research article

Relationship between sex hormones levels and ^{18}F-FDG uptake by the ovaries in premenopausal woman

Tae Hee Kim[1], Mi Ran Kim[2],Yongsik Jung[3], Young-Sil An[4]

[1] Department forRadiology, Ajou University School of Medicine, South Korea
[2] Department of Obstetrics and Gynecology, Ajou University School of Medicine, South Korea
[3] Department of Surgery, Ajou University School of Medicine, South Korea
[4] Department of Nuclear Medicine and Molecular Imaging, Ajou University School of Medicine, South Korea

Received 30 April 2019
Accepted 17 July 2019

Correspondence to: Young-Sil An MD, PhD.,Department of Nuclear Medicine and Molecular Imaging, Ajou University School of Medicine, Worldcup-ro 164, Yongtong-gu, Suwon, Gyeonggi-do, 16499, South Korea, Phone: 82-31-219-5947; Fax: 82-31-219-5950; E-mail: aysays77@naver.com

Disclosure: No potential conflicts of interest were disclosed.

Background. The study was conducted to evaluate the effect of sex hormones on F-18 fluorodeoxyglucose (^{18}F-FDG) uptake by normal ovaries.

Patients and methods. A total of 197 premenopausal women were included in this study. Based on ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) images obtained from these subjects, the association of ovarian ^{18}F-FDG uptake with levels of sex hormones, including estradiol, progesterone, testosterone, follicle-stimulating hormone, and luteinizing hormone was investigated. We also analysed the relationship between the menstrual cycle and ovarian ^{18}F-FDG uptake.

Results. The highest ovarian ^{18}F-FDG uptake occurred at 2 weeks after the onset of menstruation (median maximum standardized uptake value [SUVmax] = 3.40, median mean SUV [SUVmean] = 2.20), and the lowest ovarian ^{18}F-FDG uptake was observed during the first week of the menstrual cycle (median SUVmax = 1.60, median SUVmean = 1.20). Ovarian ^{18}F-FDG uptake was weakly positively correlated with progesterone levels (*rho* = 0.28, $p < 0.001$ for SUVmax, *rho* = 0.30, $p < 0.001$ for SUVmean), and this pattern was consistently observed in subjects in the follicular-phase group (*rho* = 0.29, $p = 0.003$ for both SUVmax and SUVmean) but not in subjects in the luteal-phase group.

Conclusions. Based on PET images, ovarian glucose metabolism in premenopausal women tended to increase slightly with increasing progesterone concentration.

Key words: ovary; fluorodeoxyglucose F18; positron-emission tomography; gonadal steroid hormones

Introduction

^{18}F-FDG PET, which utilizes a radiolabeled analogue of glucose, is widely used clinically in patients with cancer to evaluate staging and the therapeutic response.[1] However, ^{18}F-FDG uptake may be high not only in malignant lesions but also in normal tissues.[2-4] High uptake of ^{18}F-FDG in the pelvic region of women, particularly by the ovaries, can be confusing for nuclear-medicine physicians interpreting PET images.

The ovary is a major reproductive organ characterized by cyclic changes in sex hormones, which are believed to affect the degree of ^{18}F-FDG uptake by the ovary. Ovarian ^{18}F-FDG uptake is typically negligible in postmenopausal women[5,6]; if incidental ovarian ^{18}F-FDG uptake is found on PET, the possibility of a malignant lesion is sufficiently high to recommend further evaluation by magnetic resonance imaging (MRI) or ultrasonography.

However, in premenopausal women, ovarian ^{18}F-FDG uptake occurs even under normal or be-

nign conditions such as a follicular ovarian cyst or hemorrhagic corpora lutea.[7] Therefore, in daily practice, nuclear-medicine physicians do not routinely recommend further radiographic evaluation in the event of ovarian ^{18}F-FDG uptake. This makes it difficult to draw conclusions about ovarian ^{18}F-FDG uptake in premenopausal women. We investigated physiological ovarian ^{18}F-FDG uptake, since previous studies on ovarian ^{18}F-FDG uptake in premenopausal women are limited and most focused on the degree of change in ^{18}F-FDG uptake during the menstrual cycle.[5,6,8,9] Furthermore, how sex hormones affect this uptake has not been clearly determined.

The purpose of this study was to investigate the relationship between sex hormones levels and ^{18}F-FDG uptake by ovaries in premenopausal woman.

Patients and methods

Patients

This study included 197 premenopausal women (median age, 44 years) who were diagnosed with breast cancer between March 2015 and July 2017 and underwent ^{18}F-FDG PET/CT to determine pretreatment status, as well as sex-hormone assays (including estradiol, progesterone, testosterone, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). Hormone assays were performed on the same day as PET. The date of the last normal menstrual period (LNMP) of all patients was also recorded and used to divide the women into two groups based on their menstrual phase on the day of the tests: a follicular-phase group (days 1–13) and a luteal-phase group (days 14–31). We also noted how many weeks had elapsed since the date of onset of menstruation. Patients were excluded if they had a history of ovarian disease, sex hormone therapy or an irregular menstrual cycle of more than 31 days.[10]

The clinical design of this retrospective study was approved by the Institutional Review Board of Ajou University (AJIRB-MED-OBS-18-354). The need for informed consent was waived.

^{18}F-FDG PET/CT protocol

After fasting for at least 6 hours, patients were administered 5 MBq/kg ^{18}F-FDG intravenously. The blood glucose level at the time of the ^{18}F-FDG injection was < 8.3 mmol/L in all patients. Patients were instructed to rest comfortably for 60 min, and to urinate before the scan. Whole-body PET/CT images were obtained with a Discovery ST 8 slice CT scanner or Discovery STE 16 slice CT scanner (GE Healthcare, Milwaukee, WI, USA). Seven or eight frames (3 min/frame) of PET emission data were acquired in three-dimensional mode after a noncontrast CT scan from the base of the skull to the upper thigh (120 kV, 30–100 mA in the AutomA mode; section width = 3.75 mm). Emission PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with two iterations and 20 subsets; field of view = 600 mm, slice thickness = 3.27 mm) and attenuation was corrected with noncontrast CT.

Image analysis

A nuclear-medicine specialist with 13 years of PET experience, blinded to the clinical data, reviewed the ^{18}F-FDG PET/CT images on an AW workstation (version 4.4; General Electric Healthcare, Chicago, IL, USA). The volume of interest (VOI) was placed on the ovarian area showing higher ^{18}F-FDG uptake than the background activity on the PET image. If there was no PET uptake, the VOI was drawn on the right and left ovarian areas on the CT image. The SUVmax and SUVmean were calculated from these VOIs based on injected dose and body weight. The higher values of the right and left ovarian SUVs were used for the statistical analysis.

Statistical analysis

All statistical analyses were done using MedCalc Statistical Software (ver. 18.5; MedCalc Software bvba, Ostend, Belgium). First, we calculated the required sample size. A significance (a) level of 5% and statistical power (1 − b) of 80 % were considered acceptable for the purposes of the study. A sample size of 145 patients was required to attain an appropriate confidence range; thus, the obtained sample size (N = 197 patients) was sufficient for the statistical analysis.

The Kolmogorov–Smirnov test was used to assess whether the data were normally distributed. None of the data followed a normal distribution, so they are presented as medians and interquartile range (IQR). The Mann–Whitney test was used to compare groups distinguished based on the menstrual phase. The Kruskal–Wallis test was used to compare ovarian ^{18}F-FDG uptake among groups distinguished based on weeks since onset of menstruation. If the Kruskal–Wallis test was significant, a post-hoc analysis was performed for pairwise

TABLE 1. Patient characteristics

	Menstrual phase on test day		Total	p-value
	Follicular phase	Luteal phase		
Number of patients, n (%)	100 (50.8)	97 (49.2)	197 (100)	
Age, years	45 (42–47)	44 (38–47)	44 (40–47)	0.150
Sex hormone levels				
Estradiol, pg/ml	125 (76–176)	150 (84–182)	126 (81–179)	0.292
Progesterone, ng/ml	1.62 (1.26–2.53)	12.30 (3.85–18.95)	2.71 (1.42–12.11)	< 0.001*
Testosterone, ng/ml	0.34 (0.21–0.52)	0.37 (0.23–0.51)	0.36 (0.23–0.51)	0.342
FSH, mIU/ml	5.7 (3.9–8.1)	2.9 (1.7–4.1)	3.7 (2.4–6.1)	< 0.001*
LH, mIU/ml	5.9 (2.9–8.6)	3.6 (2.5–6.6)	4.6 (2.7–7.8)	0.105
SUVmax of ovary	1.70 (0–2.70)	2.10 (1.50–3.63)	2.00 (0–3.23)	0.030*
SUVmean of ovary	1.30 (0-1.85)	1.60 (0.9–2.40)	1.40 (0–2.10)	0.015*

All continuous variables are shown as medians (interquartile range). *p-value < 0.05

FSH = follicular-stimulating hormone; LH = luteinizing hormone; SUVmax = maximum standardized uptake value; SUVmean = mean standardized uptake value

comparisons of the subgroups. Spearman's rank coefficient correlation test was used to examine the correlations between the ovary SUVs and levels of sex hormones. Correlations were classified as very weak ($|rho| < 0.20$), weak ($|rho| = 0.20–0.39$), moderate ($|rho| = 0.40–0.59$), strong ($|rho| = 0.60–0.79$), or very strong ($|rho| \geq 0.80$).[11] All P values < 0.05 were considered significant.

Results

Of all patients, 100 (50.8%) underwent ^{18}F-FDG PET in the follicular phase and 97 (49.2%) in the luteal phase. Progesterone levels were significantly higher in the luteal-phase group than in the follicular-phase group (12.30 vs. 1.62 nmol/L, $p < 0.001$) and FSH was significantly higher in the follicular-phase group than in the luteal-phase group (5.7 vs. 2.9 mIU/mL, $p < 0.001$). Age, and the levels of all other sex hormones measured (estradiol, testosterone, and LH), did not differ significantly between the two groups. The median SUVmax and SUVmean values of the ovaries in all subjects were 2.00 and 1.40, respectively, and these values were significantly higher in the luteal-phase group than in the follicular-phase group (2.10 vs. 1.70, $p = 0.030$ for SUVmax, 1.60 vs. 1.30, $p = 0.015$ for SUVmean). The patient characteristics are summarized in detail in Table 1.

In total, 71, 45, 53, and 28 subjects were tested at 1, 2, 3 and 4 weeks after the onset of menstruation, respectively, and the degree of ^{18}F-FDG uptake by the ovaries differed significantly among these groups ($p < 0.001$ for both SUVmax and SUVmean). Post-hoc analysis showed that the group with the highest ^{18}F-FDG uptake was the group tested 2 weeks after the onset of menstruation (median SUVmax = 3.40 [IQR 2.00–4.93], median SUVmean = 2.20 [IQR 1.50–3.13]), and SUV values in this group were significantly higher than those in all other groups. The lowest levels of ovarian ^{18}F-FDG uptake were observed in the group tested at 1 week after the onset of menstruation; the SUV values (median SUVmax = 1.60 [IQR 0–2.18], median SUVmean = 1.20 [IQR 0–1.50]) of this group were significantly lower than those of the other groups, except those tested at 4 weeks after the onset of menstruation. ^{18}F-FDG uptake by the ovaries in the group tested at 3 weeks after the onset of menstruation (median SUVmax = 2.00 [IQR 0.68–3.33], median SUVmean = 1.40 [IQR 0.45 –2.23]) differed significantly from that in the other groups, except that in the group tested at 4 weeks after the onset of menstruation (median SUVmax = 1.80 [IQR 1.50–2.30], median SUVmean = 1.45 [IQR 1.15–1.70]). Figure 1 shows the ovarian ^{18}F-FDG uptake values by group.

The results for the entire cohort showed that the ovarian SUVmax and SUVmean values were weakly positively correlated with progesterone levels (*rho* = 0.28, $p < 0.001$ for SUVmax, *rho* = 0.30, $p < 0.001$ for SUVmean) (Figure 2). Levels of the other sex hormones (estradiol, testosterone, FSH, and LH) were not correlated with ovarian ^{18}F-FDG uptake. The ovarian SUVmean was very weakly correlated with age (*rho* = 0.15, $p = 0.035$).

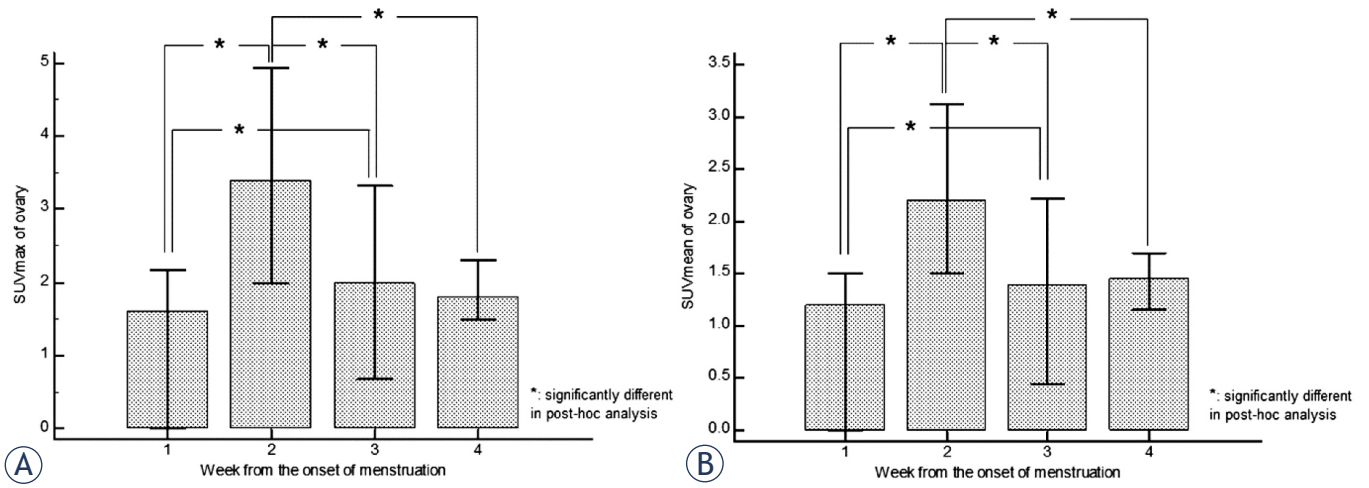

FIGURE 1. Ovarian ^{18}F-FDG uptake according to the number of weeks since the onset of menstruation. **(A)** The ovarian maximum standardized uptake value (SUVmax) was highest at 2 weeks after the onset of menstruation and lowest during the first week after menstruation. The ovarian SUVmax at weeks 3 and 4 was between that for the first and second weeks. **(B)** Comparisons of ovarian SUVmean showed a trend similar to that of SUVmax.

Analysis of the phase groups revealed that when progesterone levels were high, ovarian ^{18}F-FDG uptake was slightly higher (*rho* = 0.29, p = 0.003 for both SUVmax and SUVmean) in the follicular-phase group. In the luteal-phase group, no correlation was found between sex-hormone levels and ovarian ^{18}F-FDG uptake. The data and statistical analysis results are shown in detail in Table 2.

Discussion

Ovarian ^{18}F-FDG often presents a challenge to nuclear-medicine physicians interpreting ^{18}F-FDG PET/CT images. Ovarian ^{18}F-FDG uptake can occur depending on the phase of the menstrual cycle, particularly in premenopausal women[6, 9], but a clear mechanism for this remains unclear. We postulated that sex hormones are associated with ovarian ^{18}F-FDG uptake and aimed to evaluate this relationship.

Our study found that progesterone was weakly positively correlated with ovarian ^{18}F-FDG uptake in all subjects in the follicular-phase group, but none of the sex hormones was correlated with ovarian ^{18}F-FDG uptake in the luteal-phase group. Progesterone acts on the endometrium and plays a major role in preparing the uterus for implantation

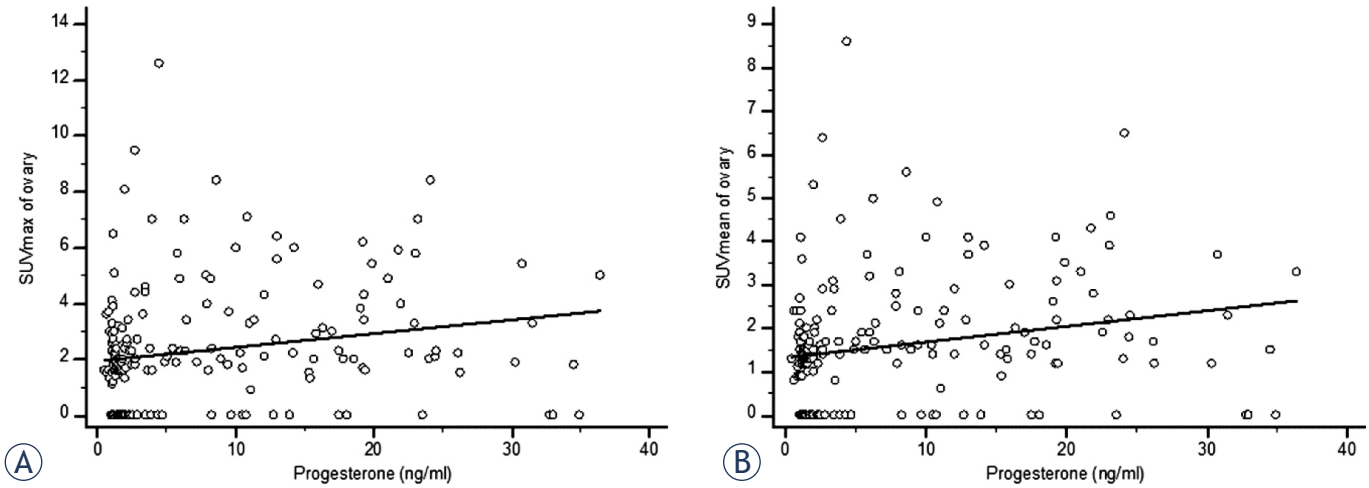

FIGURE 2. Scatter diagrams of the relationship between progesterone level and ovarian ^{18}F-FDG uptake in all subjects. **(A)** Progesterone levels were weakly correlated with ovarian SUVmax (p < 0.001, *rho* = 0.28). **(B)** A weakly positive correlation was also detected between progesterone level and ovarian SUVmean (p < 0.001, *rho* = 0.30).

TABLE 2. Correlation between ovarian ^{18}F-FDG uptake and sex hormone levels

Parameters		Follicular phase (n = 100)		Luteal phase (n = 97)		Total (N = 197)	
		Spearman's rho (95% CI)	p-value	Spearman's rho (95% CI)	p-value	Spearman's rho (95% CI)	p-value
Age	Correlation with SUVmax of ovary	−0.15 (−0.34–0.04)	0.125	−0.06 (−0.26–0.13)	0.500	−0.14(−0.27–0.01)	0.051
Estradiol		0.12 (−0.07–0.30)	0.235	−0.03 (−0.23–0.16)	0.721	0.05 (−0.08–0.19)	0.426
Progesterone		0.29 (0.09–0.45)	0.003*	0.13 (−0.07–0.32)	0.131	0.28 (0.14–0.40)	<0.001*
Testosterone		−0.08 (−0.27–0.12)	0.428	0.13 (−0.07–0.32)	0.129	0.03 (−0.11–0.17)	0.669
FSH		-0.18 (−0.37 to −0.01)	0.082	0.18 (−0.10–0.43)	0.200	−0.10 (−0.16 to −0.04)	0.174
LH		0.07 (−0.24–0.38)	0.657	−0.01 (−0.28–0.27)	0.973	−0.02 (−0.24–0.18)	0.792
Age	Correlation with SUVmean of ovary	−0.14 (−0.32–0.05)	0.164	−0.10 (−0.29–0.09)	0.318	−0.15 (−0.28–0.01)	0.035*
Estradiol		0.09 (−0.09–0.29)	0.324	−0.06 (−0.26–0.13)	0.532	0.03 (−0.10–0.17)	0.601
Progesterone		0.29 (0.09–0.46)	0.003*	0.16 (−0.04–0.35)	0.161	0.30 (0.17–0.42)	<0.001*
Testosterone		−0.13 (-0.31–0.06)	0.197	0.13 (−0.06–0.32)	0.193	0.01 (−0.12–0.15)	0.840
FSH		−0.16 (−0.33–0.07)	0.122	0.20 (−0.08–0.45)	0.154	−0.13 (−0.18 to −0.05)	0.116
LH		−0.67 (−0.39–0.27)	0.700	0.01 (−0.27–0.29)	0.954	−0.04 (−0.25–0.17)	0.690

*$p < 0.05$

CI = confidence interval; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SUVmax = maximum standardized uptake value; SUVmean = mean standardized uptake value

and pregnancy from the late proliferative phase to the luteal phase.[12, 13] The finding that progesterone levels correlated with ovarian glucose metabolism in the follicular phase may be explained as follows. During most of the follicular phase, progesterone is secreted from the adrenal cortex; this secretion is regulated by unknown elements in the ovary. Progesterone secretion switches from the adrenal cortex to the ovaries before ovulation.[14] In other words, progesterone secretion during the follicular phase is the result of a complex interaction between the adrenal cortex and the ovaries, which may account for the correlation between progesterone levels and ovarian glucose metabolism during this period. We acknowledge that this hypothesis is speculative and further research will be needed for confirmation. Estradiol and FSH, which play important roles in follicular growth, and LH, which plays a key role in ovulation[15], were not correlated with ovarian ^{18}F-FDG uptake; this has rarely been reported, so interpreting this finding is difficult. The relationship between the ovaries and sex-hormone levels is very complex and therefore difficult to elucidate. This study is significant in that it is the first to reveal a relationship between ovarian ^{18}F-FDG uptake and sex hormone levels, but more research will be needed to clarify the mechanism of their relationship.

Another noteworthy result of this study was that ovarian ^{18}F-FDG uptake was very weakly negatively correlated with age. With aging, the ovaries gradually decrease in function.[16] Our results show that changes in ovarian metabolism due to aging are reflected in ^{18}F-FDG uptake.

Lerman *et al.* reported that ^{18}F-FDG uptake was detectable in normal ovaries during the ovulatory phase in premenopausal women.[5] Nishizawa *et al.* reported increased ovarian ^{18}F-FDG uptake from the late follicular phase to the early luteal phase.[8] Kim *et al.*, demonstrated that increased ovarian ^{18}F-FDG uptake occurs mainly 10–25 days after the onset of menstruation, which corresponds to the late follicular, ovulatory, and early to mid-luteal phases.[9] Our results do not differ from those of previous studies. In our study, ovarian ^{18}F-FDG uptake was highest at 2 weeks after the onset of menstruation, when the follicle is actively proliferating, implying ^{18}F-FDG uptake by the pre-ovulatory follicle. In addition, ovarian ^{18}F-FDG uptake was higher during the luteal phase than during the follicular phase, which may have been due to increased ^{18}F-FDG uptake by the corpora lutea in this phase. A possible reason for the increased ^{18}F-FDG uptake by the pre-ovulatory follicle and corpus luteum is as follows. Active growth of pre-ovulatory follicles has been associated with increased metabolic demand and glucose-transporter-3 expression, which is regulated by interleukin-1β during the peri-ovulatory phase, leading to increased ^{18}F-FDG uptake.[17] Angiogenesis and the cytokine-mediated inflammatory reaction have been suggested as being involved in ^{18}F-FDG uptake by the

corpus luteum, because the mechanism of corpus luteal formation is similar to those of wound healing and tumour formation.[18] In our study, the lowest ^{18}F-FDG uptake observed was at 1 week after the onset of menstruation, which may have been due to lower ^{18}F-FDG uptake in small follicles before growth.[9]

This study included only subjects with regular menstrual cycles, and excluded those who had a menstrual cycle exceeding 31 days. Patients with irregular menstrual cycles were excluded from the study because of a concern that their sex hormones would not be in balance. Most previous reports included subjects with irregular menstrual cycles[5,8,9], and the results of those studies are likely to have been biased accordingly. Therefore, a strength of the present study was that it excluded such subjects.

In this study, progesterone was higher in the luteal-phase group than in the follicular-phase group, while FSH levels were significantly higher in the follicular-phase group than in the luteal-phase group. Changes in sex hormones during the menstrual cycle have been well documented, and the high progesterone levels observed during the luteal phase and elevated FSH levels observed during the follicular phase are consistent with previous data.[19] The results demonstrate that the self-reported LNMP data of our subjects accorded with the actual levels of the sex hormones, thus demonstrating the accuracy and objectivity of this study.

The limitations of this study were as follows. First, the ovarian status of the subjects was evaluated using non-contrast enhanced CT, as part of the PET/CT examination. The ovary can be examined more precisely by contrast-enhanced CT, MRI, or ultrasonography, but this study was retrospective, so it was not possible to perform these radiological examinations in all patients. However, the ovaries of the subjects showed no pathological lesions on non-enhanced CT. Future studies will require more detailed radiological examinations to validate our results. Second, this study did not report results regarding uterine ^{18}F-FDG uptake, although numerous studies have reported ^{18}F-FDG uptake by the endometrium as well as the ovaries.[5,6,8,20] However, in our study, many subjects had small or large uterine myomas (51/197; 25.8%,), so it was difficult to determine normal uterine ^{18}F-FDG uptake. Myomas are associated with varying levels of ^{18}F-FDG uptake, so we judged that assessing physiological uterine ^{18}F-FDG uptake would be problematic. Finally, this study included patients with breast cancer, but the design might have been more appropriate for healthy volunteers; unfortunately, we were constrained to retrospective use of ^{18}F-FDG PET/CT data in patients with breast cancer, albeit that we attempted to evaluate physiological ovarian uptake by omitting patients who had a previous history of ovarian disease or hormone therapy.

Conclusions

Ovarian ^{18}F-FDG uptake in premenopausal women was positively correlated with progesterone levels. This correlation was detected during the follicular phase of the menstrual cycle, while the other sex hormones measured (estradiol, testosterone, FSH, and LH) were not associated with ovarian ^{18}F-FDG uptake.

References

1. Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, et al. Recommendations on the use of 18F-FDG PET in oncology. *J Nucl Med* 2008; **49:** 480-508. doi: 10.2967/jnumed.107.047787
2. Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. *Radiographics* 1999; **19:** 61-77; quiz 150-1. doi: 10.1148/radiographics.19.1.g99ja0761
3. Rosenbaum SJ, Lind T, Antoch G, Bockisch A. False-positive FDG PET uptake--the role of PET/CT. *Eur Radiol* 2006; **16:** 1054-65. doi: 10.1007/s00330-005-0088-y
4. Israel O, Yefremov N, Bar-Shalom R, Kagana O, Frenkel A, Keidar Z, et al. PET/CT detection of unexpected gastrointestinal foci of 18F-FDG uptake: incidence, localization patterns, and clinical significance. *J Nucl Med* 2005; **46:** 758-62.
5. Lerman H, Metser U, Grisaru D, Fishman A, Lievshitz G, Even-Sapir E. Normal and abnormal 18F-FDG endometrial and ovarian uptake in pre- and post-menopausal patients: assessment by PET/CT. *J Nucl Med* 2004; **45:** 266-71.
6. Liu Y. Benign ovarian and endometrial uptake on FDG PET-CT: patterns and pitfalls. *Ann Nucl Med* 2009; **23:** 107-12. doi: 10.1007/s12149-008-0227-z
7. Cook GJ, Fogelman I, Maisey MN. Normal physiological and benign pathological variants of 18-fluoro-2-deoxyglucose positron-emission tomography scanning: potential for error in interpretation. *Semin Nucl Med* 1996; **26:** 308-14.
8. Nishizawa S, Inubushi M, Okada H. Physiological 18F-FDG uptake in the ovaries and uterus of healthy female volunteers. *Eur J Nucl Med Mol Imaging* 2005; **32:** 549-56. doi: 10.1007/s00259-004-1703-x
9. Kim SK, Kang KW, Roh JW, Sim JS, Lee ES, Park SY. Incidental ovarian 18F-FDG accumulation on PET: correlation with the menstrual cycle. *Eur J Nucl Med Mol Imaging* 2005; **32:** 757-63. doi: 10.1007/s00259-005-1771-6
10. Chiazze L, Jr., Brayer FT, Macisco JJ, Jr., Parker MP, Duffy BJ. The length and variability of the human menstrual cycle. *JAMA* 1968; **203:** 377-80.
11. Weir I. Spearman's correlation. Statstutor, Mathematics Education Centre Loughborough University *http://www statstutor ac uk/resources/uploaded/spearmans pdf Accessed*. 2016;29
12. Csapo AI, Pinto-Dantas CA. The effect of progesterone on the human uterus. *Proc Natl Acad Sci U S A* 1965; **54:** 1069-76.
13. Widmaier EP, Raff H, Strang KT. Vander's human physiology: the mechanisms of body function: McGraw-Hill Higher Education; 2008.

14. De Geyter C, De Geyter M, Huber PR, Nieschlag E, Holzgreve W. Progesterone serum levels during the follicular phase of the menstrual cycle originate from the crosstalk between the ovaries and the adrenal cortex. *Hum Reprod* 2002; **17:** 933-9.

15. Van Iten B. Estrogen and the Menstrual Cycle in Humans. Embryo Project Encyclopedia 2016.

16. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev* 2009; **30:** 465-93. doi: 10.1210/er.2009-0006

17. Kol S, Ben-Shlomo I, Ruutiainen K, Ando M, Davies-Hill TM, Rohan RM, et al. The midcycle increase in ovarian glucose uptake is associated with enhanced expression of glucose transporter 3. Possible role for interleukin-1, a putative intermediary in the ovulatory process. *J Clin Invest* 1997; **99:** 2274-83. doi: 10.1172/JCI119403

18. Balsara G, Hernandez E. The ovary: normal, physiologic changes, endometriosis, and metastatic tumors. *Clinical Gynecologic Pathology Philadelphia, PA: Saunders*. 1995; 404-9.

19. Reed BG, Carr BR. The normal menstrual cycle and the control of ovulation. *Endotext [Internet]*: MDText. com, Inc.; 2015.

20. Zhu Z, Wang B, Cheng W, Cheng X, Cui R, Huo L, et al. Endometrial and ovarian F-18 FDG uptake in serial PET studies and the value of delayed imaging for differentiation. *Clin Nucl Med* 2006; **31:** 781-7. doi: 10.1097/01.rlu.0000247261.82757.ea