
¹⁸F-FDG PET in Pregnancy and Fetal Radiation Dose Estimates

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The purpose of this study was to estimate the fetal radiation exposure resulting from ¹⁸F-FDG PET procedures performed in pregnant patients with malignancies. **Methods:** Five pregnant patients with a biopsy-proven diagnosis of malignancy who underwent ¹⁸F-FDG PET studies were retrospectively reviewed. All patients underwent PET-only studies (and not PET/CT studies) with a reduced ¹⁸F-FDG dose (except for 1 patient who had a negative pregnancy test immediately before the ¹⁸F-FDG PET procedure but was confirmed to be pregnant a few weeks later), including vigorous hydration and diuresis to minimize radiation exposure to the fetus. One patient underwent ¹⁸F-FDG PET twice during her pregnancy (in the second and third trimesters). Fetal radiation dose was independently assessed for each patient, and an analysis was made of fetal radiation doses using the measurements of activity in the fetuses at various stages of pregnancy. **Results:** Six ¹⁸F-FDG PET studies in 5 pregnant patients were analyzed. The ¹⁸F-FDG PET scans were obtained in early pregnancy ($n = 1$), the second trimester ($n = 2$), and the third trimester ($n = 3$). The fetal dose exposure from ¹⁸F-FDG PET studies was estimated to range from 1.1 to 2.43 mGy for various trimesters in pregnancy (except for the patient in the early stage of pregnancy, in whom activity in the whole uterus was considered, and the fetal dose was estimated to be 9.04 mGy). All patients delivered healthy infants with no visible abnormalities at term. **Conclusion:** The fetal radiation dose from ¹⁸F-FDG PET studies is quite low and significantly below the threshold dose for deterministic effects due to radiation exposure to the fetus. The estimated fetal radiation exposure in our cases was slightly lower than existing estimates on fetal dose exposure, and as more data become available, the current fetal dose estimates may have to be modified accordingly. By addressing an important safety issue dealing with performing medically necessary ¹⁸F-FDG PET in pregnant patients, these data are expected to help in the imaging workup of cancer patients during pregnancy.

Key Words: PET; radiation safety; ¹⁸F-FDG PET; fetal radiation dose

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Radiation exposure to patients from radiologic studies is becoming an increasingly important issue in medicine. Growing public awareness of the potential hazard of radiation has led to additional scrutiny of the medical utility and use of radiologic procedures by several medical and regulatory organizations. However, there is little doubt that modern radiologic and nuclear medicine imaging modalities offer significant information about disease and pathology and are often critical components of patient management. When used appropriately, the benefits from imaging usually outweigh the minimal risks associated with imaging procedures. This is equally applicable when imaging special, higher-risk patient populations such as pregnant women, lactating mothers, and children. Pregnant women present a particularly difficult dilemma when attempting to balance the need for the imaging study for the mother with the risk from the radiation exposure to the unborn fetus. Fortunately, cancer occurrence rates during pregnancy are lower than among nonpregnant women. Recent estimates indicate that cancer occurs in approximately 1 in 1,000 pregnancies (1). Possible pathologies include malignancies of the breast, cervix, thyroid, and ovaries; Hodgkin lymphoma; and malignant melanoma (2). Additionally, as more women delay childbearing, cancers that have an increasing incidence with age should be expected to be more frequently encountered during pregnancy (3–5). Not only has the use rate of imaging in the general patient population grown dramatically over the past few decades, but radiologic imaging in pregnant patients has also increased (6).

¹⁸F-FDG PET and PET/CT have now become the standard of care for evaluation and workup of many neoplasms, including most of the malignancies that can occur in pregnant patients. However, most of the literature addressing the safety of imaging during pregnancy omits PET and PET/CT modalities because of the lack of data regarding the safety and radiation exposure risks to the fetus (7,8). Fetal radiation exposure resulting from medical imaging may be a frightening and complicated issue for pregnant women to understand in the course of granting their consent for an imaging procedure. Lack of accurate, scientific data about

the risks and benefits of ^{18}F -FDG PET in diseased pregnant patients combined with medical liability concerns may result in a conservative and potentially inappropriate choice to withhold necessary medical imaging in such situations. The purpose of this article is to document our successful experiences with ^{18}F -FDG PET in pregnant patients and to attempt to assess the fetal radiation exposure resulting from ^{18}F -FDG PET procedures.

MATERIALS AND METHODS

Five pregnant patients referred to our PET center for oncologic ^{18}F -FDG PET scans were included in this retrospective study. All 5 patients had a biopsy-proven diagnosis of cancer, and all, except for 1, had established pregnancy at the time of ^{18}F -FDG PET. One patient was subsequently found to be pregnant a few weeks after her ^{18}F -FDG PET scan, even though she had a negative urine pregnancy test immediately before her ^{18}F -FDG PET procedure. All patients with confirmed pregnancy were counseled about the need for PET given their diagnosis and about the risks and benefits of PET in their situation. Informed consent was obtained from all patients with confirmed pregnancy before PET. The patients with a confirmed pregnancy specifically underwent PET-only scans (and not PET/CT scans) and received a smaller dose of the radiotracer ^{18}F -FDG (173.9–340.4 MBq [4.7–9.2 mCi]) instead of the dose used in our standard protocols (555 MBq [15 mCi]). The patient who tested negatively for pregnancy immediately before her imaging session received a dose of 583.12 MBq (15.76 mCi) of ^{18}F -FDG. All patients received oral (480–540 mL [16–18 oz] water) and intravenous hydration (250 mL of 0.9% saline) during the ^{18}F -FDG uptake period (~90 min) and underwent diuresis with furosemide (10 mg) administered intravenously 15 min after ^{18}F -FDG administration. On average, these patients voided 4 times during the uptake period, beginning approximately 30 min after ^{18}F -FDG administration. The PET-only images were acquired on an Advance scanner (GE Healthcare) or a Discovery LightSpeed-4 scanner in PET-only mode (GE Healthcare) operating in 2-dimensional mode with 5 min per bed position (5–6 bed positions on average). Attenuation correction was provided by a ^{68}Ge rod source transmission scan. The PET data were processed with iterative reconstruction using the ordered-subset expectation maximization method, and all appropriate corrections were included. Hydration and diuresis are a routine part of our imaging protocol, with the goal of minimizing radiation dosage to the patient and eliminating urinary tract activity. In the patients known to be pregnant, reduced ^{18}F -FDG injected dosage and performance of PET-only studies were also implemented to reduce radiation exposure to the fetus. One patient was imaged twice during her pregnancy (at 18 and 30 wk; patients 2 and 5 in the Results section). Six PET images for 5 patients were analyzed.

The fetal dose was independently assessed for each patient. Fetal volume (cm^3) and average concentration of activity in the fetus (kBq/mL) were measured. Fetal volume was estimated by manually placing a region of interest over the fetus on each slice in which the fetus was visible. The area of the region of interest was multiplied by the slice thickness to convert to a volume of interest. The values of fetal volume obtained by this technique were correlated with the expected fetal volumes for that gestational age based on published MRI and ultrasound studies (9). The total radioactivity in the volume of interest was measured on a slice-by-slice basis using the dedicated PET workstation (ADW, version 4.3; GE Healthcare). For the patient who was in the early stages of gestation

(negative pregnancy test immediately before ^{18}F -FDG PET), the fetus was not clearly delineated and only diffusely increased uptake was noted in the uterus. In this patient, the volume of the uterus (rather than that of the fetus) was used for analyzing fetal radiation exposure.

An analysis was made of fetal doses using the measurements of activity in the fetuses at various stages of pregnancy and combined with data for the standard metabolism of ^{18}F -FDG as provided by the International Commission on Radiological Protection (ICRP) in publication 106 (10). Table 1 depicts the time–activity integrals for various organs, as suggested in the ICRP publication 106 model for ^{18}F -FDG.

These integrals were entered into the OLINDA/EXM software (version 1.1) (11). For the urinary bladder, 2 assumptions were evaluated, using the ICRP publication 106 model for urinary excretion: routine 2-h bladder voiding and bladder voiding at 45, 60, 75, and 90 min. The first assumption was evaluated using the standard bladder-voiding module in OLINDA/EXM. The second assumption was evaluated using the SAAMII compartmental modeling code and introducing change conditions at these times for the bladder compartment. The adult female (nonpregnant) model was used to assign doses for patient 1, with no assignment of activity to the uterus, as per the footnote in Table 1. For the other patients, the time integrals in Table 1 were assigned to the fetus, with the 3-mo-pregnant model used for patient 2 and the 6-mo-pregnant model used for the other 3 patients.

RESULTS

The 5 pregnant patients ranged in age from 22 to 37 y and had cervical cancer (2 patients), lymphoma (2 patients), and lung cancer (1 patient). One patient underwent ^{18}F -FDG PET in an early stage of her pregnancy (presumably within 6 wk of gestation because the urine pregnancy test was negative immediately before the ^{18}F -FDG PET scan). One patient underwent ^{18}F -FDG PET during the second trimester, and 2 patients underwent ^{18}F -FDG PET during the third trimester of pregnancy. One patient underwent two ^{18}F -FDG PET scans during pregnancy: 1 in the second trimester and 1 in the third trimester. In the patient who underwent ^{18}F -FDG PET early during pregnancy, the fetus was not clearly visualized, and only diffusely increased ^{18}F -FDG activity was noted in the uterine region (Fig. 1). In all other patients, the fetus was clearly delineated with ^{18}F -FDG uptake (Fig. 2), and in some cases, ^{18}F -FDG activity was also noted in the fetal myocardium (Fig. 3), with mostly faint background ^{18}F -FDG activity elsewhere in the remaining parts of the fetus. There was no prominent focal ^{18}F -FDG uptake

TABLE 1
Time–Activity Integrals for Various Organs, as Suggested in ICRP Publication 106 Model for ^{18}F -FDG

Organ	Time–activity integral (Bq-h/Bq)
Brain	0.21
Heart wall	0.11
Lungs	0.079
Liver	0.13
Other tissues	1.7

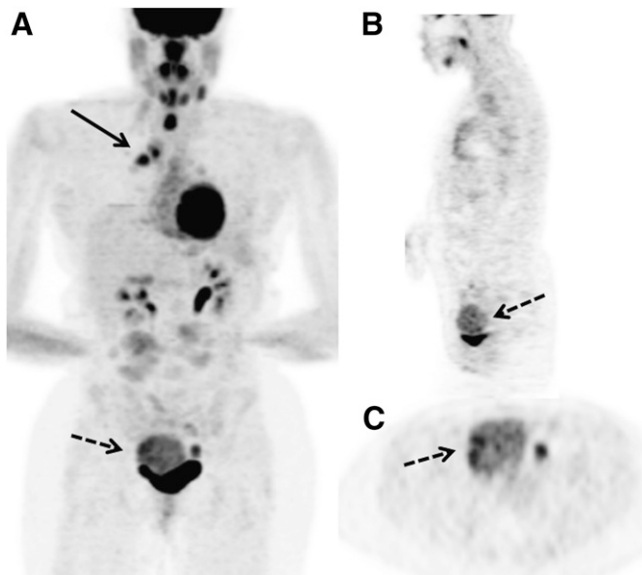


FIGURE 1. Selected attenuation-corrected ^{18}F -FDG PET images of 30-y-old woman with history of juvenile laryngeal papillomatosis and lung cancer. (A) Maximal-intensity-projection image in coronal projection showing intensely ^{18}F -FDG-avid lesions in chest corresponding to lung cancer (solid arrow) and more modestly increased ^{18}F -FDG activity in pelvis (dashed arrow). (B and C) Single sagittal and transaxial slices, respectively, showing that modestly increased ^{18}F -FDG activity represents activity in expected region of uterus (arrows). This patient had negative pregnancy test immediately before ^{18}F -FDG PET procedure but was confirmed to be pregnant 4 wk later, and hence increased ^{18}F -FDG activity in uterus was attributed to early pregnancy.

in other fetal regions in any patient. All patients delivered healthy infants with no visible abnormalities at term. The characteristics of the patients with the time-integrated activity are shown in Table 2.

The results of calculated fetal dose in our patients are summarized in Table 3. Patient 1 received more activity

than the other patients and thus had the highest fetal doses. Because there was no assigned fetal uptake, the urinary bladder was important to the total fetal dose, and changes in bladder voiding had a notable effect. Similarly, for patient 2 the assigned fetal activity was low, and the difference in fetal dose calculated by the 2 different voiding models (standard voiding and nonstandard voiding) was the highest for all patients (44% difference, whereas for others the difference was about 20%–25%). For patient 5, the assigned fetal uptake was the highest, and the influence of bladder voiding was less pronounced (~11%). This radiation dose to the fetus represents activity from the administered radiopharmaceutical alone. Because all our studies were performed as PET-only studies with ^{68}Ge rod source transmission scanning for attenuation correction, the additional radiation exposure from the transmission scanning was negligible (12,13) and was not included in the dose estimates. The observed uptake and time-activity integrals from this study are compared in Table 4 with those from 2 other studies, 1 by Stabin (14), assigned on the basis of observed activity measured in primates, and 1 by Zanotti-Fregonara et al. (15), measured in 1 human patient at about 10 wk of gestation. The values from Stabin are shown for the 3- and 6-mo cases, as were assigned to patients 2–6.

DISCUSSION

Medical imaging in pregnant patients is a delicate issue. Although radiopharmaceuticals have been administered to pregnant patients to perform nuclear medicine studies and there is literature about placental transfer of radiopharmaceuticals and dosimetry in pregnant patients (16) as well as about radiation-absorbed dose to the embryo or fetus from radiopharmaceuticals (17), these data lack information about fetal radiation exposure and dosimetry related to ^{18}F -FDG PET. ^{18}F -FDG PET was not in routine clinical use until the late 1990s and early 2000s. However, since then, ^{18}F -FDG

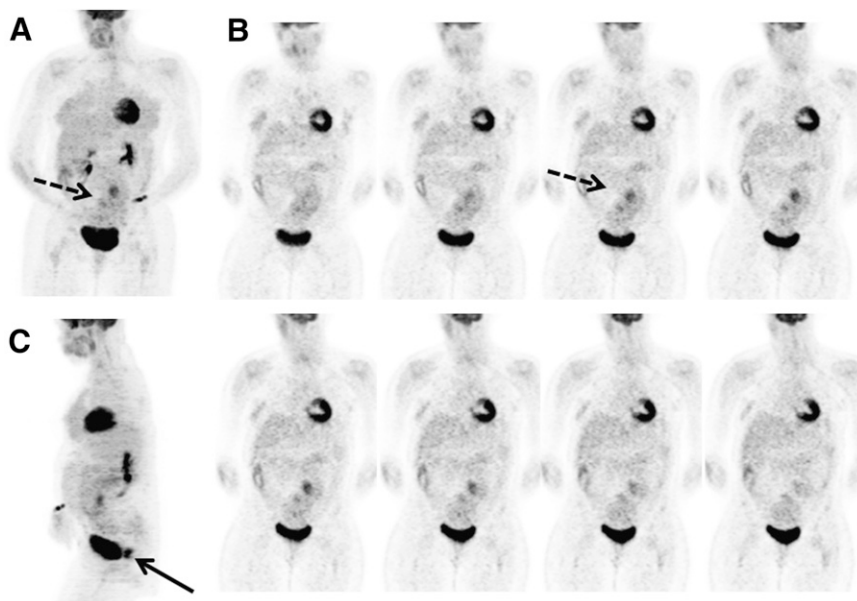


FIGURE 2. Selected attenuation-corrected PET images from ^{18}F -FDG PET study of 34-y-old woman, 28 wk pregnant and recently diagnosed with squamous cell carcinoma of cervix. (A) Maximal-intensity-projection image in coronal projection showing ^{18}F -FDG activity (dashed arrow) related to fetus in pregnant uterus in lower abdomen and pelvis. (B) Two rows of selected coronal images showing ^{18}F -FDG activity related to fetus in pregnant uterus in lower abdomen and pelvis (arrow). (C) Maximal-intensity-projection image in sagittal projection showing intense ^{18}F -FDG uptake (arrow) in cervical malignancy posterior to urinary bladder activity.

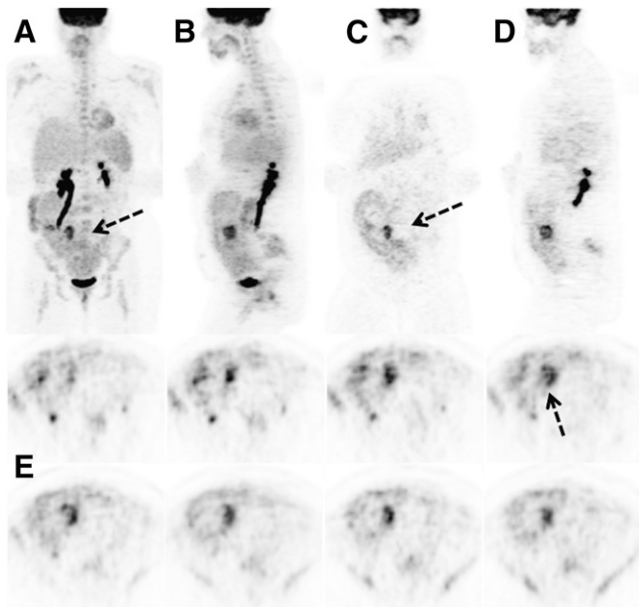


FIGURE 3. Selected attenuation-corrected PET images from ^{18}F -FDG PET in 28-y-old woman, 30 wk pregnant and with history of B-cell non-Hodgkin lymphoma that was confined to mediastinum and for which patient had recently completed 4 cycles of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone-rituximab chemotherapy. (A and B) Maximal-intensity-projection images in coronal and sagittal projections, respectively, showing uptake related to fetus (arrow). (C and D) Selected coronal and sagittal slices showing no evidence for ^{18}F -FDG-avid malignant disease related to patient's non-Hodgkin lymphoma (patient had ^{18}F -FDG-avid disease confined to mediastinum on initial staging scan performed when she was newly diagnosed with non-Hodgkin lymphoma and was 18 wk pregnant; images not shown here). ^{18}F -FDG activity related to fetus is noted in lower abdomen and pelvis (arrow). Fetal myocardial activity is clearly seen. (E) Two rows of selected transaxial slices at level of lower abdomen showing prominent ^{18}F -FDG activity in fetal myocardium (arrow). Retention of activity is seen in upper right urinary collecting system and ureter associated with enlarged gravid uterus.

PET has become an established imaging modality for evaluation of several malignancies, and it was estimated that more than 4 million ^{18}F -FDG PET studies would be performed in 2010. Despite this, ^{18}F -FDG PET studies of pregnant patients are extremely uncommon, and reports of even accidental ^{18}F -FDG PET studies of pregnant patients are rare (15,18–21). Because adequate and accurate data regarding

^{18}F -FDG uptake by the fetus are not available (other than the few case reports of accidental exposure), it is difficult to accurately calculate the fetal radiation exposure from ^{18}F -FDG PET in pregnant patients. The existing estimates for fetal dose from ^{18}F -FDG PET are mostly based on data from nonhuman primates and mathematic models (14,16,17,22). Recent case reports by Zanotti-Fregonara et al. (15,19) have raised the possibility that ^{18}F -FDG dose to the fetus in early pregnancy may be higher than estimated by current dosimetric standards. Hence, there is a need to have more data to establish the accurate fetal dose exposure from ^{18}F -FDG PET studies.

To our knowledge, this is the first and largest series of pregnant patients for whom fetal radiation exposure from ^{18}F -FDG PET was calculated. Our data add considerably to the existing literature about fetal radiation exposure from ^{18}F -FDG PET studies of pregnant patients. Moreover, our patients (except for 1) were not accidentally exposed to ^{18}F -FDG during their pregnancy but rather underwent intentional studies that were performed after adequate consideration of the risks and benefits of ^{18}F -FDG PET in these pregnant patients with malignancy.

^{18}F -FDG is known to cross the placental membrane and accumulate in the fetus (15,18,19,22–24), and in all patients except 1, we were able to clearly identify ^{18}F -FDG activity in the fetus inside the gravid uterus, confirming the ability of ^{18}F -FDG to cross the placenta and accumulate in the fetus. The exception was the patient in the early stage of pregnancy, in whom we did see diffusely increased ^{18}F -FDG activity in the uterus but not a clearly identifiable fetus. At that early stage, fetal morphology was not clearly delineated, and the activity probably represented uptake in the gestational sac and the uterus itself. Because these were stand-alone PET studies with transmission scanning for attenuation correction and not PET/CT studies, the anatomic details of various maternal regions including the intraembryonic fetus were not available from these ^{18}F -FDG PET studies. However, we did see increased ^{18}F -FDG activity in the fetal myocardial region in a few cases, as has also been documented in the past (21), with just faint background ^{18}F -FDG activity elsewhere in the remaining fetal regions. There is no scientific literature documenting fetal toxicity associated with ^{18}F -FDG in pregnant women or nonhuman primates. All of our patients delivered healthy babies at term.

TABLE 2
Characteristics of Pregnant Patients with Observed Fetal Concentrations and Time-Integrated Activity

Patient no.	Age (y)	Weight (kg)	Administered activity (MBq)	Stage of gestation	Average observed concentration in fetus (kBq/mL)	Volume (cm ³)	Fraction	Time-integrated activity (Bq-h/Bq)
1	30	67.6	583	~6 wk	16.8	124.1*	0	0
2	27	87.8	200	18 wk	1.98	86.9	0.00086	0.0023
3	22	67.1	337	25 wk	3.96	717	0.0084	0.0223
4	34	81.8	174	28 wk	2.31	535	0.0071	0.0187
5	27	88.6	229	30 wk	2.86	1,573	0.0196	0.0518
6	37	58.9	181	23 wk	2.56	552	0.0078	0.0206

*Only diffusely increased uptake in uterus was seen. Patients 2 and 5 are same patient (scanned twice during pregnancy).

TABLE 3
Summary of Results for Fetal Radiation Dose

Patient no.	Dose to fetus (mGy/MBq)		Total dose to fetus (mGy)	
	2-h voids	Irregular voiding	2-h voids	Irregular voiding
1	1.95E-02	1.55E-02	1.14E+01	9.04E+00
2	1.03E-02	7.16E-03	2.06E+00	1.43E+00
3	7.41E-03	6.23E-03	2.49E+00	2.10E+00
4	6.93E-03	5.79E-03	1.21E+00	1.01E+00
5	1.17E-02	1.06E-02	2.68E+00	2.43E+00
6	7.27E-03	6.08E-03	1.32E+00	1.10E+00

This dose is from administered radiopharmaceutical alone. Fetal radiation dose from transmission scanning with ⁶⁸Ge rod source is negligible, and hence values in this table represent effective fetal radiation dose for ¹⁸F-FDG PET-only scans. However, because most PET scanners are now PET/CT scanners and may not have option to be operated in PET-only mode, total fetal radiation exposure from ¹⁸F-FDG PET/CT would be additional 6–14 mGy from CT portion of study (this radiation dose depends on CT protocol used during PET/CT study).

The fetal volumes estimated by our methodology correlate well with the expected fetal volumes for that gestational age based on prior published MRI and ultrasound studies (9). Our results confirm that the fetal dose exposure from ¹⁸F-FDG PET studies is low and generally ranges from 1.1 to 2.43 mGy for various trimesters in pregnancy. This fetal dose exposure is significantly below the threshold dose for deterministic effects due to radiation exposure to the fetus. That threshold was postulated to be on the order of 100–600 mGy in the study of Steenvoorde et al. (25). There is no threshold for stochastic effects, but a discussion about the probability of various deterministic and stochastic effects occurring as a result of fetal exposure to radiation from ¹⁸F-FDG PET in pregnancy is beyond the scope of this article. The outlier in our data was the patient in the early stage of pregnancy, in whom we were unable to clearly delineate the fetus and instead considered the activity in the whole uterus. In this patient, the estimated total dose of 9.04 mGy is prob-

ably significantly overestimated because of technical factors but still remains well below the threshold for deterministic effects. Moreover, there are probably no deterministic or stochastic effects with radiation exposure soon after conception (26), and the threshold dose for deterministic effects is higher during the early pregnancy or embryonic period (27). More importantly, our calculations for fetal dose show that estimated fetal radiation exposure may in fact be slightly lower than existing estimates on fetal dose exposure (14,16,17) and the more recent values calculated by Zanotti-Fregonara et al. (15,19).

Our standard protocol for ¹⁸F-FDG PET studies also includes procedures such as adequate hydration in the form of oral water (when tolerated by the patient) and intravenous normal saline infusion (unless contraindicated medically), as well as vigorous diuresis using intravenous furosemide (also unless contraindicated medically) 15 min after ¹⁸F-FDG administration. These measures decrease the overall radiation exposure to the patient by more rapidly flushing the radiopharmaceutical from the body and at the same time improve the quality of images by decreasing background ¹⁸F-FDG activity. When an ¹⁸F-FDG PET scan is requested for a pregnant patient, we discuss the case with our referring clinical colleagues and after mutually determining that the study benefits indeed outweigh the risks, we counsel the patient and obtain informed consent before proceeding with the study. Our protocol for ¹⁸F-FDG PET in pregnant patients includes a few additional procedures to minimize radiation exposure to the fetus. We administer a lower dose of ¹⁸F-FDG to pregnant (185–370 MBq [5–10 mCi]) than to non-pregnant (555 MBq [15 mCi]) patients. In addition, we do not use a PET/CT technique in these patients because the CT component adds additional radiation exposure (estimated to range from 6 to 14 mGy (15,19,28,29), and depending on the CT protocol used) to the patient and the fetus. We used transmission scanning with a ⁶⁸Ge rod source for attenuation correction in lieu of CT. Although our Advance Scanner is no longer operational, our Discovery LightSpeed-4 PET/CT scanners have the ability to operate in PET-only mode and use transmission scanning with a ⁶⁸Ge rod source

TABLE 4
Comparison of Our Results with Prior 2 Studies

Patient no.	Time-integrated activity (Bq-h/Bq)*		
	Our data	Stabin et al. (14)	Zanotti-Fregonara et al. (15)
2	0.0023	0.019	0.00351
3	0.0223	0.064	
4	0.0187	0.064	
5	0.0518	0.064	
6	0.0206	0.064	

*Integrals are Bq-h in fetus per Bq administered to mother.

Early pregnancy model was used for patient 1, 3-mo-pregnant female model for patient 2, and 6-mo model for all others, because these most closely matched their state of gestation. Dose from study of Zanotti-Fregonara et al. was reasonable to use for comparisons with dose to patient, because patients were at similar stages of gestation. Because fetus of patient 1 was at early gestational age and not well visualized, that patient was omitted from this comparison.

for attenuation correction in lieu of CT. This ability facilitates further reduction in the fetal radiation exposure from ^{18}F -FDG PET in pregnant patients because the radiation dose from a ^{68}Ge rod source is negligible (12,13). Although the exact values of fetal radiation dose from transmission scanning with a ^{68}Ge rod source have not been calculated, for comparative purposes the effective dose from this method of scanning for cardiac and brain transmission studies has been estimated to be approximately 0.00077 and 0.00027 mSv/MBq·h, respectively. Hence, we have appropriately neglected this minimal amount of additional radiation exposure from the transmission scanning in our calculations. Moreover, using PET-only scanning, we were able to reduce the fetal radiation exposure by about 6–14 mGy when compared with PET/CT.

^{18}F -FDG is excreted by the kidneys and is present in the urine in the urinary bladder (30). The anatomic position of the bladder with respect to the fetus renders it a primary source of radiation, and rapid elimination of the radioactive urine from the urinary bladder can facilitate minimizing fetal radiation exposure. Urinary bladder catheterization can reduce the amount of radioactive urine in the urinary bladder by continuously draining the urinary bladder and thus potentially help in decreasing fetal radiation exposure. However, vigorous hydration and diuresis also help in rapidly eliminating the radiopharmaceutical from the body (including the urinary bladder), and, along with the additional procedures implemented in our protocol for pregnant patients, helped keep the estimated fetal radiation doses from our ^{18}F -FDG PET studies quite low and potentially safe.

CONCLUSION

Our data indicate that the fetal radiation exposure from ^{18}F -FDG PET performed, when medically necessary, in pregnant women with cancer is low. However, all efforts should be made to minimize the fetal radiation exposure by modifying the protocol appropriately. The estimated fetal radiation dose calculated in our setting is low, and as more data become available, the current fetal dose estimates may require further modification.

DISCLOSURE STATEMENT

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

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