Updated anatomical data and mathematical models for embryo/fetus dosimetry

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ABSTRACT
Purpose of the Study: It is proposed to fill in the gaps in the existing data matrix of mass/volume of uterus, its contents as well as mass of fetal organs by mathematical techniques down to 6 week gestation and relate this dynamic target mass during in-utero growth to recently revised Medical Internal Radiation Dose (MIRD) 21 schema. Materials and Methods: The existing data is subjected to numerical interpolations using a standard 4 degree polynomial for certain set of variables. Interpolations of mass, volume, etc., of various components of the uterus (placenta, embryo/fetus, brain, uterine wall, etc.) at weekly/biweekly intervals have been carried out. Subsequently, the step wise regression starting with three predictors - placental mass ($W_p$), total fetal mass ($W_f$) and greatest length ($H$) for the augmented data set led to identification of “$H$” and “$W_f$” as the most significant predictors for 10 fetal organ masses $W_i$ using standard software “MS Excel.” Results and Discussion: Further analysis utilizing allometric equations reveal that there is strong evidence in favor of $W_f$ compared to $H$ for predicting ($P < 0.001$) the individual organ mass “$W_i$”. The prediction of $W_f$-liver, heart, thymus, pancreas, and thyroid fall under the linear case of prediction ( predictor is $\ln (W_f)$); whereas the brain, lung, kidney, spleen, crown-heel length, etc., fall under linear-quadratic case (where $\ln (W_f)$ plus $[\ln (W_f)]^2$ are the predictors) respectively. The estimates indicate a rapid decline of “brain mass/total mass” ratio from 80% to 39% during 7-9 weeks. Information on specific absorbed fraction $\Phi$ ($=\phi/m$) is required to arrive at the dose estimates ($\phi$ being the absorbed fraction). The very small target mass $m$-few milligrams (for 90% of organs) to a maximum 11 g for brain during early pregnancy; the fetal thyroid, with its mass variation of about 300% during 10-13 weeks can impact $\Phi$. Reported standardized doses are presented and variation of $\Phi$ with source-target distance for individual specific scaling of $\Phi$ is discussed. Conclusion: Time dependent mass $m$ (t) of the target and consequently $\Phi(t) = \phi(t)/m(t)$ of the revised MIRD dose expression can be of relevance in fetal dosimetry when source-target distances are in reasonable limits.

Keywords: Fetus organs, interpolation, mathematical models, regression

INTRODUCTION
In-utero growth is characterized by multiple parameters including anatomical as well as biological which serves as input information for embryo/fetus dosimetry. In the absence of one single data source or standard curve for reference, “pooling of data” from various sources is necessary to cover full range of pregnancy. This also allows to approximate the growth curve to some mathematical function like a polynomial which is rather simple and crude whereas more sophisticated ones are the “Gompertz” or “Logistic” function. Simple statistical models for prediction utilizing few reliable predictors is another approach for interpolating or extrapolating data.

The basic anatomical data for use in radiological protection were recently revised and extended by ICRP 89. New compilations of up-to-date and reliable information of human embryo/fetus have become available. Utilizing these data, the mathematical models of various components of the uterus, e.g., embryo, fetus, placenta, uterine wall, etc., at different prenatal ages have also been reported for applications in dosimetry.

The body mass index (BMI), surface area (SA)—are two useful related parameters of general use in biomedical work, have also been computed in present work. SA estimates of the placenta up to about 34 weeks of gestation are also useful in internal dosimetry. The BMI-1 ($\text{wt}/\text{ht}^2$) and BMI-2 ($\text{wt}/\text{ht}^3$) are recommended for smaller and growing bodies.
Dosimetry

Embryo/fetus dosimetry poses quite a formidable challenge to deal with. The complexity arises due to peculiar scenario of in-utero growth vis-a-vis dosimetric constraints. For example, there can be several and changing sources (e.g., placenta/uterus); changing targets (e.g., fetus and its organs); formation, maturation/functionality of different organs and tissues at different stages of gestation; evolution of placenta over time and its transport quality etc. The distance between maternal source and fetal targets are constantly varying so are the sizes and shapes of fetal organs. The placenta, which plays a dominant role in transferring essential elements to enable growth is itself varying over time both in terms of size and its transport mechanism. Although, the mechanism of transport across para placenta for growth is fairly known, the bio-kinetic details for computing accumulated activity due to radionuclides of interest in pregnant female are severely limited. The detailed anatomical and biological description of the placenta and its role in fetal dosimetry can be found elsewhere. A brief overview is presented for some simple mathematical models adopted in the past and some more realistic but complex ones based on refined reference standards. MIRD pamphlet 21 has recently revised its generalized schema of average absorbed dose expression to include time variable in SAF in recognition of the dynamic target mass in many dosimetry situations like in the case of fetal growth and/or shrinking tumors during radionuclide therapy.

Anatomical models of human pregnancy and uterus

Simple models

For the purpose of dosimetry, in utero growth could be classified into the following four broad stages with notable growth feature in brackets namely:-(Ovum: 1st week after conception [solid trophoblast]); (Embryo: 7-56d [~few mg to g]-a period of major organogenesis for more than 90% organs and tissues, max. chorion diameter = 65 mm); (Fetus/later fetus: 56d-~term [few g-3500 g]-period of growth and maturation, brain being highly radiosensitive, 56d-105d is the window of Cortical sensitivity). The developing embryo and fetus are radiosensitive during whole of the prenatal period though the effect decreases with age. In particular, the brain shows pronounced sensitivity to long-term damage due to prolonged cell formation and maturation process.

As mentioned earlier, during pregnancy, the sizes and geometric shape of the target fetus in relation to the maternal sources is complex and differ greatly from the small to the term fetus. Simple geometric shapes are preferred to more complex ones in model development because it is easy to use in Monte Carlo simulations. Smith and Warner have modeled a 10-41 d conceptus as a sphere of radius 0.13 cm and mass 9.2 mg. The sphere representing embryo has been assumed located at the origin of semi-axes of a 66 cm ellipsoid uterus in 70 kg heterogeneous adult phantom. Cloutier, et al., have modeled a 3 month pregnant of 58 kg in which the uterus, the embryo, and the other contents of the uterus are non-distinguishable as a homogeneous mixture of soft-tissue. The models for maternal whole body (40-70 kg), fetus (1-4 kg) and its thyroid (1-3 g) were assumed as ellipsoid with axes ratio 1:1.89:27; 1:0.667:1.337; and 1:24 respectively by Sastry, et al., a 30 week uterus was modeled as a sphere of 20 cm diameter; placenta as a truncated spherical shell (1.7 cm thick, 9 cm radius, corresponding to mass 430 g) with both ends subtending at an angle 60° at the center. Elsasser, et al., have modeled the embryo/fetus of mass ranging from few mg to 100 g sphere at the center of the uterus or at different points along the semi-major axis of the uterus in a 15-year-old anthropometric child phantom of Henrichs and Kaul. Simple approximations have been replaced by more realistic but complex ones using updated data on reference masses of organs and tissues published in ICRP 89 report.

Refined models

In both, non-pregnant as well as pregnant woman, the uterus is a pear shaped structure about 7.5 cm in length initially. At the end of pregnancy, the size of uterus and its contents increases, the position changes but the shape remains the same. The model of uterus has been approximated by frustum of right circular cone capped at both ends by hemispheres, similar to the model of uterus at the end of third trimester developed by Stabin, et al. While this effort was directed to develop three different geometrical models of uterus at age 13.26 and 38 weeks; Chen unified these three into one which assumes a single shape but has different size and location at these stages of pregnancy. Stabin’s model of placenta has now been extended to trimester 1 also. For fetus and its organs, more than one simple geometric shape in combination were utilized to develop symmetric models for brain and whole body. The symmetry is chosen to account for constant movement of the fetus within the uterus. For example both an embryo stage brain and whole body of term fetus are approximated by right circular cylinder capped by hemispheres. Another minor but important change in earlier 3 month model of uterine contents was to distinguish fetus as separate entity from other contents.

Placenta increases in size but remains in same shape represented by hemispherical shell quite similar to the one used by Sastry, et al. The 3-dimensional mathematical equations representing the geometrical models of embryo, total fetus and the associated relevant organs-placenta, uterus, uterine walls at 8W (early fetus), 13W (trimester 1), 26W (trimester 2), 38W (term) representing four stages of pregnancy respectively have been reported.

MATERIALS AND METHODS

Interpolations on ICRP data on mass, volume and densities of components of the uterus (e.g., placenta, embryo/fetus, brain, uterine wall, etc.) at each week of gestational age have been carried out by a numerical recipe-a FORTRAN subroutine “POLINT”. A polynomial of degree 3 or 4 was applied. Incomplete data matrix was treated with either “pooling” of data or “smoothing” in order to generate complete sets of data for prediction of each fetal organ. As the pooled data came from diverse sources as well as collected over many years, it suffers
from both - the unknown measurement errors and the model error estimation. Regression analysis was done in two steps with the help of Microsoft package, “LINEST”. First, was to identify three variables \( W_i, H, \) and \( W_p \) generally believed to be important predictors, with a step down approach, fetal body mass was identified as statistically most significant predictor. The crown-rump length is often been used as substitute for time variable in human prenatal development as it is difficult to identify the day of fertilization. Where possible, the prediction data is extended to 6 weeks gestation. In the second step, mass “\( W_i \)” in its log transformation was used as predictor. Where possible, prediction was done up to 6 weeks gestational age. The two models fitted, popularly known as allometric equations are explained below.

The biology of scaling is a well-known method of modeling relationship of individual organ/tissue mass or size as a function of total body mass. The mathematical model is given by equations

\[
\ln (W_i) = \ln (a_i) + b_i \ln (W_f) \\
\ln (W_i) = \ln (a_i) + b_i \ln (W_f) + c_i (\ln (W_f))^2
\]

Where, \( W_i \) is the measured weight of the \( i \)th organ; \( W_f \) is the measured weight of the embro/fetus and \( a_i, b_i, c_i \) parameters that are determined empirically by regression over measurements. Both equations are treated with “LINEST” as above.

**RESULTS AND DISCUSSION**

In Table 1, it is seen that the “mass to volume” ratio for fetus at week 8, which is \(< 1\) is reversed to \(> 1\) at week 38, indicating an accelerated growth compared to volume. This can be largely due to rapid fat accumulation in the fetus from week 16 onwards up to 36 weeks. Similar variable growth rates are seen in Table 2 for fetal organs like brain, lungs, kidney and spleen due to additional coefficient of \( \{\ln (W_f)\}^2 \). The estimates of thyroid mass range from 0.021 to 0.85 g during 10-14 weeks showing a significant 40 times increase. Similar increase or more can be seen for most (\( \sim 90\% \)) of the organs with the exception of brain mass (\( \sim 80\% \) of 4.7 g fetus at week 8; 39% at week 9). So at 3 months gestation, the mass of the fetus excluding brain comes to about 75 g which is distributed among 90% of organs and other tissues; fetal thyroid only about 0.048 g. The time of radioiodine concentration in thyroid is 10-13 weeks when it can cross placenta. With changing mass, the source-target distance can also change especially, in the case of a large organ like liver. This can impact on the value of SAF and the resultant doses. A mean value would be appropriate for distance.

Table 3 shows standardized doses to the fetal thyroid per unit activity administered to the mother. Values are shown for four radionuclides from 3 m to 9 m gestation. In another study, Millard et al., used MIRDose3 software for computing doses to
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Table 2: Coefficients of prediction equation 1 and equation 2

| Organ       | $a$ (SE) | $b_1$ (SE) | $b_2$ (SE) |
|-------------|----------|------------|------------|
| Brain       | 0.49 (0.15) | 0.311 (0.058) | 0.045 (0.0054) |
| Liver       | -2.63 (0.22) | 0.93 (0.03) |  |
| Lungs       | -3.42 (0.344) | 1.19 (0.118) | -0.039 (0.0096) |
| Kidney      | -6.34 (0.38) | 1.66 (0.38) | -0.059 (0.01) |
| Heart       | -4.16 (0.07) | 0.89 (0.0098) |  |
| Spleen      | -12.48 (2.2) | 2.87 (0.75) | -0.123 (0.06) |
| Thyamus     | -7.1 (0.4) | 1.16 (0.057) |  |
| 2 suprarenals | -4.8 (0.18) | 0.86 (0.025) |  |
| Pancreas    | -5.59 (0.06) | 0.86 (0.009) |  |
| Thyroid     | -6.5 (0.73) | 0.85 (0.105) |  |
| Crown heel  | 2.68 (0.05) | 0.61 (0.023) | -0.022 (0.0024) |
| Bipenial diameter | 1.78 (0.037) | 0.4 (0.015) | -0.0072 (0.0015) |
| Foot length | 0.13 (0.089) | 0.781 (0.0376) | -0.033 (0.0036) |

*In agreement with the reference [2]. SE: Standard error

Table 3: Doses to the fetal thyroid per unit activity administered to the mother mGy/MBq*

| Gestational age (month) | I-123 | I-124 | I-125 | I-131 |
|-------------------------|-------|-------|-------|-------|
| 3                       | 2.7   | 24    | 290   | 230   |
| 4                       | 2.6   | 27    | 240   | 260   |
| 5                       | 6.4   | 76    | 280   | 580   |
| 6                       | 6.4   | 100   | 210   | 550   |
| 7                       | 4.1   | 96    | 160   | 390   |
| 8                       | 4.0   | 11    | 150   | 350   |
| 9                       | 2.9   | 99    | 120   | 270   |

*Values adapted from reference [18]

The radiation risks are known to depend upon time of exposure and the absorbed radiation dose during different stages of in-utero growth. The time dependent mass $m(t)$ and consequently $\Phi(t)$ of revised MIRD 21 can be useful in fetal dosimetry.

CONCLUSION

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