Volume 17, No 4 | International Journal of Radiation Research, October 2019

Assessment of fetal and maternal radiation absorbed dose in 18F-FDG PET imaging

N. Ahmadi[1], A. Karimian[2], M.N. Nasrabadi[1*], A. Rahmim[3,4]

[1]Department of Nuclear Engineering, Faculty of Advanced Sciences & Technologies, University of Isfahan, Isfahan, Iran
[2]Department of Biomedical Engineering, University of Isfahan, Isfahan, Iran
[3]Department of Radiology, Johns Hopkins University, Baltimore MD, USA
[4]Departments of Radiology and Physics & Astronomy, University of British Columbia, Vancouver BC, Canada

► ***Original article***

Corresponding authors:
Dr. M.N. Nasrabadi,
Fax: *+ 98 311 793 4215*
E-mail:
mnnasrabadi@ast.ui.ac.ir

Revised: May 2019
Accepted: July 2019

Int. J. Radiat. Res., October 2019; 17(4): 651-657

DOI: 10.18869/acadpub.ijrr.17.3.651

ABSTRACT

Background: Clinical application of PET imaging for diagnosis, staging, re-staging treatment planning and treatment response assessment have become a major focus of studies in the past decades. Fetus is more sensitive to ionizing radiation, consequently, radiation absorption risks need to be assessed carefully. The objective of this article is to accurately estimate the absorbed dose during pregnancy in PET examinations. The method adopted in this article is simulative-analytic. ***Materials and Methods***: The absorbed dose from administrating 18F-FDG during pregnancy is estimated through the BodyBuilder anthropomorphic mathematical phantom (inexpensive) together with Monte Carlo simulations in order to obtain a reliable and feasible methodology. In this simulation, the Specific Absorbed Fractions (SAF) is estimated for organs of 3, 6 and 9-months fetal. ***Results:*** The obtained results indicate that the absorbed dose of 18F-FDG PET imaging the fetal is 2.50×10-2 mGy/MBq early; 2.04×10-2 mGy/MBq first three months of pregnancy, 1.80 ×10-2 mGy/MBq second three months, and 1.50 ×10-2 mGy/MBq in the third three months of pregnancy. Maternal absorbed dose estimation here is (R2=0.965) which perfectly corresponds to ICRP publication. ***Conclusion:*** The results from Monte Carlo code with BodyBuilder anthropomorphic phantoms and ICRP recommendation are of acceptable correlation. Applying the pure BodyBuilder anthropomorphic phantoms in this simulation, which yields agreeable results in addition to its low time consumption, corresponds to the available finding by other researchers while reducing calculation times. Moreover, the fetal & maternal absorbed doses remain however well below the threshold for any deterministic effects.

Keywords: *Fetal dose, maternal dose, GATE/GEANT4, PET/CT, 18F-FDG.*

INTRODUCTION

Positron emission tomography (PET) examination usage injection of ^{18}F-fluoro-2-deoxy-Dglucose(^{18}F-FDG) has become an essential cornerstone in cancer imaging [1, 2], with a growing number over the last decade. Several millions of ^{18}F-FDG PET scans are performed annually worldwide [1, 2]. Up to now, the dosimetric assessments on ^{18}F-FDG PET imaging are mostly go on accidental imaging performed during pregnancy. The incidence rate of cancer during pregnancy is lower than its occurrence in non-pregnant women. The estimation so far indicate that about 1 out of 1,000 pregnancies become subject to cancer [3].

The advantages of PET imaging should be assessed with respect to radiation risk assessment. The fetal dose in patients with cancer must be assessed before administrating

^{18}F-FDG [4]. Fetal radiation exposure can occur either from unknown pregnancies [1, 2] or due to the necessity of performing cancer diagnosis on pregnant patients [5].

Fetal radiation exposure from ^{18}F-FDG is due to: (i) transmitted radioactivity through the placenta and accumulating in fetal tissues [1, 2], and (ii) photons radiated from maternal tissues. The first *in vivo* data estimating fetal self-dose was determined [6] by tests usage ^{18}F-FDG in-take on monkey, at the third trimester of pregnancy.

The standard dosimetry values for ^{18}F-FDG fetal exposure is obtained from monkey data, as being 2.2 $\times 10^{-2}$ mGy/MBq in early pregnancy and at three months and 1.7 $\times$ 10^{-2} mGy/MBq at six and nine months of pregnancy by Stabin [7].

The first phantoms for adult and children are designed through basic geometric shapes by Cristy and Eckerman [8]. The phantoms for pregnant women, which include modeled fetus and organs of mothers at different stages of pregnancy, are designed by Zanotti-Fregonara and Shi *et al.* [12-14], who later designed a series of new voxel-based realistic phantoms, one of which is developed by Stabin, Society of Nuclear Medicine and Molecular Imaging (SNMMI) and Radiation Dose Assessment Resource (RADAR).

Fetal absorbed doses at different trimesters of pregnancy and are being estimated through anthropomorphic phantoms by the Medical Internal Radiation DOSE (MIRDOSE) [9] and organ level internal dose assessment/ exponential modeling (OLINDA/EXM, V1.0) software. A new version of, (OLINDA/EXM,V2.0) software, is developed by applying realistic voxel-based phantoms of pregnant women that are based on actual humans images [10] and by applying body organ and fetal masses introduced by the publication of the International Commission on Radiological Protection (ICRP-89) [11].

Zanotti-Fregonara estimated fetal absorbed dose in 19 pregnant women with fetuses within 5 to 34 weeks age range (12). In 15 cases, the fetus was vividly detectable inside the uterus, and it was possible to estimate the ^{18}F-FDG intake in fetal tissues in a direct manner. New fetal doses from^{18}F-FDG PET based on human data is presented [13]. Mathematical modeling of the human data is made by extrapolation from human data, and realistic voxel-based phantoms [14], by applying for establishing new standardized values for estimation of fetal dose by Stabin.

The objective of this study is to estimate fetal absorbed dose at first, the second and third trimesters of pregnancy together with maternal absorbed dose from^{18}F-FDG in PET.

In this study, an estimate fetal and maternal dose was performed using simple anthropomorphic phantoms (expansive) and Monte Carlo code method. Also, it will demonstrate that with this method, the fetus and maternal doses are consistent with the agreeable results obtained by the researchers, while spend on reducing calculation times and the phantom cost was lower [15].

MATERIALS AND METHODS

Phantom design

The BodyBuilder software is applied to design human anthropomorphic phantoms [16] ("www.whiterockscience.com" Site address with permission). This program can simulate pregnant females at 3, 6 and nine trimesters of pregnancy including fetal details. Three pregnant female phantoms are designed by Stabin [17]; where the specific mathematical equations are provided by SNMMI applied to describe the organs of the phantom which is converted into discrete forms. The BodyBuilder numerical phantoms are designed at a spatial resolution of 2×2×3 mm^3 and converted in to a voxel phantom of 100×200×360 matrix size. In the process of digitization, the phantoms are optimized to minimize the sum of differences between the volumes of the organs in digital and mathematical phantoms [18].

To estimate fetal dose, the BodyBuilder pregnant female phantoms at 3, 6 and nine months of pregnancy is applied in this study. Human anthropomorphic BodyBuilder phantom at the first, second and third trimesters of gestation are shown in (figure 1). To estimate the maternal absorbed dose, we used the

phantom for early months, which is the same as non-pregnant women (MIRD phantom) [1, 2] is applied, because it can be compared with the ICRP recommendation report.

Monte Carlo code

The GATE/GEANT4 Monte Carlo simulation code (version 7.2.0) is applied to estimate the absorbed dose to the organs of the phantoms[1, 2]. In this simulation, photon interaction, like photoelectric absorption, Compton and Rayleigh scattering and positron (β+) are of concern. Runtime of the program is between 4-12 h, where 3×10^6 photons are tracked.

Calculation of ^{18}F-FDG Absorbed Dose

The MIRD formulization for estimating the absorbed dose was utilized. It is expressed by Eq. (1) indicating, the organ's activity contained inside source organs Eq. (2), indicates the (S-value) and Eq. (3) indicates the specific absorbed fractions (SAF) [19]. The (SAF) value was estimated by using the GATE/GEANT4 Monte Carlo simulation code.

$$D_{absorbed} = \tilde{A}(r_s) \times S(r_t \leftarrow r_s) \quad (1)$$

Where, $\tilde{A}(r_s)$ is the time-activity integral (Bq-h/Bq) or cumulated activity in source region, r_s, and $S(r_t \leftarrow r_s)$ are the S-value (i.e., absorbed dose in the target region, r_t, per unit of cumulated activity in the source region ($mGyMBq^{-1}s^{-1}$)).

$$S(r_t \leftarrow r_s) = \frac{1}{M(rt)} \sum E_i Y_i \varphi(r_t \leftarrow r_s, E_i) \quad (2)$$

Where, $\varphi(rt \leftarrow rs, Ei)$ is the absorbed fraction (AF) in energy E_i, Y_i is the radiation yield and M (rt) is the mass of the target organ [1, 2].

$$SAF = \emptyset(r_t \leftarrow r_s, E_i) = \frac{1}{M(rt)} \varphi(r_t \leftarrow r_s, E_i) \quad (3)$$

where, SAF is defined for each pair of source organ and target organ.

SAF is defined through Eq. (4):

$$SAF(r_t \leftarrow r_s) = [\text{energy absorbed in } r_t \text{ /energy emitted from } r_s]/m_T, \quad (4)$$

where, parameter *m* is the target organ *t* mass (kg) [20]. The absorbed energy in each target organ is estimated as the sum of the absorbed energy in all voxels of the organ.

In this setup, in Eq. (1) the biokinetic processes is of concern where a target region is generally irradiated through several source regions.

To estimate organ masses, the number of voxels related to an organ is calculated by multiplying voxel volume by the density of related organ by applying MIRD data [1, 2]. Cumulated activity $\tilde{A}$ in Eq.(1) is provided by ICRP 106 [21].

The mathematical analysis of biokinetic models is run in accordance with both the MIRD Pamphlet No. 12 and International Commission on Radiation Units and Measurements (ICRU-32) [22]. A dynamic urinary bladder model (MIRD Pamphlet No.14) is considered in this study [23].

For calculating each SAF in this simulation in fetal, for each one of the 3, 6 and nine months phantom (3×7=21digital phantoms) six copies of digital phantoms are designed because the simulation of seven source organs should be run in a separate manner. The activity interest in the seven organs (fetus, kidneys, lungs, pancreas, liver, spleen and adrenal glands) is distributed in a uniform manner.

Each voxel in these phantoms have their owned fined attenuation properties, based on composition and density of the appropriate tissue. The data here are based on those described in the Stabin *et al.* [1, 2].

Data analysis

An important component contributing to the calculation of absorbed dose is the organ volumes. Volumes of organs could be modified in the process of converting the original mathematical phantom into a voxelized phantom; accordingly, the relative difference (RD%) for organ volume is quantified through Eq. (5):

$$RD\% = 100\times [(V_{\_Digital})-(V_{\_Math})]/(V_{\_Math}), \quad (5)$$

where, $V_{\_Digital}$ is the organ volume of the given *voxelized* BodyBuilder phantom and $V_{\_Math}$

is the original organ volume before voxelization.

The RD% of absorbed dose between the one from Monte Carlo ($D_{\_GATE}$) and ICRP 106 ($D_{\_ICRP}$) for each photon energy is accessed through Eq. (6):

$$RD\%=100\times [(D_{\_GATE})-(D_{\_ICRP})]/(D_{\_ICRP}) \quad (6)$$

The Monte Carlo code and ICRP recommendation data arecompared through fitting a linear curve on the scatter plot of the data and calculating the Pearson correlation coefficient thereof [24]. All simulation and run was repeated three time for better precession.

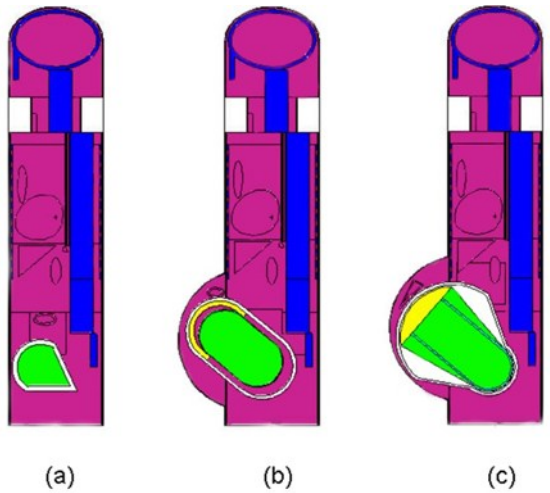

Figure 1. The anthropomorphic BodyBuilder phantom at **(a)** first, **(b)** second and **(c)** third trimesters of gestation obtained from the BodyBuilder software (White Rock Science Company).

RESULTS

The maternal absorbed dose (mGy/MBq) for ^{18}F-FDG obtained for liver, kidneys, lungs, pancreas, spleen, and adrenal glands in this study are bar charted in (figure 2) which contains the ICRP absorbed dose (mGy/MBq) for comparison [21].

The scatter plot and the linear curve fitted to the ICRP and Monte Carlo code results for maternal absorbed dose in ICRP and this study are shown in (Figure 3) where an acceptable linear correlation of (R^2=0.965) between the two series of data is evident. However, the slope of the curve is slightly below (0.884) unity, indicating a slight bias between ICRP and the Monte Carlo data. The curve fitted on the scatter plot of the data which reveals a decent straight connection between the absorbed doses derived from Monte Carlo code and the corresponding ICRP data is shown in (figure 3).

The fetal absorbed dose (mGy/MBq) for ^{18}F-FDG at early, three, six and nine months of pregnancy where this newly proposed method is applied. The dose values here are 2.5 $\times10^{-2}$, 2.04 $\times10^{-2}$, 1.80 $\times10^{-2}$ and 1.5 $\times10^{-2}$ mGy/MBq, respectively .The RD% among the available studies each report and this study are tabulated in Table 1 for comparison purposes.

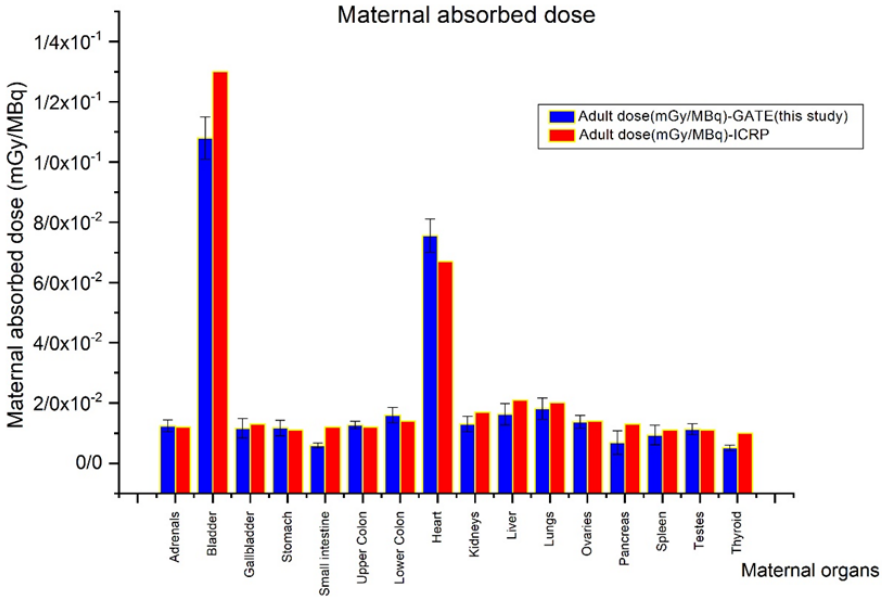

Figure 2. Maternal absorbed dose (mGy/MBq) for different organs, as obtained through this proposed method and compared with that of the ICRP report (21).

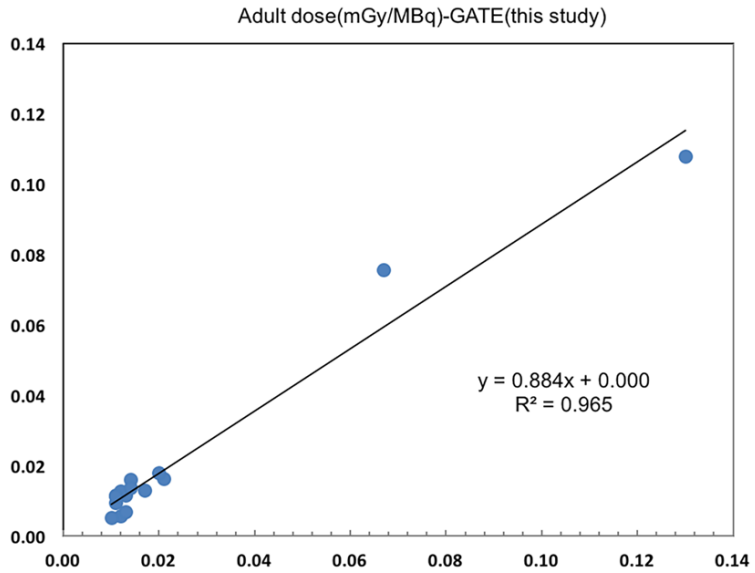

Figure 3. The scatter plot and linear curve fitted on the ICRP and Monte Carlo data for maternal absorbed dose (mGy/MBq).

Table 1. Comparison of the results obtained on fetal absorbed dose of 18F-FDG in early, three, six RD% by existing and this study.

Research	Early Pregnancy (mGy/MBq)	RD%	3-month (mGy/MBq)	RD%	6-month (mGy/MBq)	RD%	9-month (mGy/MBq)	RD%
Russell *et al.*[25]	2.70×10^{-2}	7.41	1.70×10^{-2}	20.00	9.40×10^{-3}	91.49	8.10×10^{-3}	85.19
Stabin (2004) [7]	2.20×10^{-2}	13.64	2.20×10^{-2}	7.27	1.70×10^{-2}	5.88	1.70×10^{-2}	11.76
Zanotti-Fregonara *et al.* [2]	4.00×10^{-2} (10-wk)	37.50	-	-	-	-	-	-
Zanotti-Fregonara *et al.* [26]	3.3×10^{-2} (8-wk)	24.24	-	-	-	-	-	-
Takalkar *et al.* [3]	1.55×10^{-2} (6-wk)	61.29	7.16×10^{-3} (18-wk)	184.92	6.23×10^{-3} (25-wk)	188.92	1.06×10^{-2} (30-wk)	41.51
Xie and Zaidi [27]	3.05×10^{-2}	18.03	2.27×10^{-2}	10.13	1.50×10^{-2}	20.00	1.33×10^{-2}	12.78
Zanotti-Fregonara *et al.* [12]	-	-	-	-	1.25×10^{-2}	44.00	-	-
Stabin et al. (2017) [13]	2.6×10^{-2}	3.8	1.9×10^{-2}	7.3	1.4×10^{-2}	28.57	6.9×10^{-3}	117.39
This study	2.50×10^{-2}	-	2.04×10^{-2}	-	1.80×10^{-2}	-	1.5×10^{-2}	-

DISCUSSION

Attempt is made here to estimate maternal and fetal doses from ^{18}F-FDG administration during pregnancy through the Body Builder anthropomorphic phantoms (simple phantom) followed by simulations through the Monte Carlo code (open source code) by estimating the specific absorbed fractions (SAF) .

The maternal doses obtained from voxelized BodyBuilder phantom in this study indicate a high correlation of (98%) both the ICRP recommendations data with a variation of (2.2%). The same low difference in maternal absorbed dose is observed in all organs. The difference in maternal absorbed dose in the bladder is due to the assumption that the bladder volume remains constant while as to other origins it changed.

Moreover, fetal absorbed doses at in early, three, six and nine months of pregnancy are of similar values with (Stabin 2014 and Xie and Zaidi are 13.67%, 7.27%, 5.88%, 11.76% and 18.03%, 10.13%, 20%, 12.78%, respectively) [1, 2]. In contrast, the fetal absorbed dose in three and six months of pregnancy reported by Takalkar [3] and are of high RD% because of differences in age and fetal volume as compared with this study. The fetal dose at nine months of pregnancy reported by Stabin MG [17] is of high RD%, and this is essentially related to the greater realism of the voxelized phantoms which has different volumes especially in nine months of pregnancy. The two main factors that made

the difference in fetal absorbed doses consist of fetal mass and the relative geometry differences between the source and target organs in the realistic voxel-based phantoms and stylized phantoms.

By applying these two types of phantom cases, different results are obtained for fetal absorbed dose. Here, it is recommended to be very careful in decision-making on phantom type. Voxel phantoms are very realistic in anatomic sense although subject to tissue size and position in individuals. In addition to being expensive the process of segmentation needs more time, while, the stylized phantoms anatomy can be modified in an easy manner while being not expensive [28].

Estimating the absorbed dose by fetal is essential, in the early days of pregnancy in specific, because the skeleton is not shaped yet and the outline of the fetal is not completely viewed on PET or CT.

The doses estimated through the Monte Carlo code with the BodyBuilder phantoms are similar to those obtained from old phantoms in the first and the second trimester pregnancy (RD= 7.27%, 5.88%, respectively), [7]. This is mostly described by the fact that the mass (fetus) at three and six months of pregnancy does not shift between the two sets of phantoms.

According to the results obtained here, fetal absorbed dose for this phantom and Monte Carlo code consist of: 2.5 ×10-2 mGy/MBq in early, 2.04×10-2 mGy/MBq in the three month of pregnancy, 1.80×10-2 mGy/MBq in the six months of pregnancy and 1.5 ×10-2 mGy/MBq after the nine months of pregnancy with a typical injected activities of ^{18}F-FDG (185-370 MBq within 3-8 (msv) range [29].

The ^{18}F-FDG fetal absorbed dose is subject to the limit of deterministic effects in any period of pregnancy while the indications of PET in pregnant women should be justified [30]. Therefore this issue is very important when using PET/CT machine. The CT dose for attenuation correction should be added to dose from absorbed dose from ^{18}F-FDG.

Applying the BodyBuilder anthropomorphic phantoms in this simulation, which yields agreeable results in addition to its low time consumption, corresponds to the available finding by other researchers while reducing calculation times.

ACKNOWLEDGMENTS

This study is supported by the Faculty of Advanced Sciences & Technologies, University of Isfahan.

Conflicts of interest*: *Declared none.

REFERENCES

1. Zanotti-Fregonara P, Champion C, Trébossen R, Maroy R, Devaux J-Y, Hindié E (2008) Estimation of the β+ dose to the embryo resulting from 18F-FDG administration during early pregnancy. *J Nucl Med,* **49**:679–682.
2. Zanotti-Fregonara P, Jan S, Taieb D, Cammilleri S, Trébossen R, Hindié E, Mundler O (2010) Absorbed 18F-FDG dose to the fetus during early pregnancy. *J Nucl Med*,**51**:803–805.
3. Takalkar AM, Khandelwal A, Lokitz S, Lilien DL, Stabin MG (2011) 18F-FDG PET in pregnancy and fetal radiation dose estimates. *J Nucl Med,* **52**:1035–1040.
4. Zanotti-Fregonara P, Koroscil TM, Mantil J, Satter M (2012) Radiation dose to the fetus from [(18)F]-FDG administration during the second trimester of pregnancy. *Health Phys,* **102**:217–9.
5. Zanotti-Fregonara P, Laforest R, Wallis JW (2015) Fetal Radiation Dose from 18F-FDG in Pregnant Patients Imaged with PET, PET/CT, and PET/MR. *J Nucl Med,* **56**:1218–22.
6. Benveniste H, Fowler JS RW (2003) Maternal-fetal in vivo imaging: a combined PET and MRI study. *J Nucl Med,* **44**:1522–1530.
7. Stabin MG (2004) Proposed addendum to previously published fetal dose estimate tables for 18F-FDG. *J Nucl Med,* **45**:634–5.
8. Cristy M and Eckerman KF (1987) Specific absorbed fractions of energy at various ages from

internal photon sources: 6, Newborn. ORNL/TM-8381. doi: 10.2172/6202949.
9. Stabin MG (1996) MIRDOSE: personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med*, **37**:538–46.
10. Stabin MG, Sparks RB, Crowe E (2005) OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med,* **46**:1023–1027.
11. Valentin J (2002) Basic anatomical and physiological data for use in radiological protection: reference values. *Ann ICRP,* **32**:1–277.
12. Zanotti-Fregonara P, Chastan M, Edet-Sanson A, Ekmekcioglu O, Erdogan EB, Hapdey S, Hindie E, Stabin MG (2016) New fetal doses from 18FDG administered during pregnancy: standardization of dose calculations and estimations with voxel-based anthropomorphic phantoms. *J Nucl Med jnumed*-116
13. Zanotti-Fregonara P, Stabin MG (2017) New Fetal Radiation Doses for18F-FDG Based on Human Data. *J Nucl Med,* **58**:1865–1866.
14. Shi CY, Xu XG, Stabin MG (2008) SAF values for internal photon emitters calculated for the RPI-P pregnant-female models using Monte Carlo methods. *Med Phys,* **35**:3215–3224.
15. Weissleder R (2010) Molecular imaging: principles and practice.
16. Van Riper K (2005) BodyBuilder user's guide. White Rock, NM White Rock Sci.
17. Stabin MG, Watson EE, Cristy M, Ryman JC, Eckerman KF, Davis JL, Marshall D, Gehlen MK (1995) Mathematical models and specific absorbed fractions of photon energy in the nonpregnant adult female and at the end of each trimester of pregnancy. *Oak Ridge National Lab.*, TN (United States).
18. Press WH (2007) Numerical recipes 3rd edition: The art of scientific computing. Cambridge university press.
19. Snyder WS, Ford MR, Warner GG, Watson SB (1975) S'absorbed dose per unit cumulated activity for selected radionuclides and organs. (MIRD pamphlet no. 11) *Society of Nuclear Medicine*, New York. Google Sch, **11**:5–257.
20. Shinohara A, Hanaoka H, Sakashita T, Sato T, Yamaguchi A, Ishioka NS, Tsushima Y (2017) Rational evaluation of the therapeutic effect and dosimetry of auger electrons for radionuclide therapy in a cell culture model. *Ann Nucl Med,* 1–9.
21. Valentin J (1998) Radiation dose to patients from radiopharmaceuticals: (Addendum 2 to ICRP Publication 53) ICRP Publication 80 Approved by the Commission in September 1997. *Ann ICRP,* **28**:1–1.
22. Andersson M, Johansson L, Minarik D, Leidesvegborn S, Mattsson S (2014) Effective dose to adult patients from 338 radiopharmaceuticals estimated using ICRP biokinetic data , ICRP / ICRU computational reference phantoms and ICRP 2007 tissue weighting factors. *EJNMMI Phys*, doi: 10.1186/2197-7364-1-9.
23. Thomas SR, Stabin MG, Chen C-T, Samaratunga RC (1999) MIRD Pamphlet No. 14 Revised: A Dynamic Urinary Bladder Model for Radiation Dose. *J Nucl Med,* **40**:102S--123S.
24. Bland JM and Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet,* **327**:307–310.
25. Russell JR, Stabin MG, Sparks RB, Watson E (1997) Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. *Health Phys,* **73**:756–769.
26. Zanotti-Fregonara P, Jan S, Champion C, Trébossen R, Maroy R, Devaux J-Y, Hindié E (2009) *In-vivo* quantification of 18F-FDG uptake in human placenta during early pregnancy. *Health Phys,* **97**:82–85.
27. Xie T and Zaidi H (2014) Fetal and Maternal Absorbed Dose Estimates for Positron-Emitting Molecular Imaging Probes. *J Nucl Med,* **55**:1459–1466.
28. Wayson MB (2012) Computational internal dosimetry methods as applied to the University of Florida series of hybrid phantoms. University of Florida.
29. Wahl RL and Wagner HN (2009) Principles and practice of PET and PET/CT. Lippincott Williams & Wilkins.
30. Shao F, Chen Y, Huang Z, Cai L, Zhang Y (2016) Unexpected Pregnancy Revealed on 18F-NaF PET/CT. *Clin Nucl Med,* **41**:e202–e203.