the last fourth months, FSH levels >25 μU/mL recorded during at least two readings one month apart. While in the menopausal women group the chosen criteria were including women aged between 45-52 years with amenorrhea more than one year, and serum FSH levels 6 months apart more than 25 μU/ml. The inclusion criteria for the healthy women (control) group were involved fertile, age less than 45 years, regular menstrual cycle. They have at least two children and no history of infertility. The patients with chronic and acute infections, rheumatic and other inflammatory diseases, metabolic disorders, malignancies, cardiovascular diseases were excluded from this study. And we excluded women that exposed to Oophorectomy, Hysterectomy, chemotherapy, or radiotherapy. Baseline hormone levels, and serum levels of some oxidative stress markers including MPO, SOD. Serum samples were estimated for hormonal and blood parameters; then they

were isolated by centrifugation at 3,000 rpm for 10 minutes. 5 milliliters of blood were acquired from each woman, then serum was collected and stored at -20°C until the time of use.

Oxytocin and Inhibin B were evaluated in all groups by Competitive ELISA, using the kits processed by Bioassay technology, China.

Serum **MPO** levels were analyzed by enzyme-linked immunosorbent assays (ELISA) method using the MPO ELISA kit (Bioassay technology, China).

Serum **SOD** activity was analyzed by enzyme-linked immunosorbent assays (ELISA) method using the SOD ELISA kit (Bioassay technology, China).

Statistical analysis

All statistical analysis was performed using SPSS, Windows version 23.0 software and Microsoft Excel 2010. The results were expressed as mean± standard deviations (mean ± SD) and Least Significant Difference (LSD). One-way analysis of variance (ANOVA) was used to compare parameters in different studied groups. P-values ($P< 0.05$) were considered statistically significant. Person correlation coefficient (r) is used to measure the strength at a linear association between two variables (r = +1), (r = -1). Person correlation coefficient (r) was used to test the correlation relationship among the different parameters in each patients group.

RESULTS

In current study, 90 women are involved, who are divided into 3 groups as mentioned in the methodology. Table 1 explains the special characteristics of all groups including BMI, age and menstrual cycle.

Table 1 shows the demographic characteristics of all groups regarding age, BMI, age at menarche, gravidity, parity, null parity. The mean (±SD) age of group POI was (41.36±3.76 years), while group MW with a mean age of (49.70±2.19 years) and the last group control it's mean was (32.13±5.98 years). Age differences were not significant between groups POI and control. But, there was a significant difference between the three groups. The mean (± SD) BMI of group POI was (29.11±3.53) while group MW with a mean (29.28±3.87) and the last group control it's mean was (25.66±2.20). Regarding obstetric characteristics, women with POI had significantly lower values for gravidity and parity comparison with the MW group and higher than the control group. null parity was more common among the control group.

Table 2 shows the mean (± SD) of the plasma levels of Inhibin B, Oxytocin, MPO, and SOD in all the three groups. The mean Inhibin B level in group POI was (95.58± 12.27 pg/ml), Inhibin B level in group MW was (79.02±15.02 pg/ml), while in control group the mean Inhibin B was (125.04±28.01pg/ml). This table showed that serum Inhibin B level was high in control group in comparison to POI and MW groups, which is statistically significant. The mean OT level in POI group was (97.34± 19.83 pg/ml), in MW group the mean level of OT was (134.97± 26.82 pg/ml) and the last group control. The mean OT level was (192.88 ±31.48 pg/ml). Plasma level of OT was declined in POI, and MW group in contrast to control group, which was highly significant. The mean MPO level in POI group (2.67±0.42 ng/ml), in MW group the mean was (3.34±0.30 ng/ml) and in the last group was (2.35± 0.28 ng/ml). The mean SOD level was (33.43 ±5.54 ng/ml) in POI group, in MW group the mean was (26.29±2.32 ng/ml), and in the last group was (47.30±7.16 ng/ml).

Fig. 1 shows the positive correlation between OT and Inhibin B in POI patients group with correlation coefficient (r = 0.31). While there are Negative correlation

Table 1 : The demographic data for studied groups.

Characteristics	POI Mean±SD	MW Mean±SD	Control Mean±SD	LSD
BMI (kg/m^2)	29.11±3.53a	29.28±3.87a	25.66±2.20b	1.40
Age (years)	41.36±3.76b	49.70±2.19a	32.13±5.98c	1.83
Gravidity	4.55±2.86b	5.76±2.55a	1.93±2.63c	1.15
Parity	3.86±2.40b	5.03±2.23a	1.63±2.25c	0.98
Null parity	0.69±1.03ab	0.76±1.10a	0.30±0.65b	0.40

Table 2 : Levels of OT, Inhibin B, MPO and SOD for all study's groups.

Groups	Control	MW	POI	LSD
Inhibin B Mean±SD (pg/ml)	a 28.01±125.04	c 15.02±79.02	b 12.27±95.58	8.45
Oxytocin Mean±SD (pg/ml)	a 31.48± 192.88	b 26.82±134.97	c 19.83±97.34	11.37
MPO Mean±SD (ng/ml)	2.35± 0.28 c	3.34±0.30 a	2.67±0.42 b	0.15
SOD Mean±SD (ng/ml)	47.30±7.16 a	26.29±2.32 c	33.43 ±5.54 b	2.32

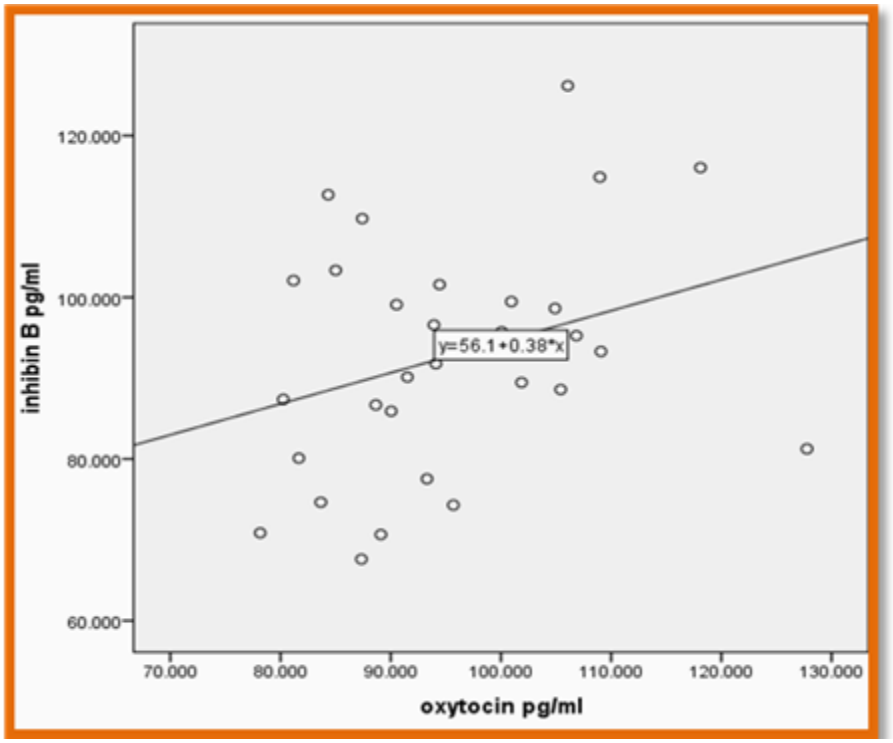

Fig. 1 : Correlation between Oxytocin hormone and Inhibin B in POI patients.

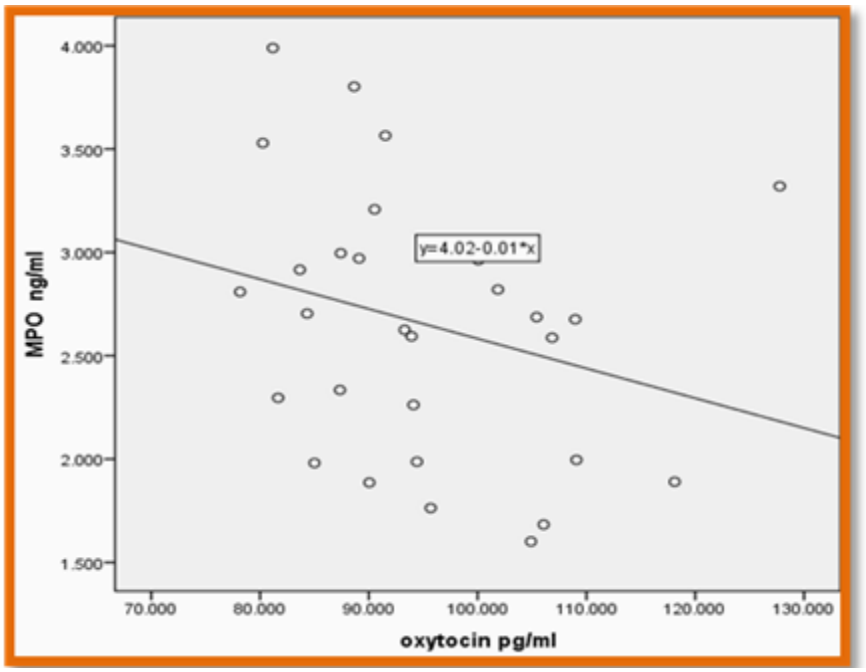

Fig. 2 : Correlation between Oxytocin hormone and MPO in POI patients.

between OT and MPO in POI patients group with correlation coefficient (r = -0.267) and positive correlation between OT and SOD in POI patients group with correlation coefficient (r = 0.252).

DISCUSSION

Inhibin B is the accurate and direct marker to measure ovarian reserve. Because, it is produced by granulosa cells in the ovary, it is considered the most important marker in this regard. It can be used as an indicator of ovarian aging because it diminishes with age due to the decrease in the number of follicles (Hofmann *et al*, 1996). The present study showed that the levels of Inhibin B decreased significantly with age. Inhibin can be considered as one of the causes of POI, depending on the hormonal patterns of POI patients A defect in Inhibin secretion has been reported in women with POI (Gimpl

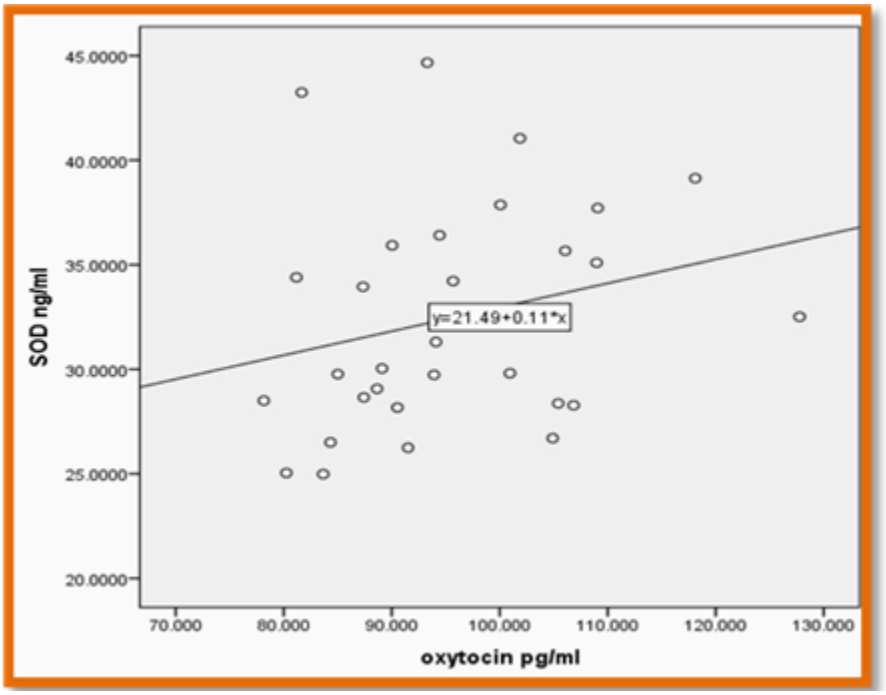

Fig. 3 : Correlation between Oxytocin hormone and SOD in POI patients.

and Falk, 2001) and Inhibin concentrations were lower in women with ovarian failure compared with fertile women with a normal ovulatory cycle (Okuda *et al*, 1997). It is believed that the main factor for the beginning of the transition to menopause is the decrease in the number of follicles in the ovary to a large extent. Inhibin B levels correlate with the number of developing follicles seen on ultrasound during the early follicular phase (Furuya *et al*, 1995) and levels decrease in parallel with the number of antral ovarian follicles (Skarzynski *et al*, 2008). The results of the current study show that the levels of OT were decreased in women with premature ovarian insufficiency more than in women at menopause and compared with fertile women with regular ovulatory cycles. Suggesting that an inverse association relates OT to POI in addition to menopause. And because OT secretion is clearly affected by mechanisms related to the hypothalamus-pituitary-gonadal system.

There is a positive relationship between oxytocin and inhibin B, which is an important marker of ovarian reserve. Because there is evidence that oxytocin is involved in reproduction through its effect on the release of gonadotropin-releasing hormone (GnRH) and the secretion of luteinizing hormone (LH) and progesterone. but the role of this hormone on endometrial growth and maturation is not exactly known (Gimpl and Falk, 2001; Mass, 1992; Hull *et al*, 1995). Furthermore, its effect on follicular development and ovulation is controversial (Tallam and Walton, 2000; King and Coetzer, 1997). Therefore, we recommend further trials to verify the role of oxytocin in maintaining ovarian follicles in women with premature ovarian insufficiency. Moreover, the main finding of this study is that serum levels MPO and SOD, are significant discriminative markers for POI. MPO is a significant marker of oxidative stress causing halogenations in stimulated immune cells like neutrophils (Vita *et al*, 2004). TOS The current study revealed an increase in the level of MPO in women with premature ovarian insufficiency and higher levels in menopausal women compared to fertile women. while the level of SOD was lower in menopausal women and women with POI compared with healthy fertile women.

Recent studies have displayed that oxidative stress (OS) is linked with reproductive system dysfunction in women (Miquel *et al*, 2006 and Suturina *et al*, 2008). Mitochondrion and NADPH oxidases are considered the main sources of ROS synthesis in cells. In mitochondria, electrons sliding from the electron transport chain, during mitochondrial respiration, may fuse with oxygen in generating O_2; at the same time, O_2 itself might subsequently be converted to H_2O_2 via superoxide dismutase (SOD) (Yu *et al*, 2016). Oxidative stress is usually classified as a source of inflammation-causing many diseases of aging caused by the action of hypochlorous acid. In1991 and through the first investigations that including MPO, it seemed to be very obvious the importance of one of myeloperoxidase's "natural" products, the HOCl implicated in the oxidation process (Casciaro *et al*, 2017).

Hypochlorous acid belongs to the group of reactive species consisting of chlorine molecules (RCS), which is formed through the myeloperoxidase action at the expense of H_2O_2 in a chloride ions-dependent reaction during phagocytosis. product of this reaction, the hypochlorite ion (OCl^-), which is in constant equilibrium with its form, hypochlorous acid (HOCl). Under physiological conditions, both compounds are strong oxidizing agents that could attack biomolecules and produce ROS and RNS, as does $ONOO^-$ and •OH [Babior, 2000 and Halliwell *et al*, 1988). Moreover, Some studies have shown an increase in the level of oxidative stress in postmenopausal women, who suffer from severe symptoms and a reduced quality of life, and attributed the reason for this to the combined effect of estradiol lack and symptoms that impact their quality of life (Rodríguez *et al*, 2013). So, if the intensity of the symptoms is elevated, psychological stress has resulted, and OS increases. From the important roles to oxytocin; enhance health and impact on behavior. there is growing evidence for the functions of oxytocin in the immune system and its main role as an anti-inflammatory and antioxidant (Szeto *et al*, 2011; Bordt *et al*, 2019; Kingsbury and Bilbo, 2019). The activity of oxytocin as a significant regulator of the mammalian immune system (Li *et al*, 2017; Kingsbury and Bilbo, 2019) that links social behavior and experiences with the ability to recover in the face of stress or trauma is particularly clear within the nervous system (Karelina and DeVries, 2011). Due to oxytocin integrates effects connected to raised social interaction, reduced stress levels, and induced healing and growth, it has been called the hormone of growth and relaxation or calm and connection (Moberg *et al*, 2014).

CONCLUSION

Inhibin B level in women with premature ovarian insufficiency is very low compared with normal cycling women and close to the levels in menopausal women. Due to its principal source in the female body is the preantral follicles, this shows Inhibin B is a good marker for ovarian reserve in women with POI. Clinically, plasma OT levels were significantly lower in menopausal women and POI patients than in healthy counterparts. Taken together, these results suggest that plasma OT levels represent a novel diagnostic marker for premature ovarian insufficiency. Additionally, an increase in the MPO level and a decrease in the SOD level at the same time were observed in menopausal women and POI patients compared to healthy women. And this indicates an increase in oxidative stress, which may be responsible for the decrease in the ovarian reserve represented by the hormone inhibin in this study. Through oxytocin's antioxidant capacity, we suggest that oxytocin may have a role in promoting endogenous antioxidant enzymes and reducing oxidative stress associated with aging. Thus, it may be promising to use oxytocin as a treatment to mitigate the harmful effects of premature ovarian insufficiency due to its antioxidant and anti-inflammatory properties and its ability to reduce the side effects of menopause.

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