Physiological ^{18}F-FDG uptake in the ovaries and uterus of healthy female volunteers

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Abstract. *Purpose:* Good knowledge of physiological ^{18}F-fluorodeoxglucose (^{18}F-FDG) uptake in the healthy population is of great importance for the correct interpretation of ^{18}F-FDG positron emission tomography (PET) images of pathological processes. The purpose of this study was to investigate the physiological ^{18}F-FDG uptake in the ovaries and uterus of healthy female volunteers.
Methods: One hundred and 33 healthy females, 78 of whom were premenopausal (age 37.2±6.9 years) and 55 postmenopausal (age 55.0±2.7 years), were examined using whole-body ^{18}F-FDG PET and pelvic magnetic resonance (MR) imaging. Focal ^{18}F-FDG uptake in the ovaries and uterus was evaluated visually and using standardised uptake value (SUVs). Anatomical and morphological information was obtained from MR images.
Results: Distinct ovarian ^{18}F-FDG uptake with an SUV of 3.9±0.7 was observed in 26 premenopausal women out of 32 examined during the late follicular to early luteal phase of the menstrual cycle. Eighteen of the 32 women also showed focal ^{18}F-FDG uptake in the endometrium, with an SUV of 3.3±0.3. On the other hand, all nine women in the first 3 days of the menstrual cycle demonstrated intense ^{18}F-FDG uptake in the endometrium, with an SUV of 4.6±1.0. No physiological ^{18}F-FDG uptake was observed in the ovaries or uterus of any postmenopausal women.
Conclusion: In women of reproductive age, ^{18}F-FDG imaging should preferably be done within a week before or a few days after the menstrual flow phase to avoid any misinterpretation of pelvic ^{18}F-FDG PET images.

Keywords: FDG – PET – Ovary – Uterus – Physiological uptake

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Introduction

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is frequently used for the management of patients with malignant tumours. Good knowledge of physiological ^{18}F-FDG uptake in the healthy population is of great importance for correct interpretation of whole-body ^{18}F-FDG PET images of pathological processes . Many physiological variations and pitfalls of whole-body ^{18}F-FDG PET images have been reported [1–3]. In the pelvic region, retention of activity within the urinary tract and ^{18}F-FDG uptake in the normal intestine over very short segments are common sources of false-positive diagnoses. In addition, increased ^{18}F-FDG uptake has been reported in the normal uterus during menstruation [4, 5], in a follicular ovarian cyst [1] and in the ovary with an inflammatory reaction during ovulation [2]. However, focal ^{18}F-FDG uptake is not always seen in the uterus of women during menstruation and is sometimes even observed in the ovaries of premenopausal women without any symptoms or morphological abnormalities. To our knowledge, there has not been a systematic investigation of physiological ^{18}F-FDG uptake in the ovaries and uterus in the healthy female population, and only one relevant article has been published recently, showing physiological ovarian and endometrial uptake in patients without known gynaecological malignancy [6]. The purpose of this study was to investigate physiological ^{18}F-FDG uptake in the ovaries and uterus of healthy female volunteers in relation to the menstrual state and the phase of the menstrual cycle.

Materials and methods

Subjects

The study was prospectively conducted in 168 consecutive healthy female volunteers who participated in our research protocol for cancer screening using ^{18}F-FDG PET in the Hamamatsu Medical Imaging Center from August to December 2003. Medical interviews, encompassing previous malignancy and gynaecological surgery, menstrual state and cycle, and the period of last menstrua-

tion, were conducted with all women. In addition, all premenopausal women were asked to report the initial day of first menstruation after the ^{18}F-FDG PET examination to ascertain the phase of the menstrual cycle at the time of examination. Those without a record of the menstrual phase at the time of examination were excluded from the study. Also excluded were women with a history of known malignancy or previous gynaecological surgery. Finally, we included 133 subjects in this study: 78 premenopausal (age 37.2±6.9 years) and 55 postmenopausal (age 55.0±2.7 years) women. Written informed consent was obtained from all subjects participating in the study, which was approved by the institutional ethics committee.

PET imaging

All subjects fasted at least for 5 h before injection of ^{18}F-FDG. Serum glucose levels measured just before the injection of ^{18}F-FDG were normal in all subjects. ^{18}F-FDG PET was performed on an SHR-92000 scanner (Hamamatsu Photonics, KK., Hamamatsu, Japan), starting 60 min after the injection of 3 MBq/kg body weight ^{18}F-FDG. All subjects voided immediately before the scan. The scanner produced 336 transverse sections with a section thickness of 3.25 mm, covering the whole body from the upper thigh to the top of the brain in two bed positions [7]. The lower part of the body was scanned first to avoid degradation of image quality by the urinary activity in the bladder. Whole-body computed tomography (CT) with a low radiation dose (5 mAs, effective radiation dose of less than 0.5 mSv) was also performed, and was used for attenuation correction of the ^{18}F-FDG PET images. Attenuation-corrected images were reconstructed in transaxial, sagittal and coronal planes by means of a dynamic row-action maximum-likelihood algorithm [8]. In addition to these images, maximum intensity projection (MIP) images were used for the interpretation.

MR imaging

Anatomical and morphological information was acquired from magnetic resonance (MR) images. MR imaging was performed with a 1.5-T MR scanner (EchoSpeed, GE Medical Systems, Milwaukee). A phased-array torso eight-coil system was used to obtain images of the pelvis. A T2-weighted fast spin-echo (FSE) sequence was used for transaxial [repetition time 4,300 ms, echo time 102 ms (4,300/102), 320×224 matrix], transaxial fat saturation (3,700/102, 256×192 matrix) and sagittal (2,400/102, 320×224 matrix) images. Two signals were averaged. Transaxial and coronal T1-weighted FSE images (470–570/minimum full, 320×224 matrix, one signal or two signals averaged) were also obtained. All images were acquired with a 30- to 36-cm field of view, a 4- to 5-mm section thickness and a 1-mm intersection gap.

Image analysis

All ^{18}F-FDG PET and MR images were interpreted separately. Whole-body ^{18}F-FDG PET images were evaluated for focal ^{18}F-FDG uptake in the ovaries and uterus visually and using standardised uptake values (SUVs). Ovarian and uterine morphological abnormalities were assessed on MR images before the interpretation of PET images. Ovarian cystic components smaller than 2.5 cm in premenopausal women were considered as normal [9, 10]. Focal ^{18}F-FDG uptake in the pelvis greater than that in the liver was considered as positive. Then, MR images were used to localise the foci of increased ^{18}F-FDG uptake. Focal retention of urinary activity and intestinal uptake of ^{18}F-FDG were excluded by anatomical correlation of ^{18}F-FDG PET images with MR images. For image correlation, direct superimposition of PET and MR images was not performed. We correlated focal uptake on PET images with anatomical structure on MR images visually by referring to the CT images for attenuation correction that could be superimposed closely on PET images

A region of interest (ROI), 10 mm in diameter, was placed on the focus of increased ^{18}F-FDG uptake in the vary and uterus for calculation of an SUV. The SUV was computed as follows: $SUV = FDG_{region}/(FDG_{dose}/WT)$, where FDG_{region} is the decay-corrected regional ^{18}F-FDG concentration in Bq/ml, FDG_{dose} is the injected ^{18}F-FDG in Bq and WT is the body weight in grams. Maximal SUVs in areas with focal ^{18}F-FDG uptake were recorded.

Results

Results of visual analysis of ^{18}F-FDG uptake in the ovaries and uterus of 78 premenopausal women are summarised in Fig. 1. Details of the individual results are shown in Table 1. Distinct ovarian ^{18}F-FDG uptake was observed in 26 out of 32 premenopausal women examined 18–8 days before the start of next menstruation, with an SUV of 3.9±0.7 (range 2.6–5.2). The SUV for the liver among the women included in this study was 2.0±0.4. The ovarian uptake was unilateral in 23 women (Fig. 2). Eighteen of the 32 women also showed focal ^{18}F-FDG uptake in the endometrium, with an SUV of 3.3±0.3 (range 2.8–4.0) (Fig. 3). On the other hand, all nine women in the first 3 days of the menstrual cycle demonstrated intense ^{18}F-FDG uptake in the endometrium, with an SUV of 4.6±1.0 (range 3.5–6.1) (Fig. 4). Endometrial uptake was noted in one of five women on the 4th day of menstruation.

Among 78 premenopausal women, MR images demonstrated uterine myomas in 13, dermoid cysts of the ovary in two, functional ovarian cysts larger than 2.5 cm in diameter in five and cystic lesion with haemorrhage suggesting endometrial cyst in three and luteal cyst in two. No ^{18}F-FDG uptake was seen in uterine myomas or ovarian lesions. One woman with endometrial cysts in both ovaries showed focal ^{18}F-FDG uptake in one of the ovaries. She was examined 9 days before menstruation and also showed endometrial ^{18}F-FDG uptake.

No ^{18}F-FDG uptake was observed in the ovaries or uterus of any postmenopausal women, with the exception of two: one with an intrauterine device (IUD) showed endometrial uptake of ^{18}F-FDG, and the other had elevated ^{18}F-FDG uptake due to a uterine myoma of 2.5 cm in diameter. MR images detected uterine myomas of 1.5–5.5 cm in diameter in 20 of 55 postmenopausal

Table 1. Individual data of the 78 premenopausal women

Patient no.	Age (yrs)	Day of cycle	FDG uptake			MR finding		
			Right ovary	Left ovary	Uterus	Right ovary	Left ovary	Uterus
1	34	−26	–	–	–	–	–	Myoma
2	40	−24	–	–	–	–	–	–
3	31	−22	–	–	–	–	–	Myoma
4	31	−22	–	–	–	ec	ec	–
5	43	−20	–	–	–	–	–	Myoma
6	42	−20	–	–	–	–	–	–
7	35	−20	–	–	–	–	–	–
8	35	−20	–	–	–	–	–	–
9	33	−19	–	–	–	–	–	–
10	26	−18	–	+ (3.4)	+ (3.6)	–	–	–
11	48	−18	–	–	+ (4.3)	–	–	Myoma
12	42	−18	–	+ (3.3)	–	–	–	–
13	36	−17	+ (3.9)	–	+ (2.9)	–	–	–
14	39	−17	+ (3.0)	+ (3.5)	+ (3.1)	–	–	–
15	27	−17	–	–	+ (3.2)	–	–	–
16	50	−16	–	+ (4.7)	+ (4.0)	nv	–	–
17	42	−15	–	–	+ (5.3)	fc	–	–
18	37	−15	–	+ (4.3)	–	fc	–	–
19	36	−15	+ (3.0)	+ (2.9)	+ (3.1)	–	–	–
20	40	−15	–	+ (4.8)	–	–	–	–
21	44	−14	–	+ (3.0)	–	ec	–	–
22	33	−14	–	+ (3.4)	–	–	–	–
23	35	−14	–	+ (4.1)	–	–	–	Myoma
24	41	−14	–	+ (5.2)	–	–	–	–
25	35	−13	–	+ (4.5)	+ (4.0)	–	–	–
26	32	−13	+ (3.7)	–	+ (3.3)	–	–	–
27	33	−13	+ (3.3)	+ (3.9)	+ (3.1)	–	–	–
28	46	−13	+ (3.5)	–	–	–	–	–
29	31	−12	+ (4.6)	–	+ (3.3)	–	–	–
30	48	−12	+ (4.9)	–	–	–	–	–
31	42	−12	–	+ (3.7)	+ (3.3)	–	–	–
32	40	−12	–	+ (2.6)	+ (3.6)	–	–	–
33	42	−11	+ (3.0)	–	+ (3.3)	–	–	–
34	41	−11	–	+ (5.2)	+ (2.8)	–	–	Myoma
35	45	−10	–	+ (3.3)	–	–	–	–
36	53	−10	+ (3.9)	–	+ (3.3)	–	–	Myoma
37	32	−9	–	–	–	–	dc	–
38	36	−9	–	+ (2.7)	+ (3.3)	ec	ec	–
39	28	−8	–	–	–	–	–	–
40	38	−8	–	–	–	–	–	–
41	44	−8	+ (3.2)	–	+ (3.3)	–	–	–
42	34	−7	–	–	–	–	fc	–
43	31	−7	–	–	–	–	–	–
44	50	−6	–	–	–	fc	fc	–
45	43	−6	–	–	–		–	–
46	37	−5	–	–	–	–	–	–
47	35	−5	–	–	–	–	–	Myoma
48	28	−5	–	–	–	–	–	–
49	36	−4	–	–	–	–	–	–
50	49	−4	–	–	–	–	–	–
51	49	−4	–	–	–	–	–	Myoma
52	39	−3	–	–	–	–	–	–
53	36	−3	–	–	–	fc	–	Myoma
54	36	−3	–	–	–	–	–	–
55	32	−3	–	–	–	dc	–	–
56	24	−3	–	–	–	–	–	–

Table 1. (continued)

Patient no.	Age (yrs)	Day of cycle	FDG uptake			MR finding		
			Right ovary	Left ovary	Uterus	Right ovary	Left ovary	Uterus
57	45	–3	–	–	–	–	–	–
58	37	–3	–	–	–	–	–	–
59	32	–1	–	–	–	–	lc	–
60	50	–1	–	–	–	–	–	Myoma
61	31	1	–	–	+ (4.2)	–	–	–
62	28	1	–	–	+ (5.1)	–	–	–
63	37	2	–	–	+ (3.2)	–	–	–
64	34	2	–	–	+ (6.1)	–	–	Myoma
65	32	2	–	–	+ (5.5)	–	–	–
66	47	2	–	–	+ (4.8)	–	–	Myoma
67	31	2	–	–	+ (4.9)	–	–	–
68	41	2	–	–	+ (3.5)	–	–	–
69	24	3	–	–	+ (3.6)	–	–	–
70	45	4	–	–	–	–	–	–
71	34	4	–	–	–	–	nv	–
72	35	4	–	–	+ (4.6)	–	–	–
73	21	4	–	–	–	–	–	–
74	35	4	–	–	–	–	–	–
75	30	5	–	–	–	lc	–	–
76	38	6	–	–	–	–	–	–
77	34	6	–	–	–	–	nv	–
78	35	7	–	–	–	–	–	–

Negative and positive values for day of cycle indicate days before and after the start of menstruation, respectively
'–' and '+' in relation to FDG images indicate no uptake and positive uptake, respectively. SUV is shown in parentheses
'–' in relation to MR images indicates no abnormal finding
fc functional cyst, *dc* dermoid cyst, *ec* endometrial cyst, *lc* luteal cyst, *nv* not visualised

women and ovarian cysts of about 2 cm in diameter in two. Uptake was not seen in these lesions other than in the above-mentioned uterine myoma.

Discussion

In this prospective study of consecutive healthy volunteers, we regularly observed focal ^{18}F-FDG uptake in the ovaries and uterus of premenopausal women during certain phases of the menstrual cycle. This suggests that focal ^{18}F-FDG uptake in these organs may be physiological and is not necessarily caused by a pathological process even if some morphological abnormalities are shown.

Focal ovarian ^{18}F-FDG uptake was seen in most premenopausal women examined 18–8 days before their next menstruation. This period corresponds roughly to the late follicular to early luteal phase, in which more energy and substrate may be needed to grow a dominant follicle and to form corpus luteum after ovulation. An inflammatory reaction is also thought to be involved in ovulatory processes [11]. Recent data suggest that cytokines play a significant role in peri-ovulatory processes. It has been speculated that ovarian glucose uptake increases in mid-cycle to meet increased metabolic demands of the growing follicle and the ovulated cumulus-enclosed oocyte, with enhanced Glut3 expression regulated by interleukin-1β [12]. The rupture of the follicle is considered to be an inflammatory reaction mediated by cytokines [13], which induces macrophages that accumulate a significant amount of ^{18}F-FDG [14]. Cytokines are also thought to be involved in angiogenesis of the corpus luteum and cellular differentiation for steroid synthesis [13]. It may be inferred that increased metabolic demands and inflammatory reactions around the peri-ovulatory phase can cause increased ovarian uptake of ^{18}F-FDG. In the present study the ovarian uptake was unilateral in 23 out of 26 women. Within a menstrual cycle, one of the two ovaries would be expected to be mainly functioning, at least after formation of a dominant follicle; this presumably explains the observed unilateral ovarian ^{18}F-FDG uptake.

The SUV of physiological ^{18}F-FDG uptake in the ovary and uterus varied among women because of individual diversity without a relationship to the phase of the menstrual cycle. There was a difference between the ovary and the uterus in the pattern of change in ^{18}F-FDG uptake during the late follicular to early luteal phase.

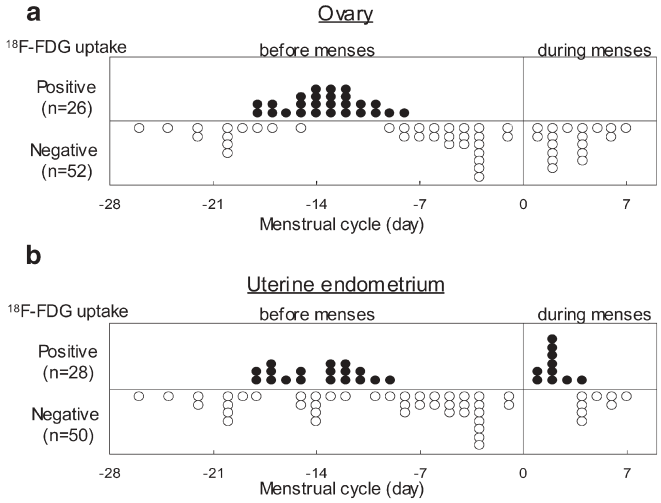

Fig. 1. Results regarding the relationship between the menstrual cycle and ^{18}F-FDG uptake in the ovary (**a**) and uterus (**b**), obtained in 78 premenopausal women. A *black circle* indicates a woman with, and a *white circle* a woman without, focal ^{18}F-FDG uptake in the ovary or uterus. Focal ^{18}F-FDG uptake in the ovary and uterus was observed in the late follicular to early luteal phase. Endometrial uptake was also seen in the early menstrual period.

Ovarian ^{18}F-FDG uptake was consistently observed during this phase. Although endometrial uptake of ^{18}F-FDG was seen in more than half of the women in this phase, no endometrial uptake was observed in women around the presumed day of ovulation (ca. 14 days before menstruation). Glucose uptake and metabolism in the ovaries and uterus are known to alter in relation to the functional state of the organs under the influence of pituitary gonadotropins and/or ovarian hormones [15–17]. An abrupt change in the hormonal environment may affect endometrial ^{18}F-FDG uptake in the ovulatory phase.

Women in the first 3 days of menstruation also showed focal ^{18}F-FDG uptake in the uterine endometrium, as reported previously [2–5]. However, after the 4th day of menstruation, most women demonstrated no ^{18}F-FDG uptake. Endometrial ^{18}F-FDG uptake during the initial days of menstruation may be related to the prominent bleeding in the degenerating and necrotising endometrium at this time. Another mechanism of uptake might be the peristaltic movements of the subendometrial myometrium that effect discharge of menstrual blood [18–20]. Peristaltic movements of the uterus are also recognised in the peri-ovulatory phase. Further investigation will be needed to achieve a thorough understanding of the mechanism of physiological ^{18}F-FDG uptake in the uterus.

Physiological ovarian ^{18}F-FDG uptake typically appeared round or oval and was noted as an intense focal abnormality with an SUV greater than 3.0. It would seem difficult to distinguish focal ^{18}F-FDG uptake in the normal ovary from that in malignant lesions. Detailed comparison with anatomical and morphological structures on MR images, in addition to knowledge of the menstrual phase, would appear helpful in ensuring accurate interpretation of ^{18}F-FDG PET images of the ovaries. On the other hand, the shape of endometrial ^{18}F-FDG uptake was variable and dependent on the

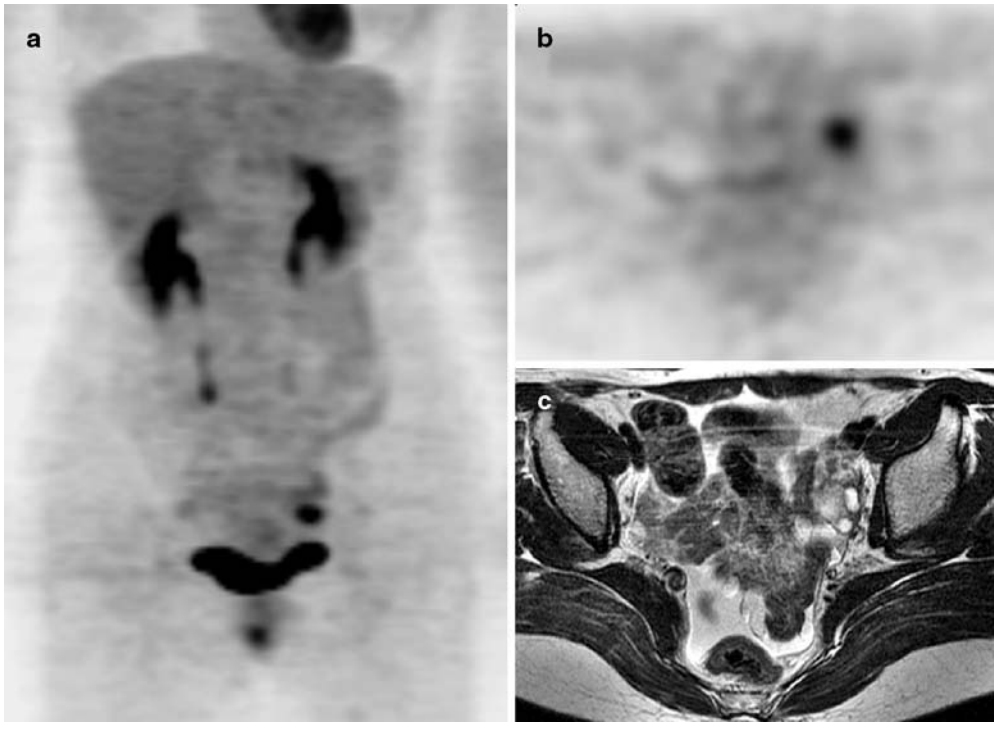

Fig. 2. A MIP image derived from ^{18}F-FDG PET data (**a**) in a 37-year-old woman around the ovulation phase. Focal ^{18}F-FDG uptake is present in the left pelvis. Transaxial PET (**b**) and MR (**c**) images at the same level indicate that the focal ^{18}F-FDG uptake corresponds to the left ovary. Most women showed ovarian uptake unilaterally.

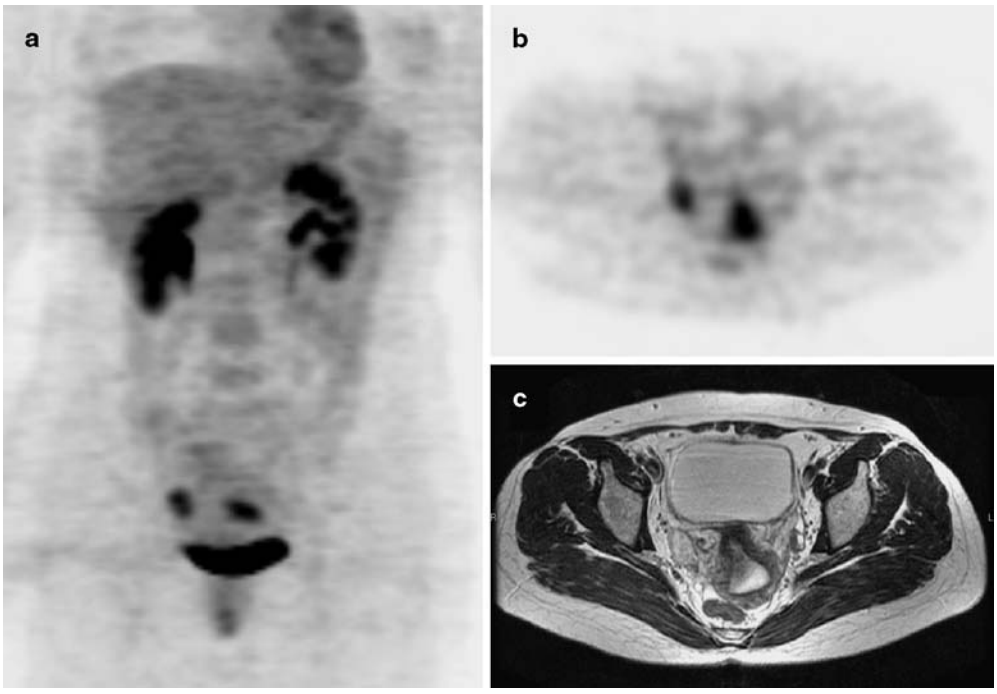

Fig. 3. A MIP image derived from ^{18}F-FDG PET data (**a**) in a 42-year-old woman during the early luteal phase of the menstrual cycle (11 days before menstruation). Two foci of intense ^{18}F-FDG uptake are demonstrated in the pelvis. Transaxial PET (**b**) and MR (**c**) images at the same level reveal that the foci of uptake correspond to the right ovary and the endometrium of a retroverted uterus.

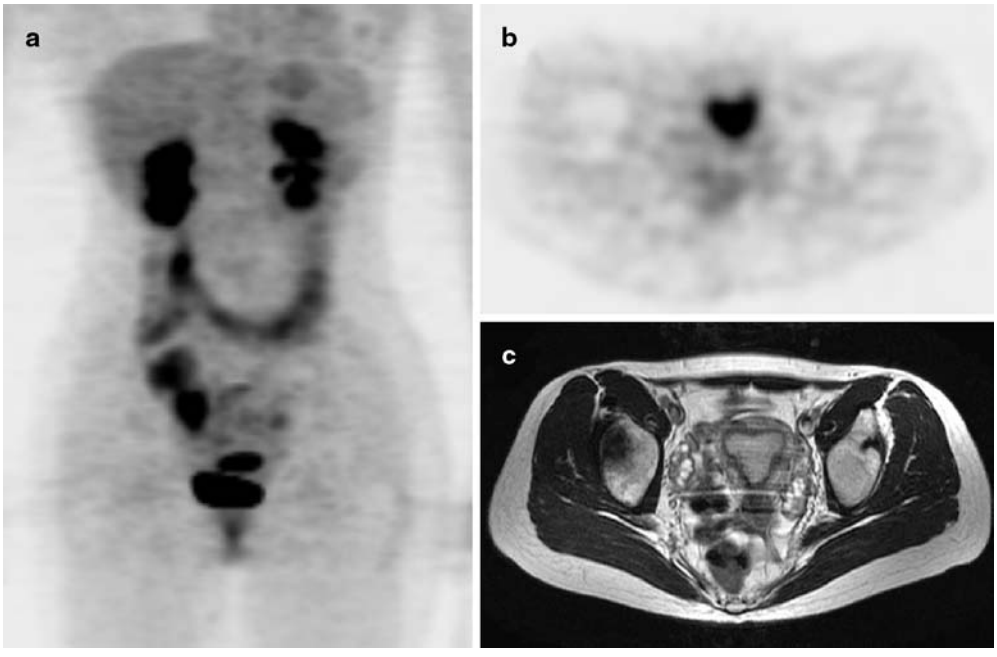

Fig. 4. A MIP image derived from ^{18}F-FDG PET data (**a**) in a 32-year-old woman examined on the 2nd day of menstruation. A focus of intense ^{18}F-FDG uptake is present above the urinary bladder. Transaxial PET (**b**) and MR (**c**) images at the same level show the ^{18}F-FDG uptake to be confined to the uterine endometrium.

shape of the endometrium. Typically, endometrial ^{18}F-FDG uptake appeared as an inverse triangle on axial images and curvilinear or ellipsoid over the urinary bladder on sagittal images. However, the position and shape of the uptake were not always typical, and anatomical confirmation was mandatory to avoid misinterpretation.

Recently, Lerman et al. [6] described physiological ovarian and endometrial ^{18}F-FDG uptake in relation to the menstrual phases in pre- and postmenopausal patients without known gynaecological malignancy. They used PET/CT to localise the uptake in relation to the anatomical structures. Assessing ovarian and endometrial ^{18}F-FDG uptake during the four phases of the menstrual cycle by means of the SUV, they showed endometrial uptake during the menstrual flow and ovulation phases and ovarian uptake during the ovulation phase. They underscored the importance of knowing the phase of the menstrual cycle in premenopausal patients in order to avoid misinterpretation. Our results, obtained prospec-

tively in normal volunteers, confirmed their findings. In addition, we more accurately identified the phase of the menstrual cycle, and obtained new information of clinical value on physiological ovarian and endometrial ^{18}F-FDG uptake, such as the frequency of such uptake in relation to the individual menstrual phases.

In our study, we used MR images as an anatomical and morphological reference, which provided exquisite soft tissue contrast and tissue characterisation permitting precise identification of the ovaries and uterus and accurate diagnosis of pathology without ionising radiation. The comparison of PET images with MR images was especially useful in identifying the ovaries and any corresponding focus of ^{18}F-FDG uptake. Precise identification of the ovaries would be rather difficult on CT images. However, there was a drawback in our image correlation. We did not perform direct fusion of PET and MR images because of lack of the requisite software. To reduce errors in the comparison of PET and MR images, we used CT images for attenuation correction, which superimposed closely on PET images. Direct PET/MRI fusion would enable more accurate functional and morphological correlation of pelvic organs.

In our series of volunteers, some benign lesions were detected on pelvic MR images. Among the postmenopausal women, we observed focal ^{18}F-FDG uptake in one uterine myoma, and in the endometrium of a woman with an IUD that had been neglected for years. Increased ^{18}F-FDG uptake in uterine myomas is rare but has been reported in the literature [21, 22]. Inflammatory processes are well known to cause increased ^{18}F-FDG uptake [14], and may have been responsible for the endometrial uptake in the patient with an IUD. One premenopausal woman with endometrial cysts in both ovaries showed focal ^{18}F-FDG uptake in one of the ovaries. In this case, the uptake was considered physiological because it was confined to the ovary of normal appearance, sparing the cystic lesion, and because the woman was in the early luteal phase and also showed endometrial ^{18}F-FDG uptake. Several benign lesions and conditions of the ovary and uterus have been reported to cause focal ^{18}F-FDG uptake [1, 2, 21–23]. However, even if there is an ovarian or uterine morphological abnormality, physiological uptake should be taken into consideration when interpreting pelvic ^{18}F-FDG PET images of women of reproductive age.

Conclusion

Most premenopausal women in the late follicular to early luteal phase of the menstrual cycle showed physiological ^{18}F-FDG uptake in the ovary and uterine endometrium. ^{18}F-FDG uptake was also seen in the endometrium of women during the first few days of menstruation. Knowledge of the menstrual phase and a detailed anatomical reference are required when interpreting pelvic ^{18}F-FDG PET images of women of reproductive age. In addition, to avoid misinterpretation the ^{18}F-FDG PET study should preferably be done within a week before or a few days after the menstrual flow phase.

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