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Evaluation of ^{18}FDG PET-CT in the Diagnosis of Endometriosis: A Prospective Study

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Abstract

Background: Noninvasive techniques have poor sensitivity and specificity in diagnosing endometriosis, which is often associated with an inflammatory process. In several benign diseases, measurement of hypermetabolism using fluorodeoxyglucose (^{18}F ^{18}FDG) reflects the degree of inflammation and aggressiveness of the disease. This prospective study evaluated the value of ^{18}FDG positron emission tomography (PET)-computed tomography (CT) in assessing the presence of endometriosis. **Methods:** Ten consecutive patients suspected with endometriosis were prospectively included in this study. A preoperative ^{18}FDG PET-CT was performed in all the patients during the follicular phase of their cycle, which preceded laparoscopic surgery. Surgical endometriosis staging and histopathological analysis of removed tissue were confronted with the results from ^{18}FDG PET-CT. **Results:** Of the 10 patients, 9 had endometriosis confirmed by laparoscopy; 6 had advanced stage of the disease and 5 had histologically proven lesions. Nevertheless, none of the patients had ^{18}FDG-demonstrated hypermetabolism at PET-CT. **Conclusions:** In this preliminary series, we did not observe hypermetabolic activity in relation to endometriosis using ^{18}FDG PET-CT. This study's most important limitation is the use of ^{18}FDG as an isotopic tracer, which is not specific to endometrial tissue.

Keywords

endometriosis, diagnosis, laparoscopy, PET-CT, isotopic tracer

Introduction

Endometriosis is a very common disease. It is characterized by the presence of endometrial tissue outside the uterine cavity. Its prevalence ranges between 4% and 17% in fertile women.[1] Endometriosis causes pelvic inflammation, which leads to pelvic pain, including dysmenorrhoea, and infertility. In the group[1] of women with chronic pelvic pain, the prevalence of endometriosis is estimated to be higher, between 25% and 38.3%. Similarly, it has been reported in 25% to 50% of infertile women.[2]

Noninvasive techniques, such as transvaginal sonography (TVS), magnetic resonance imaging (MRI), serum CA-125 measurements, have shown a low sensibility and specificity in diagnosing endometriosis.[3-5] Both TVS and MRI have no value in diagnosing peritoneal endometriosis, as they can only be used to exclude or confirm the diagnosis of ovarian endometrioma and deep infiltrating endometriosis.[3,5,6] The definitive diagnosis of endometriosis relies upon laparoscopic findings, which remains the "gold standard" of investigation, unless the disease is visible in the vagina or elsewhere.[3] Difficulties in diagnosing endometriosis partially explain the large ranges of reported prevalence.

Good surgical practice consists of documenting in detail the type, location, and extent of all lesions and adhesions in order to obtain an accurate staging of the disease, using, for instance, the American Society for Reproductive Medicine (ASRM) classification.[7] Still, classification systems for endometriosis are subjective and poorly correlated with pain symptoms. They are used for the prognosis and management of infertility.[8,9] During laparoscopy, deeply infiltrating endometriosis may appear minimal, resulting in an underestimation of the disease severity.[10] The diagnosis of endometriosis can be confirmed microscopically, but negative histology does not exclude the presence of disease.

Hypermetabolism of endometriosis has been reported in some "case reports" using fluorodeoxyglucose (^{18}FDG)

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positron emission tomography (PET), when performed for other indications.[11-14] This is not surprising, as in other benign diseases associated with inflammation (such as rheumatoid arthritis or vasculitis), higher levels of hypermetabolism expressed by the standardized uptake value (SUV), a semi-quantitative measurement of the avidity for ^{18}FDG, have also been observed.[15,16] We, therefore, wanted to verify whether endometriosis lesions could be visualized during ^{18}FDG PET and whether the SUV would be correlated with the degree of inflammation associated with endometriosis.

The purpose of this pilot study was thus to evaluate the value of ^{18}FDG PET-CT (computed tomography) in the diagnosis of endometriosis and to correlate ^{18}FDG PET-CT results with the laparoscopic findings.

Materials and Methods

Patients

Patients aged 18 years or more with suspected severe endometriosis (based on chronic pelvic pain and/or dysmenorrhoea resistant to medical therapy and/or infertility), for whom a laparoscopy was indicated, were prospectively included in this study. Exclusion criteria were pregnancy or possible pregnancy. All patients had undergone preoperative transvaginal ultrasound and/or MRI. The study was approved by the institutional review board. Informed consent was obtained from all the participants. All patients included in this study had a preoperative ^{18}FDG PET–CT during the follicular phase of the menstrual cycle that preceded surgery in order to avoid any risk of pregnancy.

Fluorodeoxyglucose PET-CT

A PET-CT Discovery LS (GE Medical Systems, Milwaukee, Wisconsin) was used for data acquisition. Prior to ^{18}FDG injection, patient fasted for at least 6 hours. Sixty minutes after intravenous injection of 220 to 315 MBq of ^{18}FDG, acquisition was performed with the patient in supine position, from mid-thigh to the base of the skull. No iodine-based contrast was administered. The CT parameters were 120 kV, 120 mA, pitch 1.5:1, speed 15 mm/rot. The PET element operated in 2-dimensional (2D mode), for 4 minutes per bed position. Attenuation correction was based on the CT data.

Positron Emission Tomography Data Analysis

All PET and CT images were analyzed by the same experienced nuclear medical physicians. Any focal or diffuse ^{18}FDG uptake above background in location incompatible with normal anatomy and/or physiology was considered pathologic and correlated with the corresponding CT slices.

Laparoscopy

Patients underwent bowel preparation consisting of a 5-day fiber-free diet and 2 complete intestinal enemas the day before the procedure. Classical laparoscopic investigation was carried out. Laparoscopy was performed in blind versus the ^{18}FDG PET-CT data. The peritoneal cavity was inspected and lesions of endometriosis were described using the ASRM classification.[7]

Biopsies of lesions suspected of endometriosis were performed. Removed tissues were sent for histopathologic examination to confirm diagnosis. When the presence of endometrial tissue could not be assessed by microscopic examination, anti-CD10 immunohistochemistry was used to confirm the diagnosis of endometriosis.[17,18] Even in cases where endometriosis was not confirmed by histology, patients were considered having endometriosis if typical endometriosis lesions were observed at visual inspection during laparoscopy.

Statistical Analysis

Since this was a pilot study, we decided arbitrarily to study 25 patients. The primary aim was to correlate data collected from ^{18}FDG PET-CT with laparoscopic findings. The second goal was to correlate ^{18}FDG PET-CT results with the histopathological findings. A preliminary analysis was conducted after examining the first 10 patients.

Results

Ten patients were prospectively enrolled in this study between September 2008 and August 2009. Their main demographic characteristics are presented in Table 1. Their mean age ($\pm$ SD) was 31 years ($\pm$ 10). Laparoscopy was indicated for infertility and/or pelvic pain (including dysmenorrhoea) or presence of an adnexal mass. Of the 10 patients, 3 had previous history of endometriosis and had previously undergone a laparoscopy for this reason. All patients were surgically treated for their endometriosis during laparoscopy, including adhesiolysis, coagulation of all visible peritoneal lesions, and cystectomy of ovarian endometriomas. We did not encounter any major pre- or postoperative morbidity. The principal laparoscopic, histological, and ^{18}FDG PET-CT findings are summarized in Table 2. Of the 10 patients, 9 had documented endometriosis lesions among which 6 had at least stage III (ASRM) endometriosis. Five patients had histological lesions proven by positive anti-CD10 immunostaining, and 1 patient had an ovarian cyst removed. Three other patients had no specimen removed because of insufficient available tissue although typical endometriosis lesions were documented during laparoscopy. None of the ^{18}FDG PET-CT performed preoperatively detected any hypermetabolic lesion. Standardized uptake value was, therefore, not measured.

Discussion

Although endometriosis is a very common disease, its diagnosis remains difficult, especially for superficial peritoneal lesions, and requires an invasive procedure. Indeed, nowadays laparoscopy is the only technique with sufficiently high specificity and sensitivity in diagnosing endometriosis.

Table 1. Principal Patients' Demographic Characteristics

Patient	Age (years)	Gestity	Parity	Indication for laparoscopy	Associated symptoms	Past history of laparoscopy for endometriosis
1	32	0	0	Dysmenorrhoea	Menorragia	–
2	41	0	0	Infertility	Dysmenorrhoea	–
3	27	0	0	Infertility	Chronic pelvic pain & dysmenorrhoea	+
4	28	0	0	Dysmenorrhoea	–	–
5	27	0	0	Infertility	–	+
6	35	1	0	Infertility	Dysmenorrhoea, dyspareunia	–
7	21	2	0	Adnexal mass	–	+
8	25	1	0	Infertility	Dysmenorrhoea, rectorragia	–
9	41	0	0	Dysmenorrhoea	Umbilical bleeding during menstruations	–
10	29	0	0	Infertility	dysmenorrhoea	–

Table 2. Laparoscopic, Histological, and ^{18}FDG PET – CT Principal Findings

Patient	Observed lesions	Endometriosis staging*	Laparoscopic treatment	Histopathology (anti CD10 immunohistochemistry)	^{18}FDG PET–CT findings
1	None	0	None	No specimen	–
2**	Bilateral ovarian adhesions and superficial bilateral ovarian endometriosis lesions	2	Adhesiolysis, ovarian cystectomy	–	–
3	Complete posterior culdesac obliteration, bilateral ovarian adhesions and unilateral ovarian endometrioma > 3 cm	4	Adhesiolysis, ovarian cystectomy	+	–
4	Unilateral ovarian endometrioma > 3 cm, bilateral ovarian adhesions, superficial peritoneal lesion < 1 cm	3	Adhesiolysis, ovarian cystectomy	+	–
5	Complete posterior culdesac obliteration and unilateral ovarian endometrioma > 3 cm	4	Adhesiolysis, ovarian cystectomy	+	–
6	Unilateral ovarian and tubal adhesions, superficial peritoneal lesion < 1 cm	2	Adhesiolysis, peritoneal biopsy	+	–
7**	Bilateral ovarian and tubal adhesions, unilateral ovarian endometrioma < 1 cm	2	Adhesiolysis, drainage and coagulation of ovarian endometrioma	No specimen	–
8**	Complete posterior culdesac obliteration, unilateral adnexal dense adhesions	4	Adhesiolysis	No specimen	–
9	Partial posterior culdesac obliteration, unilateral adnexal dense adhesions, superficial peritoneal lesion < 1 cm, and sub coetaneous para umbilical endometriosis mass	3	Adhesiolysis, endometriosis sub coetaneous mass dissection	+	–
10**	Complete posterior culdesac obliteration, unilateral adnexal dense adhesions	4	Adhesiolysis	No specimen	–

* Staging of endometriosis was obtained using the American Society for reproductive Medicine classification.
** Visual inspection during laparoscopy observed typical lesions of endometriosis.

A few case reports suggest that endometriosis lesions could be detected using ^{18}FDG PET, as endometriosis is often accompanied by important inflammatory reactions.[11-14,19,20]

Lapela et al[19] studied a series of 13 patients with suspect ovarian tumors. In 3 patients with ovarian endometriomas, the tumor either appeared as an area with little tracer uptake or was not clearly distinguished; the SUV was very low in contrast to ovarian cancers, which were associated with much higher SUV. Holder et al[20] evaluated a series of 103 PET-SCAN performed in 76 patients with advanced melanoma, searching for

metastases. These authors reported 1 false positive in a patient with endometriosis. Similarly, Rieber et al[21] reported, in a series of 103 women with suspicious adnexal findings on sonography that 20 women had false positive findings on PET (hypermetabolism of benign processes), including 4 cases of endometriosis. Jeffry et al[14] reported a case report of a woman with endometrioma who had a positive result on FDG-PET. They suspected that this was due especially to inflammation.

^{18}FDG PET has been used to quantify the inflammatory response and measure the aggressiveness of other benign diseases.[15,16] For these reasons, we prospectively studied the use of ^{18}FDG PET in diagnosing endometriosis. However, in this study, we did not observe any hypermetabolic anomaly that could be related to endometriosis using ^{18}FDG PET-CT. Endometriosis was confirmed by laparoscopy in 9 of the 10 included patients and was histologically proven in 5 cases. None of the patients diagnosed with endometriosis presented hypermetabolism in the ^{18}FDG PET-CT. This was not even the case in women with an advanced stage of the disease or severe symptoms, suggesting deep infiltrating endometriosis.[22-24] We, therefore, decided to prematurely interrupt the protocol. In clinical practice, ^{18}FDG PET – CT may be an acceptable technique, provided that it has an acceptable sensitivity. We calculated the chance of having sensitivity of respectively at least 80% or 60%. With the results obtained in this series, the likelihood is respectively lower than 0.0000001 percent and lower than 0.01 percent. Still, it is possible that women who present an endometrioma with potential malignant degeneration will have an early positive PET SCAN. Indeed, Bourdel et al[25] used recently PET SCAN to allow staging in such a case – report. Our findings are also limited to the use of ^{18}FDG as isotopic tracer, which may be insufficiently specific. It is possible that better results would be obtained using more specific tracers to endometrial tissue. For instance isotopic imaging of oestrogen receptors have been reported in breast cancer patients (26). 4-Fluoro-11β-methoxy-16-^{18}F-fluoroestradiol (4FMFES) is a radiolabeled estradiol analog for ER imaging with PET. This tracer exhibited significant, most likely ER – mediated, uterus uptake in both pre – and postmenopausal patients (27). Further research may explore the value of specific tracers in endometriosis and compare results of PET with other imaging techniques in diagnosing respectively ovarian endometriomas, recto – vaginal lesions and peritoneal lesions.

Currently, in clinical practice, we do not recommend ^{18}FDG PET – CT as diagnostic tool for endometriosis. Laparoscopy remains, up to this day, the gold standard for diagnosing endometriosis.

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Author's role

M Fastrez was responsible of the patients recruitment, participated to laparoscopies, collected data and drafted the manuscript.

C Nogarède analyzed all ^{18}FDG PET – CT, with the help of **M Tondeur**.

N Sirtaine analysed all tissue specimens.

S Rozenberg participated to the design of the study and the writing of the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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