JBM
J Bone Metab 2022;29(3):175-183
https://doi.org/10.11005/jbm.2022.29.3.175
pISSN 2287-6375 eISSN 2287-7029

Original Article

Roles of Follicle-Stimulating Hormone on Bone Metabolism in Late Postmenopausal Women

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Received: July 14, 2022
Revised: July 31, 2022
Accepted: July 31, 2022

Background: The effects of elevated follicle-stimulating hormone (FSH) levels on physiological changes in the bone remain unclear. This study aimed to clarify the association between FSH concentrations and bone mineral density (BMD) and bone turnover markers (BTM) in late postmenopausal women. **Methods:** A total of 169 Korean women were enrolled. The participants' ages ranged from 60 to 84 years (mean age, 69.0±5.1) and reported a mean duration of 19.4±6.6 years since menopause (YSM). The participants showed an average body mass index (BMI) of 24.4±2.8 kg/m^2. Age, YSM, estradiol, testosterone, and BMI were confounders in the Pearson's partial correlation. A test for trends across the quartiles of FSH levels was performed for each variable. **Results:** The mean FSH and estradiol concentrations were 61.5 IU/L and 2.9 pg/mL, respectively. Serum FSH concentration was not significantly associated with BMD (lumbar, r=0.09, P=0.30; total hip, r=0.00, P=0.96; and femoral neck, r=0.05, P=0.62). BTM across the FSH quartiles did not show any trend association (bone-specific alkaline phosphate, P=0.31; cross-linked C-terminal telopeptide of type I collagen, P=0.90). Instead, FSH levels were negatively correlated with BMI (r=-0.34, P=0.00). In the multivariate regression model adjusted for age, testosterone, and estradiol, only BMI showed a negative value across the FSH quartiles (β coefficient -0.11, P=0.00). **Conclusions:** This study identified that high FSH concentrations were not associated with bone loss or high bone turnover in women in the late postmenopausal period.

Key Words: Body mass index · Bone density · Follicle stimulating hormone · Postmenopause

INTRODUCTION

Follicle-stimulating hormone (FSH) plays a role as a reproductive hormone. However, several studies have suggested the probable extragonadal effects of FSH on bone mass [1-14] and body mass.[15,16] Traditionally, increased bone resorption during menopause has been attributed to reduced estrogen levels. However, recent clinical data have shown that high FSH levels are positively associated

with loss of bone mineral density (BMD) and high bone turnover.[1-4,6,8,17] Sun et al. [1] reported that, irrespective of the nature or severity of estrogen deficiency, high FSH levels are prerequisites for hypogonadal bone loss. Multiple animal studies have demonstrated that FSH aggravates bone loss,[14,18] and that inhibiting FSH is osteoprotective.[19,20] Likewise in humans, the Study of Women's Health Across the Nation (SWAN) found a negative correlation between serum FSH levels and BMD in perimenopausal women.[2-4,6] Additionally, a cross-sectional study has shown that bone turnover markers (BTMs), such as serum osteocalcin and serum cross-linked C-terminal telopeptide of type I collagen (ICTP), positively correlate with serum FSH but not with serum estradiol in early postmenopausal women.[8] However, conflicting results have been reported regarding the correlation between FSH and BMD/BTM in the late postmenopausal period,[21-23] eliciting doubt regarding the pure effect of FSH on bone metabolism in older women. This disagreement in the association between FSH levels and BMD/BTM in the late postmenopausal period needs to be clarified.

To summarize, there are considerable knowledge gaps regarding the association between FSH levels and bone metabolism in postmenopausal women. Regulation of bone by the hypothalamic-pituitary-gonadal axis is now a challenging and controversial subject that includes not only simple estrogen deficits but also gonadotropin hormones.[24] While the effects of estradiol have been extensively studied, the effect of elevated FSH levels on physiological changes in the bone is not well understood. Thus, the present study aimed to clarify this controversy by investigating the association between FSH concentrations and BMD/BTM and body mass index (BMI) in late postmenopausal women with physiologically trace or undetectable estrogen levels irrespective of the severity of estrogen deficiency.

METHODS

1. Participants

Postmenopausal Korean women who visited the Health Promotion Center of Yeouido St. Mary's Hospital were enrolled in the study. The inclusion criteria were women aged 60 years or older in the late postmenopausal period (cessation of menstruation for at least 5 years) were included.[25] Participants who previously used osteoporosis medications were included; if any, the washout period dependent on previous use was considered sufficient (e.g., previous use of ≥48 weeks required 2 years of washout). Women who had received prior hormone replacement therapy were excluded from the study. Participants with cardiac, liver, or renal disease; endocrine or metabolic abnormalities; or inflammatory disease were excluded. Smoking habits were categorized as current or never smoker. Of the 276 women, 169 were considered eligible for the study. All the participants in this cross-sectional study provided written informed consent.

2. Biochemical analysis

Blood samples were collected from the antecubital vein between 8 AM and 9 AM following overnight fasting. Blood was collected in tubes, placed on ice, and centrifuged immediately under cold conditions. The serum was stored immediately at -70°C until assayed. Serum luteinizing hormone (LH-IRMA; Immunotech, Prague, Czech Republic) and FSH (FSH-IRMA; Biosource Europe S.A., Nivelles, Belgium) levels were measured using an immunoradiometric assay. Serum estradiol (estradiol MAIA; Biodata Diagnostics, Bologna, Italy) was measured using a radioimmunoassay. Serum bone specific alkaline phosphatase (BALP) concentrations were determined using ELISA (Metra BAP EIA kit; Quidel Corp., San Diego, CA, USA). The maximum inter- and intra-assay coefficients of variation (CVs) for the range of concentrations were 5.8% and 7.6%, respectively. The ICTP generated by matrix metalloproteinase concentrations were measured using a radioimmunoassay (Telopeptide ICTP; Orion Diagnostica, Espoo, Finland). The maximum inter- and intra-assay CVs values were 10.7% and 3.6%, respectively.

3. Bone densitometry

The BMD of the lumbar spine (lumbar vertebrae L1-4), total hip, and femoral neck were measured using dual energy X-ray absorptiometry (Hologic Delphi W; Hologic Inc., Bedford, MA, USA). The CVs according to precision were determined to be 1.2% and 1.9% at the lumbar spine and femoral neck, respectively.

4. Statistical analysis

All data were statistically analyzed using R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Aus-

https://doi.org/10.11005/jbm.2022.29.3.175

tria). All figures were produced using R. All descriptive data are presented as mean±standard deviation for continuous measures and percentages for categorical measures. Statistical significance was set at $P \leq 0.05$. Pearson's partial correlation coefficient was used to assess the associations between variables. Age, years since menopause (YSM), and estradiol and testosterone levels were considered confounders. Multivariate regression analysis was used to examine the relationship between serum FSH levels and BMI. The least-squares mean procedure was used to determine the association between quartiles of serum FSH and BMD/BTM, BMI, and other indices. A test for trends across the quartiles of FSH levels was performed for each association.

RESULTS

1. Clinical characteristics

Table 1 describes the general characteristics of the 169 enrolled women. The participants' ages ranged from 60 to 84 years (mean age, 69.0±5.1), with an average BMI of 24.4±2.8 kg/m^2. The participants had a mean YSM of 19.4±6.6, suggestive of late postmenopausal women. The mean FSH and estradiol concentrations were 61.5 IU/L and 2.9 pg/mL, respectively, while the BMD for lumbar spine, total hip, and femoral neck were 0.768±0.139 g/cm^2, 0.730±0.102 g/cm^2, and 0.618±0.097 g/cm^2, respectively. The mean BALP and ICTP values were 34.9 IU/L and 4.6 ng/mL, respectively. Fragility fractures were prevalent in 43 participants (25.4%).

Table 1. General characteristics of the study participants at the time of enrollment

Variables	Value (N=169)
Age (yr)	69.0±5.1 (60–84)
BMI (kg/m^2)	24.4±2.8 (16.0–31.2)
YSM (yr)	19.4±6.6 (6–36)
Menopause age (yr)	49.7±3.8 (38–60)
Current smoker	6 (3.6)
Diabetes	19 (11.2)
Hypertension	66 (39.1)
LH (IU/L)	23.1±8.8 (4.0–60.9)
FSH (IU/L)	61.5±21.8 (7.0–126.4)
Testosterone (pg/mL)	11.9±14.6 (0.0–93.0)
TSH (IU/L)	2.2±4.8 (0.0–60.0)
E2 (pg/mL)	2.9±2.5 (0.0–12.9)
BALP (IU/L)	34.9±11.7 (11.9–84.0)
ICTP (ng/mL)	4.6±0.9 (2.8–7.7)
BMD lumbar spine (g/cm^2)	0.768±0.139
BMD total hip (g/cm^2)	0.730±0.102
BMD femoral neck (g/cm^2)	0.618±0.097
History of fragility fracture	43 (25.4)

The data is presented as mean±standard deviation (range) or N (%).
BMI, body mass index; YSM, years since menopause; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; E2, estradiol; BALP, bone specific alkaline phosphatase; ICTP, cross-linked C-terminal telopeptide of type I collagen; BMD, bone mineral density.

2. Pearson partial correlations between serum reproductive hormones and BMD, BTM and BMI

The Pearson partial correlation coefficients between hormone concentrations and BMD/BTM measurements are shown in Table 2. Serum FSH concentration was not significantly associated with BMD at any of the 3 sites (lumbar, $r=0.09$, $P=0.30$; total hip, $r=0.00$, $P=0.96$; and femoral neck, $r=0.05$, $P=0.62$) (Fig. 1). Serum FSH levels were significantly associated with BALP ($r=0.21$, $P=0.01$) but not with ICTP ($r=0.01$, $P=0.38$). There was no association between serum estradiol concentrations and any of the BMD measures or between serum testosterone levels and BMD. However, BMI was significantly associated with FSH levels. BMI was negatively correlated with FSH levels ($r=-0.34$, $P=0.00$) (Fig. 2).

3. Comparisons of BMD/BTM and BMI according to FSH quartiles

FSH concentrations showed a normal distribution, which

Table 2. Pearson partial correlations between serum reproductive hormones and BMD, BTM and BMI

	Age	YSM	FSH	E2	T	BMI
BMI	-0.11	0.09	-0.34[b]	0.09	0.04	1.00
BALP	0.06	-0.12	0.21[a]	0.10	0.15	0.00
ICTP	0.28[b]	-0.80[a]	0.01	0.02	0.09	0.15
BMD						
Lumbar spine	0.03	0.03	0.13	0.03	-0.03	0.24[b]
Total hip	-0.25[b]	0.13	0.11	0.02	-0.09	0.39[b]
Femoral neck	-0.27[b]	0.15	0.13	0.01	-0.08	0.37[b]

[a] $P<0.05$.
[b] $P<0.005$.
BMI, body mass index; BTM, bone turnover marker; BALP, bone specific alkaline phosphatase; ICTP, cross-linked C-terminal telopeptide of type I collagen; BMD, bone mineral density; YSM, years since menopause; FSH, follicle-stimulating hormone; E2, estradiol; T, testosterone.

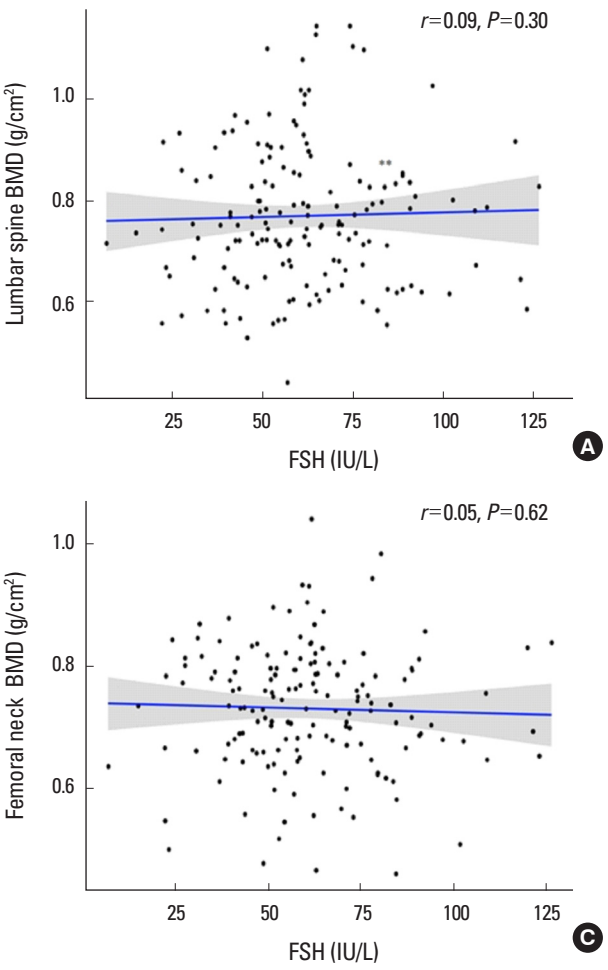

Fig. 1. Pearson partial correlations between follicle-stimulating hormone (FSH) and (A) lumbar spine bone mineral density (BMD), (B) total hip BMD, and (C) femoral neck BMD.

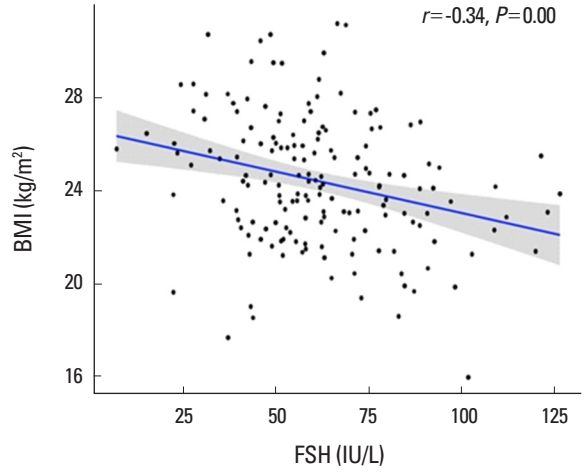

Fig. 2. Pearson partial correlation between body mass index (BMI) and follicle-stimulating hormone (FSH).

followed a bell-shaped curve (data not shown). Participants were categorized into quartiles of FSH levels (Table 3). The median FSH concentration was 58.7 IU/L. Twenty-fifth and seventy-fifth percentiles were 48.2 IU/L and 74.2 IU/L, respectively. There were no statistically significant differences in age, YSM, serum testosterone, or serum estradiol levels across the quartiles of FSH. Neither the BMD at the 3 sites (lumbar, $P=0.17$; total hip, $P=0.28$; femoral neck, $P=0.20$) nor the levels of BTM (BALP, $P=0.31$; ICTP, $P=0.90$) showed any trend. Additionally, the prevalence of fractures did not show a significant association ($P=0.91$). However, there was a significant trend in BMI levels across the FSH quartiles ($P=0.03$). In the multivariate regression model adjusted for age, total testosterone, and estradiol, BMI showed a negative value across FSH quartiles (β coefficient -0.11, $P=0.00$).

https://doi.org/10.11005/jbm.2022.29.3.175

Table 3. Comparisons and results of test for trends in BMD, BMI, and other indices across FSH quartiles (N=169)

	Q1 (N=42)[b]	Q2 (N=42)[c]	Q3 (N=43)[d]	Q4 (N=42)[e]	*P*-value
Age (yr)	69.4±5.6	68.3±4.2	69.4±4.8	69.1±5.8	0.72
YSM (yr)	19.0±6.5	20.1±7.0	20.0±6.5	18.6±6.5	0.68
BMI (kg/m^2)	25.1±3.1	24.6±2.4	24.7±2.8	23.4±2.7	0.03[a]
Current smoker	0 (0.0)	1 (2.4)	2 (4.7)	3 (7.1)	0.33
Diabetes	4 (9.5)	4 (9.5)	4 (9.3)	7 (16.7)	0.61
Hypertension	19 (45.2)	14 (33.3)	20 (46.5)	13 (31.0)	0.36
Testosterone (pg/mL)	10.6±10.8	15.3±16.9	7.9±5.7	14.3±20.3	0.09
LH (IU/L)	15.5±6.2	22.3±8.04	24.3±6.6	30.4±7.2	0.00[a]
E2 (pg/mL)	3.3±2.3	3.2±2.3	2.8±2.9	2.4±2.2	0.21
TSH (IU/L)	3.5±9.4	1.8±1.2	2.2±1.8	1.3±0.9	0.23
BALP (U/L)	34.0±13.5	34.7±10.0	33.8±11.3	37.2±12.1	0.31
ICTP (ng/mL)	4.7±0.9	4.5±0.9	4.7±0.9	4.7±1.0	0.90
Fracture	11 (26.2)	11 (26.2)	12 (27.9)	9 (21.4)	0.91
Lumbar spine (g/cm^2)	0.746±0.126	0.764±0.132	0.815±0.155	0.765±0.131	0.17
Total hip (g/cm^2)	0.740±0.086	0.720±0.101	0.754±0.114	0.731±0.115	0.28
Femoral neck (g/cm^2)	0.617±0.082	0.604±0.085	0.644±0.115	0.629±0.103	0.20

The data is presented as mean±standard deviation (range) or N (%).
[a] $P<0.05$.
[b] FSH quartile=7.0–48.2 IU/L.
[c] FSH quartile=48.2–58.7 IU/L.
[d] FSH quartile=58.7–74.2 IU/L.
[e] FSH quartile=74.2–126.4 IU/L.
BMD, bone mineral density; BMI, body mass index; FSH, follicle-stimulating hormone; YSM, years since menopause; LH, luteinizing hormone; E2, estradiol; TSH, thyroid-stimulating hormone; BALP, bone specific alkaline phosphatase; ICTP, cross-linked C-terminal telopeptide of type I collagen.

DISCUSSION

This study aimed to investigate the association between serum FSH levels and bone metabolism in healthy late postmenopausal women with physiological trace or undetectable estrogen levels. The present study showed that high serum FSH levels were not associated with BMD/BTM but were negatively associated with BMI.

Several previous studies have shown that serum FSH levels are associated with the rate of bone turnover and loss during the menopausal transition.[2-4,6-13,26-30] However, our study did not demonstrate a significant association between FSH and BMD/BTM or a trend in the prevalence of self-reported fractures across FSH quartiles in the late postmenopausal period. These observations correspond well with those found in a clinical study [21-23,31] and animal studies.[32] Wu et al. [21] reported no association between baseline FSH level and bone loss in the AGES-Reykjavik cohort, with a mean age of 80.9±4.2 years.

Participants were in their perimenopausal or early postmenopausal (mean YSM <8 years) period in previous studies,[2-13] which reported that FSH correlates with BMD loss and high bone turnover. However, the present study group comprised of women with a mean age of 20 YSM. The participants in this study were relatively older than those in the aforementioned studies. Therefore, meaningful differences in mean estradiol levels were found between our study and other studies (Table 4). In this study, FSH concentrations were not associated with low bone mass or high bone turnover, while the mean estradiol concentrations were as low as 2.9±2.5 pg/mL. The difference in the results of the current study compared to those of other studies could be attributed to the contrasting levels of estrogen. Another possibility is that longstanding exposure to high FSH levels in late postmenopausal women might have resulted in the desensitization of gonadotropin responses in osteoclast cells. In granulosa cells, prolonged stimulation of both luteinizing hormone and FSH receptors leads to desensitization, which is proven by the reduction of cyclic adenosine monophosphate accumulation in target cells followed by downregulation of steroidogenesis,

Table 4. Differences in mean levels of hormones in studies evaluating the relationship between FSH and BMD/BTM

References	Age	FSH (mIU/mL)	E2 (pg/mL)	Relationship with BMD
Sowers et al. [2-4][a]	46.4±2.7	24.1±25.4	75.3±76.3	Negative
Devleta et al. [5][a]	32.3±6.1	34.3±42.3	65.7±67.9	Negative
Cannon et al. [7]	20–50	27.3±46.4	80.1±112	Negative
García-Martín et al. [8]	56.2±3.6	73.8±28.3	10.6±10.1	Negative
Cheung et al. [30]	47.7±2.2	27.7±32	65.1±83	Negative
Gourlay et al. [31]	57.6±3.6	63.0±35.1	NA	No relationship
Shieh et al. [6]	46.1±2.6	15.1	52.5	Negative
Veldhuis-Vlug et al. [35][b]	80.8±4.2	71.6±23.2	5.1±4.2	Negative
Wu et al. [21][b]	80.9±4.2	71.6±21.9	5.3±4.5	No relationship
Current study	68.9±5.1	61.5±22.2	2.9±2.5	No relationship

The data is presented as mean±standard deviation.
[a]The Study of Women's Health Across the Nation (SWAN) cohort study.
[b]The Age, Gene/Environment Susceptibility (AGES)-Reykjavik cohort study.
FSH, follicle-stimulating hormone; E2, estradiol; BMD, bone mineral density; BTM, bone turnover marker; NA, not applicable.

even in the presence of hormones.[33] This desensitization to hormones is essential for blocking overstimulation of gonadal cells. We postulate that a similar phenomenon might also occur in osteoclast cells. Postmenopausal hormone-dependent bone loss has a biphasic pattern with a rapid phase followed by a decelerated phase in the trabecular bone after 7 years of menopause.[34] According to a prospective longitudinal study about menopause-related bone mass reduction, bone turnover has been shown to increase rapidly, reaching a peak of 2 to 3 YSM and remaining elevated thereafter.[34] During 3 to 5, YSM the skeletal balance tends to return to equilibrium, indicating that the negative effects on skeletal balance progressively cease. In other words, if FSH is attributable to bone loss in postmenopausal women, rather than the lack of estrogen, the bone would escape from the direct negative effects of FSH after 3 to 5 YSM. Likewise, Crandall et al. [23] documented in the SWAN cohort that serum FSH was no longer associated with rates of lumbar spine or hip bone loss in the 2 to 5 years after the final menstrual period when FSH levels plateaued and remained relatively stable. Additionally, a trial of 105 days' use of gonadotropin releasing hormone agonists to suppress FSH in postmenopausal women in their sixties did not demonstrate a decrease in BTM [22] supporting the presumption of desensitization.

However, 1 cross-sectional analysis [35] suggested a negative correlation between FSH and BMD in postmenopausal women in their eighties. The conflicting results between Veldhuis-Vlug et al. [35] and ours might have resulted from the interference of BMI on the relationship between FSH and BMD. BMI is well known to correlate with BMD.[36] Unlike Veldhuis-Vlug et al. [35], our study considered BMI a confounder in the partial correlation analysis. The negative association between FSH and BMD in previous studies might not be a causal relationship but a reflection of a negative association between FSH and BMI. Moreover, a subsequent study using the same cohort [21] showed no relationship between FSH and BMD.

The relationship between FSH levels and BMI remains controversial. In the regression model adjusted for age, testosterone, and estradiol, BMI showed a negative value across the FSH quartiles. This finding is consistent with the results of Kim et al. [16], who showed an increase in FSH levels with weight loss in 382 overweight women with a mean age of 58.7±9.0 years. In disagreement with our data, other studies [27,37] have also reported a positive correlation between FSH concentration and BMI in the early menopausal transition. Likewise, the effect of FSH on BMI might vary depending on menopausal status. Further research is required to clarify this issue.

Taken together, regarding the period of dynamic changes in hormone levels, as observed in the perimenopausal period and early menopausal phase, FSH level is a good surrogate marker of estrogen deficiency and could be a good predictor of BMD/BTM. However, in late postmenopausal women who have been estrogen deficient for a long period, FSH levels were not associated with increased bone resorption and low bone mass.

https://doi.org/10.11005/jbm.2022.29.3.175

The strength of this study includes the ability to adjust for several indices representing serum estradiol, testosterone levels, and BMI in a homogenous population cohort. This study has several limitations. First, the current analysis did not evaluate lean mass and fat tissue separately in study participants. BMI was the only index used in this study. Several studies have reported an association between FSH levels and body fat.[31,35] Since lean mass and fat tissue both affect BMI, it would have been more reliable if we had measured lean mass or fat tissue using proper assessment tools. Secondly, we evaluated the ICTP level instead of the C-terminal telopeptide of type I collagen (CTX) level as a bone resorption marker due to the limited laboratory equipment at the time of the study. Although serum ICTP is a sensitive marker for detecting osteolysis related to bone metastasis, it is reportedly less sensitive to osteoporosis than serum CTX.[38] Finally, the established cohort was limited to older women in South Korea, and the results may not apply to other populations.

In conclusion, the present study identified that high FSH concentrations were not associated with bone loss or high bone turnover in women in the late postmenopausal period. FSH levels were negatively correlated with BMI. Due to the cross-sectional nature of the analysis, we could not determine causality associations. Longitudinal studies are required to better understand the relationship between FSH levels and other indices.

DECLARATIONS

Funding

This research did not receive any specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent prior to enrollment.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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