



Evaluation of the relations between reproduction-related pituitary and ovarian hormones and abdominal fat area-related variables determined with computed tomography in overweight or obese women who have undergone bariatric surgery: a cross-sectional study

Hao Guo^{1,2#^}, Bo Yang^{1,3#^}, Shigeru Kiryu^{4^}, Qing Wang¹, Dexin Yu¹, Zehua Sun^{2^}, Yang Chen^{2,5^}, Xin Li^{1,6^}, Fang Wang^{1^}, Xinru Ba^{7^}

¹Department of Radiology, Qilu Hospital of Shandong University, Jinan, China; ²Department of Radiology, Yantai Yuhuangding Hospital, Qingdao University School of Medicine, Yantai, China; ³Department of Radiology, Qingzhou People's Hospital, Qingzhou, China; ⁴Department of Radiology, Narita Hospital, International University of Health and Welfare, Narita City, Chiba, Japan; ⁵Department of Medical Imaging, Weifang Medical University, Weifang, China; ⁶Department of Radiology, Tengzhou Central People's Hospital, Tengzhou, China; ⁷Department of Radiology, Yantaishan Hospital, Yantai, China

Contributions: (I) Conception and design: X Ba, F Wang; (II) Administrative support: X Ba, F Wang; (III) Provision of study materials or patients: X Ba, H Guo, B Yang, S Kiryu, Q Wang, D Yu, Z Sun, X Li; (IV) Collection and assembly of data: H Guo, B Yang, S Kiryu, Q Wang, D Yu, Y Chen, Z Sun; (V) Data analysis and interpretation: H Guo, B Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work.

Correspondence to: Fang Wang, MD. Department of Radiology, Qilu Hospital of Shandong University, No. 107 Wenhua West Road, Jinan 250012, China. Email: 329571483@qq.com; Xinru Ba, MD. Department of Radiology, Yantaishan Hospital, No. 91 Jiefang Road, Yantai 264000, China. Email: baxinru2@163.com.

Background: An understanding of the associations between midregion fat depots and systemic hormone levels will be crucial for developing health-promotion messages aimed at overweight or obese women. However, related research in this area is rare. The present study was performed to identify and quantify fat-related reproduction pituitary and ovarian hormones in overweight or obese women.

Methods: A total of 250 eligible overweight or obese women scheduled to undergo laparoscopic sleeve gastrectomy (LSG) from a single center were retrospectively included in this study. Computed tomography (CT) images at the level of the umbilicus were selected, and abdominal fat areas were measured and calculated. The reproduction-related pituitary and ovarian hormones were also measured. The correlations among the parameters were examined using Spearman correlation test. Multiple linear regression analysis was performed after log and β -transformation of the hormone levels and fat area-related variables.

Results: Positive correlations were detected for prolactin (PRL) with total fat area (TFA) [$\beta=0.045$; $P=0.029$; 95% confidence interval (CI): 0.004–0.085] and subcutaneous fat area (SFA) ($\beta=0.066$; $P=0.023$; 95% CI: 0.009–0.123), whereas estradiol showed a negative correlation with visceral fat area (VFA) ($\beta=-0.056$, $P=0.005$; 95% CI: -0.096 to -0.017) and relative VFA (rVFA) ($\beta=-0.068$; $P=0.001$; 95% CI: -0.109 to

[^] ORCID: Hao Guo, 0000-0003-0231-3345; Bo Yang, 0000-0003-0794-0006; Shigeru Kiryu, 0000-0003-1440-9483; Zehua Sun, 0000-0002-4922-3200; Yang Chen, 0000-0002-2524-5966; Xin Li, 0000-0003-4469-6401; Fang Wang, 0000-0001-6489-4507; Xinru Ba, 0000-0001-6971-5934.

-0.027) and a positive correlation with SFA ($\beta=0.036$; $P=0.042$; 95% CI: 0.001–0.071). Progesterone (PROG) was negatively correlated with both VFA ($\beta=-0.037$; $P=0.002$; 95% CI: -0.061 to -0.013) and rVFA ($\beta=-0.039$; $P=0.002$; 95% CI: -0.063 to -0.014). The final results revealed that TFA was increased by 3.1% and SFA was increased by 4.7% with a doubling of PRL concentration; VFA was reduced by 2.5% and rVFA was reduced by 2.6% with a doubling of PROG concentration; and VFA was reduced by 3.8%, rVFA was reduced by 4.6%, and SFA was increased by 2.5% with a doubling of estradiol concentration.

Conclusions: There exist certain associations between some reproduction-related pituitary and ovarian hormones and fat areas. Our findings provide new insights into the associations between midregion fat depots and systemic hormone levels in overweight or obese women.

Keywords: Obesity; overweight; ovarian hormones; abdominal; computed tomography (CT)

Submitted Nov 20, 2022. Accepted for publication Aug 22, 2023. Published online Sep 14, 2023.

doi: 10.21037/qims-22-1283

View this article at: <https://dx.doi.org/10.21037/qims-22-1283>

Introduction

A rise in the prevalence of individuals who are overweight or obese is a major public health problem around the world (1,2). Obesity is associated with a number of adverse health conditions, including metabolic syndrome, type II diabetes, and cancer (2,3). Recent studies have shown that obesity has both population-specific and sex-specific effects (4,5). In general, women tend to have greater hormonal fluctuations and effects. This is manifested as body composition and fat distribution varying with hormone concentration. Follicle-stimulating hormone (FSH) stimulates the growth and development of ovarian follicles in females, and it is released by the gonadotropes in the anterior pituitary gland. FSH levels increase due to decreased negative feedback from estrogen and inhibin during menopause. Some researchers have reported that older postmenopausal women with higher FSH levels have a lower weight, lower visceral adipose tissue (VAT), and lower fat mass independent of estradiol (E2) and testosterone (TEST) levels (6). Prolactin (PRL) is primarily secreted by the lactotroph cells in the anterior pituitary gland and stimulates milk production. It also plays a role in breast development and fertility regulation. A study showed that spontaneous PRL release was considerably enhanced in obese women in proportion to the size of their visceral fat mass (7). Estrogens act synergistically with adipose tissue (AT) genes to increase gluteofemoral subcutaneous AT (SAT) mass and decrease central AT mass in reproductive-age women (8). These data demonstrate the important role of hormones in regulating the distribution pattern of accumulated fat. The variations of fat distribution in females have been found

to be associated with specific physical and physiological challenges in overweight or obese women (9,10). Estrogen is effective in modulating lipogenesis, which may be related to the expression of estrogen in AT and monocyte infiltration and macrophage activity induced by estrogen, as revealed by 2 animal studies (11,12). Obesity affects ovarian function through several pathways (13), which can lead to a cascade of abnormal conditions such as polycystic ovary syndrome (PCOS), low menstruation, or amenorrhea (14). However, the specific mechanisms underlying these sex-specific effects have yet to be elucidated. Leptin, which is secreted by AT, may be involved in maintaining normal ovarian function (15). These findings illustrate the complex interactions of AT and hormones across diverse populations. However, there have been few reports providing quantitative clinical data on this topic. Previous studies on obesity have shown that fat distribution provides a better definition of obesity than does body mass index (BMI) (4,5). AT is not homogeneous throughout the body, and different AT depots exhibit distinct characteristics that influence their functional roles and their impact on health. SAT is generally considered to be a metabolically benign depot, as it releases fatty acids slowly and is less prone to insulin resistance and inflammation than is VAT (16). VAT is considered to be a metabolically active and harmful depot, as it releases fatty acids rapidly and promotes insulin resistance, inflammation, and other metabolic disturbances (16). Computed tomography (CT) is considered the gold standard for measuring body composition and fat distribution by virtue of its high accuracy and reproducibility (5,17,18). Therefore, we

conducted CT-based abdominal fat measurements in overweight or obese women undergoing laparoscopic sleeve gastrectomy (LSG) to determine the correlations between AT and reproductive-related pituitary and ovarian hormones. The results of this study represent initial clinical data for understanding the underlying mechanisms of the population-specific and sex-specific effects of fat. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-1283/rc>).

Methods

This retrospective, single-center cross-sectional study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Yantai Yuhuangding Hospital (No. 2021-398). Individual consent for this retrospective analysis was waived.

Patients

Abdominal CT images were analyzed from the picture archiving and communication system (PACS) of Yantai Yuhuangding Hospital between January 2018 and July 2021. Overweight/obese women (BMI >25 kg/m²) who underwent LSG were screened for inclusion in the study. The hormone dataset that we analyzed were collected during the late follicular phase (239 sets out of 250 total sets; 3–7 days after cessation of menstruation), and a portion of the hormone data were collected at any time in the menstrual cycle in perimenopausal women (11 sets out of 250 total sets). Perimenopause refers to the period of a woman's life characterized by physiological changes associated with the end of reproductive capacity, terminating with the completion of menopause (19). An electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Basel, Switzerland) was used to analyze the serum hormone concentrations of the enrolled patients. The lower detection limit (specificity) of Roche analyzer (cobas e601) for hormone concentration was as follows: antimullerian hormone (AMH) =0.01 ng/mL, PRL =1 mIU/L, follicle-stimulating hormone (FSH) =0.1 mIU/mL, luteinizing hormone (LH) =0.1 mIU/mL, TEST =0.087 nmol/L, progesterone (PROG) =0.159 nmol/L, E2 =18.4 pmol/L. The exclusion criteria were a lack of available preoperative CT images free of artifacts; any congenital defects, endocrine diseases (metabolic syndrome, type II diabetes, hyperprolactinemia, infertility, or insulin

resistance status), or tumors; long-term medication (e.g., all any-time contraceptive/hormone replacement therapy users or current users); individuals with a history of drinking; and significant recent weight changes (more than 3% change in body weight over the previous 3 months). Based on the above criteria, 250 female obese or overweight (BMI >25 kg/m²) patients (Chinese Han women) were retrospectively enrolled in this study (Figure 1). The data collected for each participant included age, height, weight, BMI, waistline (the level of the umbilicus), hipline (the maximum circumference over the buttocks), and waist: hip ratio; the measured hormones were AMH, PRL, FSH, LH, TEST, PROG, and E2 (Table 1).

Fat measurement and calculation

Preoperative abdominal CT images were extracted and subsequently imported into ImageJ 1.51 software (National Institutes of Health, Bethesda, MD, USA) for analysis and measurement (Figure 2). The images at the level of the umbilicus were selected as the most representative of body fat mass according to a previous report (20). First, we drew a complete continuous line along the abdominal wall. Fat regions inside and outside of this line were classified as a subcutaneous fat area (SFA) or a visceral fat area (VFA), respectively, according to standard Hounsfield unit (HU) threshold ranges (–150 to –50). The SFA and VFA were then summed to determine the total fat area (TFA). Relative VFA (rVFA) was calculated by the following formula: $rVFA = (VFA/TFA) \times 100\%$. All measurements and calculations were conducted in a blinded manner by 2 well-trained radiologists (radiologist 1: 14 years of diagnostic radiology experience; radiologist 2: 16 years of diagnostic radiology experience). Within-group correlation coefficients were calculated separately for abdominal fat area-related variables to evaluate the reliability of the values measured by the 2 radiologists.

Statistical analysis

The Shapiro-Wilk test was used to test the normality of the data distribution, where $P > 0.05$ was taken to indicate a normal distribution. For continuous variables, data with a normal distribution are presented as the mean \pm standard deviation (SD) or otherwise as the median with interquartile range. The correlations among the parameters (serum hormone levels, abdominal fat area-related variables, and clinical characteristics) were examined using Spearman

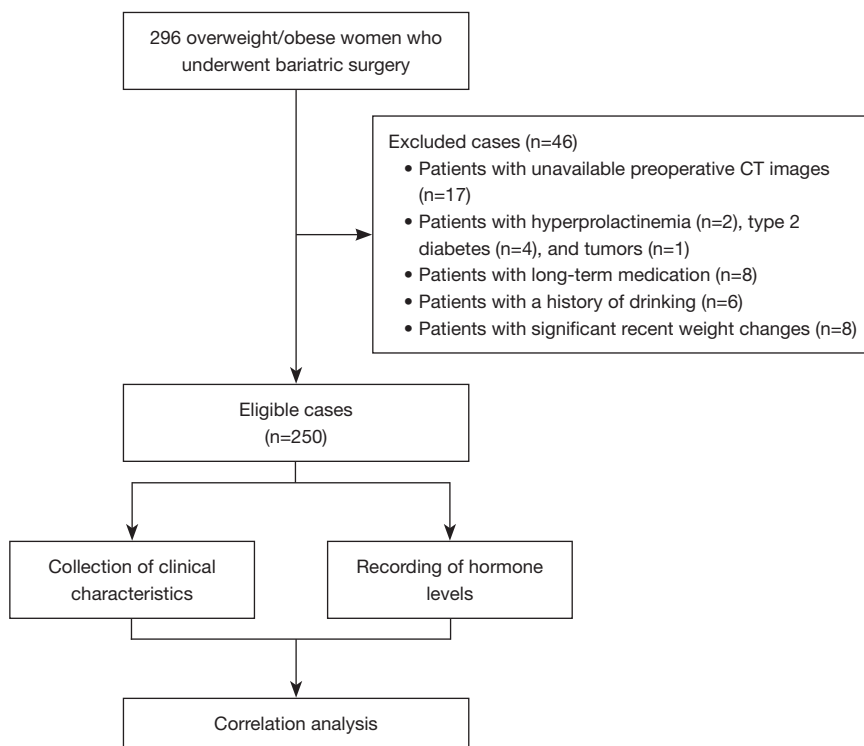


Figure 1 Flowchart of patient enrollment. CT, computed tomography.

correlation coefficient. After adjusting for age and BMI, we assessed the correlations between reproductive-related pituitary and ovarian hormones and abdominal fat area-related variables. Multiple linear regression analysis was performed after log and β -transformation $\{[(2^{\beta}) - 1] \times 100\}$ of the hormone levels and fat area-related variables.

All statistical analyses were performed using R v. 4.0.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria), and $P < 0.05$ was taken to indicate statistical significance.

Results

A total of 250 overweight or obese women with a mean age of 32.480 ± 7.490 years and a BMI of 38.508 ± 5.187 kg/m² were enrolled in this study. The age of the patients ranged from 15 to 58 years. The clinical characteristics of the participants are shown in *Table 1*.

Consistency of observers

The test-retest reliability was evaluated using an intraclass correlation coefficient (ICC). Interobserver agreement between the 2 radiologists was high for TFA (ICC = 0.997), VFA (ICC = 0.992), SFA (ICC = 0.995), and rVFA (ICC = 0.991). The results indicated that the evaluations from the 2 independent radiologists were highly consistent.

Analysis of the relations between clinical characteristics and serum reproductive-related pituitary and ovarian hormones and abdominal fat area-related variables

The variables negatively correlated with age were AMH ($r = -0.442$; $P < 0.001$), PRL ($r = -0.314$; $P < 0.001$), PROG ($r = -0.154$; $P = 0.015$), TEST ($r = -0.357$; $P < 0.001$), TFA ($r = -0.129$; $P = 0.042$), and SFA ($r = -0.205$; $P = 0.001$), while the variables positively correlated with age were FSH ($r = 0.249$; $P < 0.001$), VFA ($r = 0.147$; $P = 0.02$), and rVFA ($r = 0.272$;

Table 1 The clinical characteristics of overweight or obese women

Characteristics	Values
General features, mean \pm SD	
Age, year	32.480 \pm 7.490
Height, cm	164.772 \pm 5.263
Weight, kg	104.488 \pm 15.575
BMI, kg/m ²	38.508 \pm 5.187
Waistline, cm	114.060 \pm 12.217
Hipline, cm	122.659 \pm 10.535
Waist to hip ratio	0.929 \pm 0.073
Biological values, median (IQR)	
AMH, ng/mL	3.000 (1.820–4.880)
PRL, mIU/L	272.632 (185.076–387.600)
FSH, mIU/mL	5.650 (4.110–6.830)
LH, mIU/mL	6.720 (3.990–10.300)
PROG, nmol/L	0.509 (0.254–1.018)
E2, pmol/L	167.700 (111.385–275.947)
TEST, nmo/L	1.284 (0.850–1.770)
TFA, cm ²	648.521 (545.175–771.505)
VFA, cm ²	169.908 (137.933–203.762)
SFA, cm ²	482.541 (369.509–587.087)
rVFA, %	26.816 (21.401–32.356)

SD, standard deviation; BMI, body mass index; IQR, interquartile range; TFA, total fat area; VFA, visceral fat area; SFA, subcutaneous fat area; rVFA, relative VFA. Reference limits (follicular phase), Electrochemiluminescence (Elecys 2010, Roche Diagnostics, Basel, Switzerland) immunoassay. AMH, antimullerian hormone (0.89–9.85 ng/mL); PRL, prolactin (102.00–496.00 mIU/L); FSH, follicle-stimulating hormone (3.50–12.50 mIU/mL); LH, luteinizing hormone (2.40–12.60 mIU/mL); PROG, progesterone (0.181–2.840 nmol/L); E2, estradiol (45.40–854.00 pmol/L); TEST, testosterone (0.101–1.670 nmo/L).

$P < 0.001$) (Figure 3). BMI was negatively associated with PROG ($r = -0.166$; $P = 0.009$) and rVFA ($r = -0.295$; $P < 0.001$) but was positively associated with TFA ($r = 0.757$; $P < 0.001$), VFA ($r = 0.307$; $P < 0.001$), and SFA ($r = 0.706$; $P < 0.001$) (Figure 3 and Table S1).

Correlations between serum reproductive-related pituitary and ovarian hormones and abdominal fat area-related variables

Reproductive-related pituitary and ovarian hormones and fat area-related variables were log-transformed for inclusion into multiple linear regression models. VFA was inversely correlated with PROG ($r = -0.249$; $P < 0.001$) and E2 ($r = -0.229$; $P < 0.001$) and positively correlated with FSH ($r = 0.137$; $P = 0.03$). rVFA was positively correlated with FSH ($r = 0.133$; $P = 0.03$) and negatively correlated with PRL ($r = -0.184$; $P = 0.004$), PROG ($r = -0.144$; $P = 0.02$), and E2 ($r = -0.205$; $P = 0.001$) (Figure 4). After adjustment for age and BMI (Table 2), PRL was positively correlated with both TFA ($\beta = 0.045$; $P = 0.029$) and SFA ($\beta = 0.066$; $P = 0.023$), and PROG was negatively correlated with VFA ($\beta = -0.037$; $P = 0.002$) and rVFA ($\beta = -0.039$; $P = 0.002$). E2 was negatively correlated with both VFA ($\beta = -0.056$; $P = 0.005$) and rVFA ($\beta = -0.068$; $P = 0.001$) but was positively correlated with SFA ($\beta = 0.036$; $P = 0.042$); apart from these, no other correlations between other fat variables and hormones remained. Finally, β -transformation showed that TFA was increased by 3.1% [95% confidence interval (CI): 0.311–6.044%; $P = 0.029$] and that SFA was increased by 4.7% (95% CI: 0.633–8.929%; $P = 0.023$) with doubling of PRL concentration; VFA was reduced by 2.5% (95% CI: 0.928–4.115%; $P = 0.002$), and rVFA was reduced by 2.6% (95% CI: 0.956–4.287%; $P = 0.002$) with doubling of PROG concentration; VFA was reduced by 3.8% (95% CI: 1.184–6.407%; $P = 0.005$), rVFA was reduced by 4.6% (95% CI: 1.879–7.269%; $P = 0.001$), and SFA was increased by 2.5% (95% CI: 0.090–5.055%; $P = 0.042$) with doubling of E2 concentration (Table 2).

Discussion

In this study, we examined reproduction-related pituitary and ovarian hormones in relation to fat area-associated variables in overweight or obese women. VFA showed a negative relationship with PROG and E2, and SFA was positively associated with PRL and E2. The visceral and subcutaneous fat types exhibited wide variability in their correlation with reproductive-related pituitary and ovarian hormones.

The increasing prevalence of obesity has become

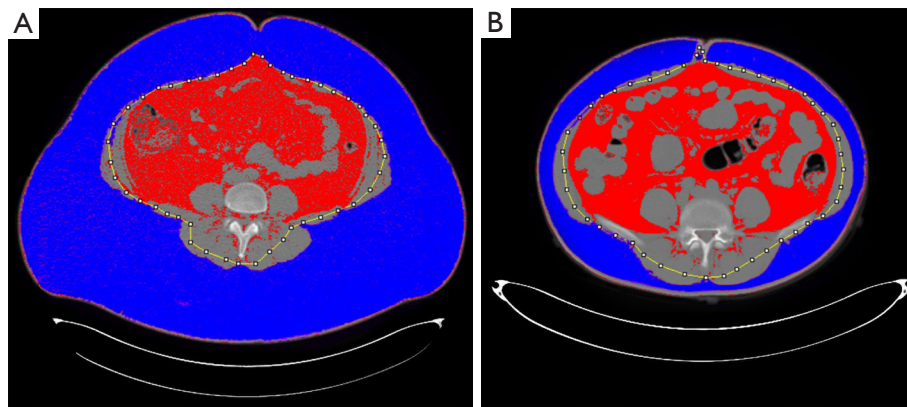


Figure 2 Fat measurements on CT images. Blue area: SFA; red area: VFA; yellow line: a linear structure drawn along the abdominal skeletal muscle. (A) CT image of a 32-year-old woman with a rVFA of 22.9% and a BMI of 48.9 kg/m². (B) CT image of a 43-year-old woman with a rVFA of 55.2% and a BMI of 32.0 kg/m². CT, computed tomography; SFA, subcutaneous fat area; VFA, visceral fat area; rVFA, relative visceral fat area; BMI, body mass index.

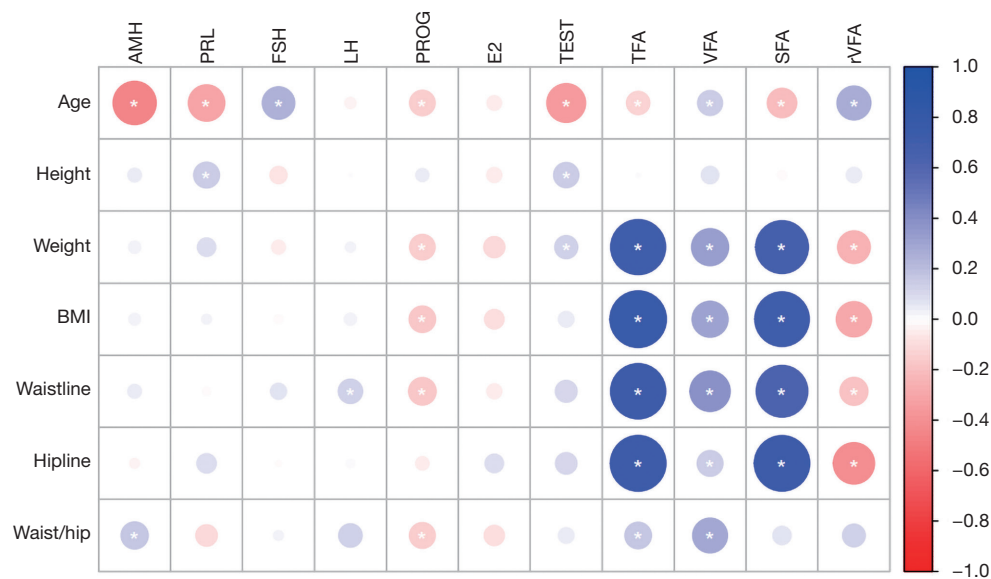


Figure 3 The correlation of general characterizations with reproductive-related pituitary and ovarian hormones and abdominal fat area-related variables. Circles with “*” represent a significant difference ($P < 0.05$). A blue color indicates a positive correlation, and a red color indicates a negative correlation (the circle size indicates the absolute value of the correlation coefficient, with the color representing the direction and degree of correlation). AMH, antimüllerian hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PROG, progesterone; E2, estradiol; TEST, testosterone; TFA, total fat area; VFA, visceral fat area; SFA, subcutaneous fat area; rVFA, relative VFA; BMI, body mass index.

a global health problem (1,2). It was found that PRL release was enhanced in proportion to excess visceral fat in obese women, and this may be attributable to the lack of dopamine D2 receptor (D2R)-binding sites in their brain, which is the main inhibitory factor for pituitary PRL

release (7). In this study, we found that PRL concentration was positively correlated with SFA; meanwhile, VFA and the concentration reduction of PROG and E2 also had positive correlation coefficients. Therefore, it appears that the possible synergistic effects between these hormones

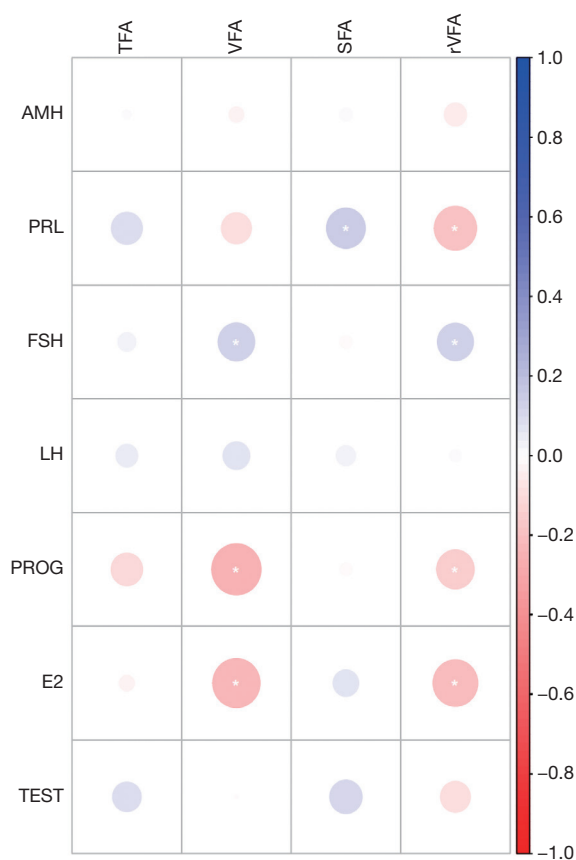


Figure 4 The association between reproductive-related pituitary and ovarian hormones and abdominal fat area-related variables. Circles with “*” represent a significant difference ($P < 0.05$). A blue color indicates a positive correlation, and a red color indicates a negative correlation (the circle size indicates the absolute value of the correlation coefficient, and the color indicates the direction and degree of correlation). AMH, antimüllerian hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PROG, progesterone; E2, estradiol; TEST, testosterone; TFA, total fat area; VFA, visceral fat area; SFA, subcutaneous fat area; rVFA, relative VFA.

may be a nonnegligible contributor to fat distribution. For females, endocrine or metabolic disorders associated with obesity may also have adverse effects on fertility (21). Increasing evidence suggests that the outcomes in women are different before and after menopause (6,22). The effect of being obesity or overweight on breast cancer incidence differs before and after menopause (22). Other research has shown that postmenopausal women have an increased risk of breast cancer, and the risk is more significant among postmenopausal women not receiving hormone therapy (22).

An analysis of 5,373 women from China aged ≥ 40 years suggested that the risk of visceral obesity may be higher in postmenopausal than in premenopausal women (23). Taken together, it is important to identify the hormones associated with fat distribution to explore both obesity-specific mechanisms and therapeutic interventions.

A recent multicenter study showed that increased BMI was related to a reduction of AMH (24); however, there have also been contradictory reports. Gorkem *et al.* found no significant differences in ovarian reserve parameters between groups with differences in BMI (25). The impact of obesity on ovarian reserve remains inconclusive based on current evidence. Indeed, we did not detect any associations between fat area-related variables and AMH in the present study. In addition, BMI does not accurately reflect the distribution of accumulated fat, and fat distribution has been shown to be more predictive of obesity-related disorders than has BMI (4,5). One study reported that visceral fat accumulation, but not BMI, was associated with cardiovascular disease (CVD) in individuals with type II diabetes (26). Another study in adolescents concluded that a high level of AT or stored fat in midadolescence is associated with a high risk of arterial stiffness, while BMI indicates no such predictive capability (27). The fat distribution pattern varies across sexes, age groups, and races (28). Women tend to accumulate more subcutaneous fat, while men store more visceral fat. Notably, individual fat distribution varies continuously with age throughout life (29), and BMI does not accurately describe all of these changes. Therefore, we examined obesity-related reproductive pituitary and ovarian hormones using CT-based abdominal fat area measurements. Our results provided insights into the sex-specific effects of obesity.

As mentioned above, we found that increased VFA was associated with decreased concentrations of E2 and PROG in overweight or obese women. Furthermore, these relationships persisted after adjusting for potential confounders, such as age and BMI. Additionally, there is also increasing evidence that obesity affects ovarian function (13). This may be a result of ovarian inflammation due to obesity (13). Conversely, in a study by Frank *et al.*, estrogen was found to affect the pattern of adipocyte tissue distribution and facilitate the accumulation of visceral fat in menopausal women (30). In the present study, this inverse association between visceral fat and E2/PROG persisted even with the inclusion of all age groups. This point is especially important for premenopausal women. The accumulation of visceral fat will precipitate a cascade

Table 2 The association between serum ovarian hormone levels and abdominal fat area-related variables after adjustment for age and BMI

Analysis	Fat variables	Parameter	AMH	PRL	FSH	LH	PROG	E2	TEST
Multiple linear regression analysis	TFA	β	-0.009	0.045	0.006	0.005	0.001	0.012	0.015
		P	0.516	0.029*	0.739	0.697	0.843	0.348	0.421
		Low	-0.035	0.004	-0.031	-0.022	-0.013	-0.013	-0.022
		Up	0.018	0.085	0.044	0.033	0.016	0.036	0.052
	VFA	β	0.021	-0.001	0.042	0.018	-0.037	-0.056	0.000
		P	0.349	0.968	0.172	0.417	0.002*	0.005*	0.988
		Low	-0.023	-0.067	-0.018	-0.026	-0.061	-0.096	-0.061
		Up	0.064	0.064	0.102	0.063	-0.013	-0.017	0.060
	SFA	β	-0.020	0.066	-0.004	0.003	0.014	0.036	0.027
		P	0.307	0.023*	0.893	0.890	0.194	0.042*	0.310
		Low	-0.059	0.009	-0.057	-0.037	-0.007	0.001	-0.026
		Up	0.019	0.123	0.050	0.042	0.035	0.071	0.080
	rVFA	β	0.030	-0.046	0.036	0.013	-0.039	-0.068	-0.016
		P	0.211	0.185	0.268	0.586	0.002*	0.001*	0.623
		Low	-0.017	-0.114	-0.028	-0.034	-0.063	-0.109	-0.079
		Up	0.076	0.022	0.099	0.059	-0.014	-0.027	0.047
β transformation	TFA	β	-0.608	3.138	0.441	0.379	0.104	0.819	1.062
		P	0.516	0.029*	0.739	0.697	0.843	0.348	0.421
		Low	-2.425	0.311	-2.136	-1.524	-0.925	-0.889	-1.513
		Up	1.243	6.044	3.086	2.319	1.144	2.556	3.705
	VFA	β	1.447	-0.091	2.946	1.281	-2.535	-3.831	-0.031
		P	0.349	0.968	0.172	0.417	0.002*	0.005*	0.988
		Low	-1.570	-4.511	-1.264	-1.794	-4.115	-6.407	-4.112
		Up	4.557	4.533	7.336	4.452	-0.928	-1.184	4.223
	SFA	β	-1.388	4.699	-0.254	0.193	0.975	2.543	1.917
		P	0.307	0.023*	0.893	0.890	0.194	0.042*	0.310
		Low	-4.007	0.633	-3.885	-2.506	-0.497	0.090	-1.765
		Up	1.302	8.929	3.515	2.967	2.470	5.055	5.737
	rVFA	β	2.068	-3.131	2.494	0.898	-2.636	-4.612	-1.082
		P	0.211	0.185	0.268	0.586	0.002*	0.001*	0.623
		Low	-1.165	-7.594	-1.893	-2.306	-4.287	-7.269	-5.300
		Up	5.406	1.547	7.077	4.208	-0.956	-1.879	3.324

P<0.05 is indicated by asterisk (*). The percent difference was calculated by the following formula: $[(2^{\beta}) - 1] \times 100$, where β is the coefficient from linear regression models in which both the abdominal fat area-related variables and ovarian hormone levels were natural log-transformed. Models were adjusted for age (continuous) and BMI (continuous). BMI, body mass index; AMH, antimullerian hormone; PRL, prolactin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PROG, progesterone; E2, estradiol; TEST, testosterone; TFA, total fat area; VFA, visceral fat area; SFA, subcutaneous fat area; rVFA, relative VFA; low, lower 95% confidence interval; up, upper 95% confidence interval.

of complex endocrine changes or even infertility. One animal experimental study showed that obesity caused by a high-fat diet could promote the development and loss of ovarian follicles, which could further contribute to premature ovarian failure (POF) (31). In addition, there is evidence that PCOS is related to VAT (32). Adipokines and inflammatory cytokines produced by adipocytes are involved in several physiological processes, including inflammatory reactions (33). As mentioned above, chronic inflammation was shown to degrade the quality of oocytes (13). Therefore, the impact of visceral fat on fertility should not be underestimated in women of childbearing age. Our findings not only shed light on the relationship between visceral fat and E2 or PROG but also quantifies these changes. It is important to focus on the variation of visceral fat for women desiring bariatric surgery or other avenues to lose weight. Modest weight loss can generate a preferential loss of VAT, but with greater weight loss, this effect may be attenuated (34). In other words, weight loss progression should also ensure the loss of visceral fat to reduce inflammation (and thus create a good environment for ovarian health). Our results could help develop more personalized intervention strategies for overweight or obese women. By closely observing and quantifying visceral fat and hormone levels, it would be possible to formulate a rational, scientific method for weight loss that also benefits the ovaries.

Recent studies have clearly shown that there are functional discrepancies between visceral fat and subcutaneous fat (35). In comparison with visceral fat, subcutaneous fat shows a poor correlation with aberrant metabolism (35). An experimental study in mice showed that fibroblast growth factor 21 (FGF21) can improve insulin resistance by increasing the accumulation of subcutaneous fat (36). Such a mechanism is likely to be relevant to subcutaneous fat-mediated adiponectin release (36). In addition, there is a well-known inverse relationship between adiponectin and insulin resistance (37). In one animal study, inflammation was less prominent in subcutaneous fat relative to visceral fat, which may be attributable to the increased expression of the protein inhibitor of activated STAT 1 (PIAS1) in subcutaneous fat (38). However, the precise role of subcutaneous fat is controversial. It was also reported that people with more subcutaneous fat do not exhibit more dyslipidemia and inflammation (39). Although the possible beneficial effect of subcutaneous fat remains controversial, it is clear that its mechanisms differ from those of visceral fat. The level of α -2A adrenergic receptors

in subcutaneous fat could be increased by increasing estrogen-mediated ER α , while the lipolytic response could be suppressed by increasing α -2A adrenergic receptors (40). These observations suggest that there may be positive feedback between estrogen and subcutaneous fat, speculation which was supported by findings of the present study. Moreover, we found that FSH levels are weakly positively correlated with VFA, meaning that as FSH levels increase, so does the VFA. The exact mechanism behind this correlation is not yet fully understood, but it is thought to be related to the fact that FSH receptors are present in AT, including visceral fat, as indicated in an animal study (41). One theory is that FSH may stimulate adipogenesis, the process by which new fat cells are formed, in visceral fat. Another theory is that FSH may affect the expression of genes involved in lipid metabolism, leading to an increase in visceral fat accumulation in women during menopause (42). Nevertheless, the correlation between FSH and visceral fat is weak. We hope that the slope of the linear relationship between AT and reproductive-related pituitary and ovarian hormones presented will provide the basis for further studies aimed at clarifying the mechanism behind this association.

This study had some limitations. First, we recruited only overweight or obese women with available abdominal CT images, not all women. Second, the days of the follicular phase during which the hormones were measured were not accurately recorded, and the results could not be fully applied to postmenopausal women. A more standardized approach would have involved measuring the hormone levels at days 1–3 during the cycle, when the menstrual cycle-related hormones are more stable. In addition, we employed a single-center, retrospective study design, and a center-specific effect was unavoidable. Finally, postoperative recovery results were not analyzed because the long-term postoperative follow-up is still underway. Overall, we believe that this exploration of quantitative relationships is productive for further exploring their associations.

Conclusions

The results of the present study reveal an association between reproduction-related pituitary and ovarian hormones and abdominal fat area-related variables, with this relation being quantifiable to a degree. VFA is inversely associated with PROG and E2, while SFA is positively correlated with PRL and E2. The close monitoring of the gradual changes in fat mass and reproduction-related

pituitary and ovarian hormones is important for overweight or obese women. Further research is needed to elucidate the potential underlying mechanisms related to sex stratification and individualized fat quantification.

Acknowledgments

Funding: This work was supported by the China Postdoctoral Science Foundation (No. 2018M642670) and the Yantai Science and Technology Innovation Project (No. 2023YD002).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-22-1283/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-1283/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective, single-center cross-sectional study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Yantai Yuhuangding Hospital (No. 2021-398). Individual consent for this retrospective analysis was waived.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- World Health Organization. Obesity and overweight. WHO 2021; June 9. Available online: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- Sung H, Siegel RL, Torre LA, Pearson-Stuttard J, Islami F, Fedewa SA, Goding Sauer A, Shuval K, Gapstur SM, Jacobs EJ, Giovannucci EL, Jemal A. Global patterns in excess body weight and the associated cancer burden. *CA Cancer J Clin* 2019;69:88-112.
- Daghestani MH, Daghestani MH, Warsy A, El-Ansary A, Omair MA, Omair MA, Hassen LM, Alhumaidhi EM, Al Qahtani B, Harrath AH. Adverse Effects of Selected Markers on the Metabolic and Endocrine Profiles of Obese Women With and Without PCOS. *Front Endocrinol (Lausanne)* 2021;12:665446.
- Guo H, Zhao W, Wang A, Li M, Ma H, Wang F, Wang Q, Ba X. The value of sex-specific abdominal visceral fat as measured via CT as a predictor of clear renal cell carcinoma T stage. *Adipocyte* 2021;10:285-92.
- Nguyen GK, Mellnick VM, Yim AK, Salter A, Ippolito JE. Synergy of Sex Differences in Visceral Fat Measured with CT and Tumor Metabolism Helps Predict Overall Survival in Patients with Renal Cell Carcinoma. *Radiology* 2018;287:884-92.
- Veldhuis-Vlug AG, Woods GN, Sigurdsson S, Ewing SK, Le PT, Hue TF, Vittinghoff E, Xu K, Gudnason V, Sigurdsson G, Kado DM, Eiriksdottir G, Harris T, Schafer AL, Li X, Zaidi M, Rosen CJ, Schwartz AV. Serum FSH Is Associated With BMD, Bone Marrow Adiposity, and Body Composition in the AGES-Reykjavik Study of Older Adults. *J Clin Endocrinol Metab* 2021;106:e1156-69.
- Kok P, Roelfsema F, Frölich M, Meinders AE, Pijl H. Prolactin release is enhanced in proportion to excess visceral fat in obese women. *J Clin Endocrinol Metab* 2004;89:4445-9.
- Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. *Hum Reprod Update* 2017;23:300-21.
- Dudek JE, Białaszek W, Gabriel M. Quality of life, its factors, and sociodemographic characteristics of Polish women with lipedema. *BMC Womens Health* 2021;21:27.
- Chella Krishnan K, Vergnes L, Acín-Pérez R, Stiles L, Shum M, Ma L, Mouisel E, Pan C, Moore TM, Péterfy M, Romanoski CE, Reue K, Björkegren JLM, Laakso M, Liesa M, Lusis AJ. Sex-specific genetic regulation of adipose mitochondria and metabolic syndrome by Ndufv2. *Nat Metab* 2021;3:1552-68.
- Asghari A, Ishikawa T, Hiramitsu S, Lee WR, Umetani J, Bui L, Korach KS, Umetani M. 27-Hydroxycholesterol Promotes Adiposity and Mimics Adipogenic Diet-Induced Inflammatory Signaling. *Endocrinology* 2019;160:2485-94.
- Lim CL, Or YZ, Ong Z, Chung HH, Hayashi H, Shrestha

- S, Chiba S, Lin F, Lin VCL. Estrogen exacerbates mammary involution through neutrophil-dependent and -independent mechanism. *Elife* 2020;9:e57274.
13. Snider AP, Wood JR. Obesity induces ovarian inflammation and reduces oocyte quality. *Reproduction* 2019;158:R79-90.
 14. Perovic Blagojevic IM, Vekic JZ, Macut DP, Ignjatovic SD, Miljkovic-Trailovic MM, Zeljkovic AR, Spasojevic-Kalimanovska VV, Bozic-Antic IB, Bjekic-Macut JD, Kastratovic-Kotlica BA, Andric ZG, Ilic DS, Kotur-Stevuljevic JM. Overweight and obesity in polycystic ovary syndrome: association with inflammation, oxidative stress and dyslipidaemia. *Br J Nutr* 2022;128:604-12.
 15. Childs GV, Odle AK, MacNicol MC, MacNicol AM. The Importance of Leptin to Reproduction. *Endocrinology* 2021;162:bqaa204.
 16. Schoettl T, Fischer IP, Ussar S. Heterogeneity of adipose tissue in development and metabolic function. *J Exp Biol* 2018;221:jeb162958.
 17. Zaffina C, Wyttenbach R, Pagnamenta A, Grasso RF, Birolì M, Del Grande F, Rizzo S. Body composition assessment: comparison of quantitative values between magnetic resonance imaging and computed tomography. *Quant Imaging Med Surg* 2022;12:1450-66.
 18. Greco F, Mallio CA. Artificial intelligence and abdominal adipose tissue analysis: a literature review. *Quant Imaging Med Surg* 2021;11:4461-74.
 19. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97:1159-68.
 20. Kobayashi J, Tadokoro N, Watanabe M, Shinomiya M. A novel method of measuring intra-abdominal fat volume using helical computed tomography. *Int J Obes Relat Metab Disord* 2002;26:398-402.
 21. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril* 2017;107:840-7.
 22. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *CA Cancer J Clin* 2017;67:378-97.
 23. Chen X, Xi H, Ji L, Liu W, Shi F, Chen Y, Wang X, Zhang W, Sui X, Wang X, Zhang H, Liu H, Li D. Relationships between menstrual status and obesity phenotypes in women: a cross-sectional study in northern China. *BMC Endocr Disord* 2020;20:91.
 24. Jaswa EG, Rios JS, Cedars MI, Santoro NF, Pavone MEG, Legro RS, Huddleston HG. Increased Body Mass Index Is Associated With A Nondilutional Reduction in Antimüllerian Hormone. *J Clin Endocrinol Metab* 2020;105:3234-42.
 25. Gorkem U, Kucukler FK, Togrul C, Gulen Ş. Obesity Does not Compromise Ovarian Reserve Markers in Infertile Women. *Geburtshilfe Frauenheilkd* 2019;79:79-85.
 26. Fukuda T, Bouchi R, Takeuchi T, Nakano Y, Murakami M, Minami I, Izumiyama H, Hashimoto K, Yoshimoto T, Ogawa Y. Ratio of visceral-to-subcutaneous fat area predicts cardiovascular events in patients with type 2 diabetes. *J Diabetes Investig* 2018;9:396-402.
 27. Dangardt F, Charakida M, Georgiopoulos G, Chiesa ST, Rapala A, Wade KH, Hughes AD, Timpson NJ, Pateras K, Finer N, Sattar N, Davey Smith G, Lawlor DA, Deanfield JE. Association between fat mass through adolescence and arterial stiffness: a population-based study from The Avon Longitudinal Study of Parents and Children. *Lancet Child Adolesc Health* 2019;3:474-81.
 28. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, Ravussin E, Ryan DH, Smith SR, Katzmarzyk PT. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. *Obesity (Silver Spring)* 2011;19:402-8.
 29. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. *Ageing Res Rev* 2009;8:339-48.
 30. Frank AP, de Souza Santos R, Palmer BF, Clegg DJ. Determinants of body fat distribution in humans may provide insight about obesity-related health risks. *J Lipid Res* 2019;60:1710-9.
 31. Wang N, Luo LL, Xu JJ, Xu MY, Zhang XM, Zhou XL, Liu WJ, Fu YC. Obesity accelerates ovarian follicle development and follicle loss in rats. *Metabolism* 2014;63:94-103.
 32. Kałużna M, Człapka-Matyasik M, Wachowiak-Ochmańska K, Moczko J, Kaczmarek J, Janicki A, Piątek K, Ruchała M, Ziemnicka K. Effect of Central Obesity and Hyperandrogenism on Selected Inflammatory Markers in Patients with PCOS: A WHtR-Matched Case-Control Study. *J Clin Med* 2020;9:3024.
 33. Santoni M, Cimadamore A, Massari F, Piva F, Aurilio G, Martignetti A, Scarpelli M, Di Nunno V, Gatto L, Battelli N, Cheng L, Lopez-Beltran A, Montironi R. Key Role of Obesity in Genitourinary Tumors with Emphasis on Urothelial and Prostate Cancers. *Cancers (Basel)*

- 2019;11:1225.
34. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. *Int J Obes (Lond)* 2008;32:619-28.
 35. Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. *Int J Obes (Lond)* 2017;41:672-82.
 36. Li H, Wu G, Fang Q, Zhang M, Hui X, Sheng B, Wu L, Bao Y, Li P, Xu A, Jia W. Fibroblast growth factor 21 increases insulin sensitivity through specific expansion of subcutaneous fat. *Nat Commun* 2018;9:272.
 37. Yanai H, Yoshida H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. *Int J Mol Sci* 2019;20:1190.
 38. Liu Y, Ge X, Dou X, Guo L, Liu Y, Zhou SR, Wei XB, Qian SW, Huang HY, Xu CJ, Jia WP, Dang YJ, Li X, Tang QQ. Protein Inhibitor of Activated STAT 1 (PIAS1) Protects Against Obesity-Induced Insulin Resistance by Inhibiting Inflammation Cascade in Adipose Tissue. *Diabetes* 2015;64:4061-74.
 39. Daily JW, Yang HJ, Liu M, Kim MJ, Park S. Subcutaneous fat mass is associated with genetic risk scores related to proinflammatory cytokine signaling and interact with physical activity in middle-aged obese adults. *Nutr Metab (Lond)* 2019;16:75.
 40. Pedersen SB, Kristensen K, Hermann PA, Katzenellenbogen JA, Richelsen B. Estrogen controls lipolysis by up-regulating alpha2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor alpha. Implications for the female fat distribution. *J Clin Endocrinol Metab* 2004;89:1869-78.
 41. Liu P, Ji Y, Yuen T, Rendina-Ruedy E, DeMambro VE, Dhawan S, et al. Blocking FSH induces thermogenic adipose tissue and reduces body fat. *Nature* 2017;546:107-12.
 42. Mao L, Wang L, Bennett S, Xu J, Zou J. Effects of follicle-stimulating hormone on fat metabolism and cognitive impairment in women during menopause. *Front Physiol* 2022;13:1043237.

Cite this article as: Guo H, Yang B, Kiryu S, Wang Q, Yu D, Sun Z, Chen Y, Li X, Wang F, Ba X. Evaluation of the relations between reproduction-related pituitary and ovarian hormones and abdominal fat area-related variables determined with computed tomography in overweight or obese women who have undergone bariatric surgery: a cross-sectional study. *Quant Imaging Med Surg* 2023;13(10):7065-7076. doi: 10.21037/qims-22-1283