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Review paper

Performing nuclear medicine examinations in pregnant women

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ABSTRACT

The number of nuclear medicine examinations performed worldwide has been steadily increasing over the last few years. By consequence, an ever increasing number of pregnant women are likely to be exposed to radioisotopes.

The range of doses encountered in nuclear medicine practice is well below the threshold for deterministic effects, such as embryonic death, birth defects or mental retardation. According to the linear no-threshold hypothesis, however, stochastic effects (e.g. an increased risk of cancer) remain possible even at this dose range.

This purely hypothetical radiation risk to the fetus should however be put in perspective with the risk of having a scan of low diagnostic quality for a life-threatening medical condition. In recent years there has been a push to reduce as much as possible the dose from radiological imaging, for example by using acquisition protocols specific to pregnant women and by injecting lower activities. These approaches, in our opinion, overweigh the radiation risk and actually may put the life of both the mother and the fetus in danger.

Since imaging protocols already seek to use the lowest possible dose compatible with a quality scan for all patients, pregnant women should be imaged using the protocols applied to any other patient. Encouraging bladder voiding by natural means after injection will significantly reduce fetal exposure without compromising image quality.

Contents

1. Introduction

The number of nuclear medicine examinations performed worldwide has been steadily increasing over the past few years. By consequence, an ever increasing number of pregnant women is likely to be exposed to radioisotopes. In addition, the doses delivered when using recent hybrid machines (i.e. SPECT/CT and PET/CT) can be significantly higher than the doses from traditional nuclear medicine scans. Therefore, the decision of performing a nuclear medicine examination in a pregnant woman must be taken after carefully weighing the clinical benefit to the mother and the potential harm to the fetus from radiation exposure. While the expected clinical benefit to the mother is often easily quantifiable, a correct assessment of the potential harm to the fetus is fraught not

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only with scientific uncertainties, but also with psychological factors [1].

Even with hybrid machines, the dose to the fetus is at least one order of magnitude below the threshold for deterministic effects, such as embryonic death or mental retardation [2]. By contrast, stochastic effects, such as cancer, may in theory originate from a single radio-induced mutation in a single viable cell, and therefore may appear without a dose threshold. Since carcinogenic effects have never been conclusively observed for doses lower than 100–200 mGy [3], the carcinogenic risk at low doses is obtained by extrapolating to zero with a linear function the risk observed at high doses (i.e. linear no-threshold hypothesis). However, a large body of work in the scientific literature has demonstrated that the linear no-threshold hypothesis is inconsistent with radiation biologic and experimental data [4–7].

Unfortunately, the idea that even the tiniest amount of radiation is dangerous not only is still adopted as the basis to regulate radiation protection, but it has seeped into the consciousness of the general public. Despite adequate patient counseling, harmful choices caused by an emotion-based risk perception are not uncommon. For instance, parents are less likely to agree to perform an emergency CT scan on their child when they are informed of a possible link between low doses of radiation and cancer [8]. Indeed, about 6% of medically necessary CT scans for children seen in an emergency setting (head injury) are refused by parents concerned about radiation risk [8].

In our opinion, sometimes also physicians and scientific societies overweigh the radiation risk. In a series of papers about the management of pregnant women with gynecological and hematological cancers published by the *Lancet*, the use of ^{18}F-FDG in pregnant women was explicitly discouraged [9,10]. It is our contention that medically justified examinations should not be withheld in pregnant women for fear of radiation exposure [11]. Once the decision to perform the examination in the pregnant patient is taken, preserving the diagnostic power of the examination is of paramount importance. If a center already uses the smallest possible amount of radiopharmaceutical that will provide the appropriate diagnostic information [12], then pregnant women should be scanned with the standard procedure used for any other patient.

In this review, we first outline some principles of fetal dose calculation when the mother is injected with radioactive isotopes, then we provide an estimate of the potential harm to the fetus, and finally we conclude with some dose optimization considerations.

2. How do we know the dose to the fetus?

The total dose to the fetus is the sum of the dose from the photons coming from the mother's organs and the self-dose deposited by the radionuclide accumulating in the fetal tissues. If a radionuclide emits a significant percentage of charged particles, the self-dose can be significant [13,14]. By knowing the distribution of the organs inside the body and their mass, one can calculate the mathematical factors to convert the disintegrations in a given source organ into the absorbed dose in a target region. These dose factors are generally calculated by using anthropomorphic phantoms. The first phantoms were composed of basic geometric shapes, such as Cristy and Eckerman's phantoms for children and adults [15]. Early phantoms of pregnant women, which modeled the changes to the fetus and the mother's organs through different stages of pregnancy, were developed by Stabin in 1995 [16].

As computing power increased, it has become possible to develop highly realistic phantoms [17,18], including new ones for the pregnant woman [19–21]. One of these pregnant phantom series, created by Stabin and the SNMMI RADAR task force [21], was included in the version 2.0 of the OLINDA/EXM software [22].

Despite the anatomical precision of these new phantoms, the distribution of the radiopharmaceutical inside the body, and thus the amount of radioactivity to be assigned to the individual organs, can be determined only from in vivo data. The photon dose coming from the mother's organs can be reliably approximated by using data from non-pregnant women [23–25]. The uptake in the fetal tissues, however, can only be obtained by studying the images of actual pregnant women injected with radioactive tracers. Ethical considerations of course prevent enrolling healthy pregnant women in this type of research protocols. Therefore, in vivo data must come from animal studies or from occasional case-reports in which women were injected in a clinical setting out of medical necessity or by mistake. This data is very hard to come by. Indeed, when Russell and colleagues summarized the radiation absorbed dose to the fetus from different radiopharmaceuticals [26], most of the fetal doses were determined only by using the maternal contributions because the information about placental transfer was rarely available, and if it was, it was mostly from animal studies [27]. Biological data extrapolated from monkeys and, *a fortiori*, from rodents should be taken with caution because they are often poorly correlated with human values [28]. In addition, animals are usually imaged under anesthesia and this may alter the biodistribution of the drugs [29,30].

For ^{18}F-FDG, in vivo data were nonexistent until very recently. In 2003, Benveniste et al. published the images of three late-pregnancy monkeys who were injected with ^{18}F-FDG [31]. This study demonstrated for the first time that ^{18}F-FDG crosses the placenta in primates and accumulates in fetal tissues. Using this monkey data, Stabin established the standard values of fetal dosimetry for humans [32]. Only in 2008 the first dosimetric study involving a single patient was published [33], followed by others [23–25,34–39]. As of today, about 20 cases of pregnant women injected with ^{18}F-FDG are available in the literature [25]. These images suggest that ^{18}F-FDG uptake is much higher in the early phases of pregnancy, when the fetal cells are still relatively undifferentiated and rapidly proliferating, whereas in late stages the uptake is comparable to that in the mother's tissue.

Calculating the dose to the fetus is very challenging, especially in the early phases of pregnancy, because the skeleton is not yet formed and the fetal contours are not well visible on either PET or CT. Small variations in the estimated fetal mass may lead to important changes in the estimated dose. Therefore, in early pregnancy, the fetal dose is more reliably approximated by the uterus dose [25]. Other sources of uncertainty in dose calculation are due to the fact that clinical scans usually consist of a single static image, and therefore the evolution of the activity concentration in the fetal tissues is unknown. Thus, to perform dose calculations, a number of (conservative) assumptions are generally made. For example, the biological half-life of ^{18}F-FDG has been considered equal to its physical half-life [23–25]. It would not however be difficult to obtain data of dosimetric quality, even in a clinical setting. When a pregnant woman is scheduled to undergo a scan for cancer staging, a dynamic scan on the pelvic region would provide the fetal residence time without increasing the radiation dose. In addition, the abdominal aorta could be used as an acceptable input function to calculate the glucose metabolic rates in the living fetus.

Finally it should not be forgotten that dosimetric values obtained from phantoms are doses to a model, not to a patient. Changes in the model can have important consequences on the final dose, even if the organ uptake does not change. For instance, using the same input data, the ^{18}F-FDG dose to the first-trimester fetus is about 70% higher when using RADAR's voxelized phantoms [21], compared to the geometric phantoms of Cristy and Eckerman [15], mainly because of a different fetal mass in the two sets of phantoms [25]. Also, the dose to the fetus in early pregnancy can change by a factor of almost 2 according to slightly different

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