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Fetal outcome after technetium scintigraphy in early pregnancy

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ABSTRACT

Objective: Occasionally, either for urgent diagnostic reasons or by accident, pregnant women are exposed to technetium scintigraphy, the consequences of which were unknown, due to lack of systematic data. Therefore, clinical data was needed to assess the risk and safety of technetium scintigraphy with respect to prenatal development.
Methodology: Requests for information with regard to technetium scintigraphy from pregnant women or their physicians were followed by the Berlin Institute for Clinical Teratology. A prospective observational cohort study was performed using data collected between 1991 and 2008. Pregnancy outcome for a cohort of pregnant women exposed to Tc-99m-scintigraphy of thyroid ($n = 102$) or bone ($n = 20$) during pregnancy was compared with a control group without teratogenic exposure ($n = 366$).
Results: Major birth defects were no more common in the study group than in the control group (OR 1.00; 95% CI 0.23–3.38) and no specific pattern of birth defects was found. Spontaneous abortion rate (OR 0.51), preterm deliveries, and birth measurements of newborns were not significantly different from controls.
Conclusion: This prospective observational study suggests that the inadvertent exposure to Tc-99m-scintigraphy in early pregnancy is relatively safe for the fetus.

1. Introduction

Radiopharmaceuticals are occasionally administered to pregnant patients either because the mother is not aware of her pregnancy or for urgent diagnostic reasons. The commonly administered radiopharmaceuticals in scintigraphy used for thyroid, lung, gallbladder, kidney, bone, and bleeding scans contain technetium-99m (Tc-99m). Tc-99m is a gamma-emitting radionuclide, with a half-life of 6 h. Tc-99m has been incorporated into a number of radiopharmaceuticals, including Tc-99m sodium pertechnetate for thyroid scans, Tc-99m methylene diphosphonate (MDP) for bone scans, and Tc-99m diethylenetriaminepentaacetic acid (DTPA) for kidney scans [1]. Earlier Tc-99m had also been used to locate the placenta [2].

Tc-99m has been shown to cross the placenta in experimental animals [3–5]. Generally the percent of the administered activity localizing in the placenta or crossing into the fetus of the animal was assumed to be the same percent that would localize in the human placenta or cross into the human fetus [1].

Estimates of the radiation dose to the fetus are important in nuclear medicine. The energy dose reaching the embryo or fetus through maternal scintigraphy is dependent on the isotope used, the applied activity and the distribution and elimination of the drug [6]. Individual fetal dosimetry is not possible but the dose can be assessed based on anatomical data of the patient and radiopharmaceutical kinetics. Estimated fetal doses of some common applications are shown in Table 1. They are based on dose coefficients published by Russell [7] and represent the highest estimated values. In principal, dose and dose coefficient decrease with gestational age. Fetal thyroid dose of Tc-99m pertechnetate is shown in Table 2.

Radiopharmaceuticals excreted predominantly through urine (e.g. kidney scan with Tc-99m DTPA) cause the doses to the embryo to be 40–90% higher than gonad doses [8]. For this reason the induction of diuresis has been recommended in order to minimize fetal radiation exposure [9,10]. One case report [11] calculated absorbed dose in fetuses of two patients who underwent bone scintigraphy with Tc-99m methylene diphosphonate (MDP). Neither fetus demonstrated radionuclide uptake above maternal background levels. The uterine activity showed rapid clearance, with an effective half-life of 12 min after reaching a maximum within 1 min after injection. The authors state that major contribution to fetal dose comes from the presence of the radionuclide in the maternal bladder. A Tc-99m macroaggregated albumin (MAA) perfusion lung scan and a Tc-99m DTPA aerosol ventilation scan were performed for suspicion of pulmonary embolism (PE) in a patient who was 10 weeks pregnant [9]. In this case as well as in other reports (e.g. [12])

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Table 1
Energy dose to the embryo of diagnostical procedures with radiopharmaceuticals [7].

Organ or method	Radionuclide	Radiopharmaceutical	Dose coefficient (μGy/MBq)	Applied activity (MBq)	Energy dose (embryo/fetus) mGy
Bone	Tc-99m	MDP, HDP	6.1	750	4.6
Thyroid	Tc-99m	Pertechnetate	11	75	0.8
Kidneys	Tc-99m	DTPA	12	150	1.8
Kidneys	Tc-99m	MAG3	18	200	3.6
Lung	Tc-99m	Mikrospheres	2.8	200	0.6

Dose coefficient = the relation between applied activity and energy dose in the embryo. Largest values for early pregnancy were taken, according to Russell et al. [7].
Gy = Gray; energy dose of ionizing radiation absorbed by a body (1 Gy = 100 rad = 1 J/kg).
MBq = Mega-Becquerel; 1 Bq = 1 decay/s.
Applied activity = mean "dose" used for scintigraphy.

Table 2
Fetal thyroid dose after thyroid scintigraphy with Tc-99m pertechnetate at different gestational stages [23].

Method	Radiopharmaceutical	Applied activity (MBq)	Fetal thyroid dose (mGy)		
			95 days	130 days	250 days
Thyroid-scintigraphy	Tc-99m pertechnetate	75	0.7	1.7	0.6

Applied activity = mean "dose" used for scintigraphy.
MBq = Mega-Becquerel; 1 Bq = 1 decay/s.
Gy = Gray; energy dose of ionizing radiation absorbed by a body (1 Gy = 100 rad = 1 J/kg).

the Standard Medical Internal Radiation Dose (MIRD) estimates to the fetus from radiopharmaceuticals containing technetium 99m are all well below 5 m Gy.

This dose is not considered to be teratogenic in humans. However, there are only few case reports in the literature describing fetal outcome of scintigraphy in pregnant women. Therefore, there is a lack of clinical data confirming low risk to the fetus with respect to prenatal development. We present the first prospective observational study of fetal outcome after exposure to Tc-99m.

2. Materials and methods

Requests for information with regard to exposure to technetium scintigraphy from pregnant women or their physician between 1991 and 2008 were followed by the Berlin Institute for Clinical Teratology. Subjects were prospectively enrolled using a structured questionnaire for details of exposure at the first contact during (early) pregnancy before the pregnancy outcome was known. The following information was obtained: details of scintigraphy and other drug exposure, in particular timing in pregnancy, maternal demographics, medical and obstetric history. Approximately 8 weeks after the expected date of delivery, follow-up was conducted by questionnaires and structured phone interviews. The goal was to obtain the gestational age at birth, sex, birth weight, length, head circumference, umbilical artery pH, Apgar scores and complete results of neonatal exams up to the third pediatric check-up at the age of 6 weeks. In Germany a structured pediatric examination program has been established that follows a detailed check list of anatomical features and developmental milestones. Furthermore, information about complications during pregnancy including infections, gestational diabetes, preeclampsia, details in case of pregnancy loss were obtained. Primary contact for follow-up is the person who sought for advice in our TIS during pregnancy, mostly the pregnant patient or her obstetrician. Independent of the exposure status, they are asked for the details mentioned above and the address of the pediatrician.

In the exposed cohort follow-up data including pediatric exams were reported in 23.8% by the patient, in 51.4% by the gynecologist, in 19.0% by the pediatrician, and in 5.7% by other specialists, e.g. geneticists. In the control cohort follow-up data were reported in 51.0% by the patient, in 27.8% by the gynecologist, in 18.1% by the pediatrician, and in 3.0% by other specialists, e.g. geneticists.

Patient data recorded during pregnancy and follow-up data were checked for plausibility. For details of the methodology see [22]. In case of questionable plausibility of the reported follow-up data we try to improve the data quality by repeated contacts to the involved health care professionals and the mother. If, at the end, major concerns persist, the case will be considered as lost for follow-up. To our experience there are no general differences in terms of data quality and completeness between primary reports from the patient and her health care professionals.

Women in the exposed groups (Tc-99m pertechnetate, $n = 102$ and Tc-99m bone, $n = 20$) and their pregnancy outcomes were compared to a control group ($n = 366$) consisting of pregnant women who had been counseled during pregnancy after exposures known to be non-teratogenic. In order to increase the statistical power we chose a 3-fold size of the control cohort. All controls were prospectively enrolled in the same year as the exposed pregnancies. Data collection at first contact and follow-up were similar for all cohorts.

The main point of interest was the rate of major birth defects, defined as structural abnormalities of medical, surgical or cosmetic relevance. All birth defects were classified according to Merks [13] and Rasmussen [14]. Secondary endpoints were the rates of miscarriage, stillbirth, preterm delivery (<37 weeks), gestational age at delivery and birth weight. Weeks of pregnancy were defined from the last menstrual period.

3. Statistical analysis

The birth defect rate was calculated using live births and aborted fetuses with pathology. For calculating rates of major birth defects, genetic or chromosomal disorders were excluded. Since crude rates of miscarriages based on observational data may be biased we analyzed cumulative incidences considering elective terminations of pregnancy (ETOP) and live births as competing risks. It is known that many spontaneous abortions occur very early in pregnancy, often when the mother is unaware of her pregnancy. This may induce a bias if the average gestational age at call in the research group is lower than that in the control group. For events occurring over time, crude rate estimates – the number of events divided by the total number of subjects under study – are only appropriate when all subjects are followed over the full period of interest, i.e. from fertilization until the end of pregnancy. In practice, however, pregnant women enroll in TIS databases at various stages of pregnancy dependent on when pregnancy was diagnosed, a drug exposure was realized as a potential risk, and she or her physician contacted the TIS. Such delayed study entry is also called left truncation. Furthermore, elective terminations of pregnancy have to be taken into account as a "competing risk" or "competing event", respectively. This can be done by an event-history-based analysis. This method was recently introduced for investigating observational pregnancy outcome data [15].

We applied logistic regression analysis for comparing birth defect rates between cohorts, adjusting for possible confounders (maternal age, smoking, and alcohol consumption). We compared quantitative data like birth weight and length using analysis of covariance with maternal age, gestational age at delivery, smoking, and sex of the newborn as possible confounders. All statistical calculations were performed using the open source statistics software R [16].