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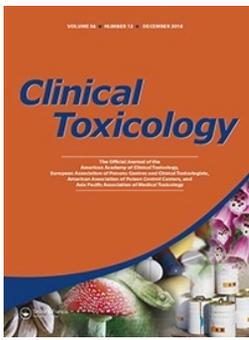
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CLINICAL RESEARCH



Birth outcomes in women exposed to diagnostic radiology procedures during first trimester of pregnancy: a prospective cohort study

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ABSTRACT

Introduction: Exposure of the embryo or fetus to ionizing radiations is a potential danger since it may induce clinically relevant fetal and/or neonatal damages. The aim of the present study was to examine fetal and neonatal outcomes after maternal exposure to radio-diagnostic procedures during first trimester of pregnancy, and to evaluate whether these effects might be related to the fetal absorbed dose of ionizing radiations.

Methods: A 10-year prospective cohort study was performed on 1979 pregnant women who underwent a radio-diagnostic procedure within the first trimester of pregnancy. Women were divided into two groups: those exposed to abdominal or lumbar radio-diagnostic procedure (Cohort A, $n = 130$), and those exposed to radio-diagnostic procedures in any other body regions (Cohort B, $n = 415$). Health physicists performed tailored fetal radiation dose calculation. Multivariate logistic regression model was used to estimate the risk of adverse pregnancy outcomes.

Results: The tailored fetal radiation dose was calculated for a total of 97 women (range 0.05–92 mSv). Major congenital malformations were detected in four infants in Cohort A, six infants in Cohort B, and 24 infants in controls ($p = 0.445$). Multivariate analysis confirmed the negative association between age and adverse pregnancy outcomes (OR 1.08 [1.06–1.11]), and the protective role of folic acid. A higher rate of small for gestational age seems to be present in women who underwent radio-diagnostic procedures that involve maternal thyroid.

Conclusion: Despite several limitations, our study confirms that exposure to radio-diagnostic procedures that may involve uterus at doses below 100 mSv does not increase the risk of embryo-fetal toxicity. The relationship between maternal thyroid irradiation and small for gestational age needs to be further investigated.

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Introduction

Exposure of the embryo or fetus to ionizing radiations (IRs) is a potential danger since it may induce damage ranging from implant failure to an increased risk of spontaneous miscarriage, major malformations (i.e., neurological and motor deficiencies), fetal growth restriction and stillbirth, depending on radiation dose and gestational age [1–5].

Biological effects of IRs are due to both physical and chemical mechanisms, which occur immediately after the passage of radiations through cellular barriers. Once a cell is exposed to IRs, there is a high probability of an interaction between IRs and water molecules which represent most of

cell's volume. It is known that IRs interaction with intracellular water could break the bonds that hold water molecules together, thus producing fragments such as hydrogen (H) and hydroxyls (OH) [6]. These fragments may form hydrogen peroxide (H_2O_2) and other reactive oxygen species, which are able to induce cell death or DNA damage [7].

Interestingly, not all human cells are equally sensitive to IRs. In particular, those cells which are actively dividing are more sensitive. This is because dividing cells require correct DNA information for the cell's offspring to survive, and a direct interaction of IRs with an active cell could result in the death or mutation of the cell itself. The effects of IRs exposure can be classified as “stochastic” or “deterministic”.

Stochastic effects can occur from months to years after exposure and consist in damage to nuclear material even in a single cell, which can cause radiation-induced cancer or mutations that may be transmitted to the offspring of exposed individuals. On the contrary, deterministic effects are linked with multicellular death, occur only above a threshold dose (the death of few cells does not induce any clinical damage), and their severity increases with increased dose.

The American College of Radiology (ACR) and the Society of Pediatric Radiology (SPR) stated that there are no potential deterministic effects for fetus with a radiation exposure under 50 milliSievert (mSv) and there is “probably no effect” when exposure levels are between 50 and 100 mSv [8]. Currently, doses above 100 mSv, especially above 150 mSv, are considered as the minimum amount of dosage at which negative fetal consequences could occur. It should be noted that the majority of diagnostic studies performed during pregnancy are well below this threshold level [4,9]. Radio-diagnostic procedures such as computed tomography (CT) of the pelvis, chest or abdomen are estimated to expose a patient to a mean effective dose of 6 mSv (range 3.3–10), 7 mSv (range 4.0–18) or 8 mSv (range 3.5–25), respectively, while standard X-ray of the abdomen to 0.7 mSv (range 0.04–1.1) [10].

Despite more than 100 years of research on IRs, the exact effects of radiation exposure in early stages of pregnancy have not been completely assessed. Pregnancy could go undetected until early organogenesis and, even after detection, it is difficult to identify retrospectively the potentially dangerous effect of an unintentional exposure to such radiations, especially in women who do not yet know they are pregnant.

The aim of the present study was to examine fetal and neonatal outcomes after maternal exposure to radio-diagnostic procedures during the first trimester of pregnancy, and to evaluate whether these effects might be related to the fetal absorbed dose of IRs.

Methods

Participants

We conducted an observational prospective cohort study on pregnant women who referred to the Teratology Information Service of Careggi University Hospital, Florence (Italy), between 2005 and 2015 for a teratogen risk counselling, after undergoing a radio-diagnostic procedure (without radionuclide administration) between the 10th and the 104th day after the last menstrual period.

At first contact, after obtaining informed consent to participate in the study, pregnant women were asked to answer an *ad hoc* questionnaire. Information on maternal age, education, occupation, gravidity (defined as the number of times that a woman has been pregnant), parity (defined as the number of times that a woman has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn), maternal medical and obstetrical history, current and past

pharmacological treatments (indication of use, dosage and timing), and exposure to IRs including exam type (CT or X-ray), irradiated district, timing of exposure, hospital, and name and telephone number of the radiologist were collected. The questionnaire is available from the authors upon request.

Information regarding newborns (both demographic and clinical parameters) were provided by the mothers through the medical record of the hospital where the child was born or from the medical record of the community pediatrician, during the follow-up recall performed after 3 months from the presumed date of birth.

Women reporting a history of three or more previous spontaneous miscarriages, assisted fertilization, preeclampsia or eclampsia, gestational hypertension, infections (human immunodeficiency virus, hepatitis B virus, C virus, rubella virus, and *Toxoplasma gondii*), drugs of abuse exposure, alcohol consumption (>2 alcoholic unit/day), or treatment with teratogenic medications (including sodium valproate, mycophenolate, methotrexate, thalidomide, retinoids), were not included in the study. In addition, we excluded non-Caucasian women or women with non-Caucasian partners, as well as women with current multiple gestation, in order to be able to compare our data with the reference growth charts for singleton pregnancy of Caucasian infants [11].

Based on the body region exposed to the radio-diagnostic procedure, women enrolled in the study were divided into two groups: (i) women exposed to abdominal or lumbar radio-diagnostic procedure (Cohort A), and (ii) women exposed to radio-diagnostic procedures in any other body regions (Cohort B). In addition, a control group was randomly selected among pregnant patients who referred to the Teratology Information Service during pregnancy for reasons other than the exposure to IRs. Women in the control group were asked to answer the same structured questionnaire to collect the above-mentioned demographic and clinical data.

Fetal radiation dose

Fetal radiation dose was calculated only for women who were exposed to abdominal or lumbar radio-diagnostic procedures (Cohort A), that is, when the uterus is directly invested by the IRs beam. In these cases, the radiologist who performed the radio-diagnostic procedure was assisted by a health physicist, to collect technical parameters and calculate the fetal radiation dose [12]. When technical parameters were collected, the health physicist calculated the radiation doses. Calculations were always retrospectively performed using computational methods, such as Monte Carlo simulations [13]. As these calculations are affected by a large uncertainty, the health physicist provided a range for the calculated dose value, expressed as minimum and maximum values. For the purposes of this study, we considered only the maximum value of the fetal radiation dose, expressed in terms of dose equivalent, measured in milliSievert (mSv). Based on the estimated maximal radiation dose, women

were advised about the teratogenic risk and provided clinical counselling [14].

We did not perform any calculation when the dose was surely below 1 mSv, defined as a nonrisk value by national and international guidelines [8].

Study outcomes

Three months after the expected date of birth, women were contacted by specifically trained clinical toxicologists for a follow-up telephone interview to collect information about pregnancy outcomes.

Info on gestational age at birth was collected, and the occurrence of preterm birth, defined as a birth taking place before the 37th week of gestation (WOG), and very preterm birth, defined as a birth taking place before the 34th WOG, was also evaluated. Auxological parameters measured at birth were recorded, including birth weight in grams, head circumference (HC) in centimeters, and 1-minute and 5-minute postnatal Apgar score.

Birth outcomes of interest were: (1) adverse pregnancy outcomes (APO), defined as stillbirths, spontaneous miscarriages, elective termination of pregnancy (ETOP, within the 90th day of gestation), and therapeutic termination of pregnancy (TTOP, after the 90th day of gestation); (2) occurrence of major congenital anomalies defined as structural anomalies of medical, surgical or cosmetic relevance. Women with prenatal diagnosis of fetal defects and woman with spontaneous miscarriage and/or TTOP were also included in the study. Birth defects rate was calculated with ultrasound or after autoptic evidence of anomalies. Cardiac septal defects were considered as major anomalies, unless they spontaneously closed during the neonatal period. Chromosomal anomalies and genetic syndromes were excluded; (3) Newborns with a birth weight <10th percentile for gestational age were defined small for gestational age (SGA) infants, following routinely used criteria [15]. Furthermore, we identified all newborns with a HC <10th percentile for gestational age, classifying SGA newborns into two groups: symmetric SGA (sSGA), where body weight and HC are both <10th percentile for gestational age; and asymmetric SGA (aSGA), where the HC is "preserved" [16].

Women without available 3-month follow-up data were excluded from the study.

Statistical analysis

Continuous data were reported as median value and related interquartile range (IQR) and compared between the three groups: Cohort A (women exposed to abdominal or lumbar radio-diagnostic procedures), Cohort B (women exposed to radio-diagnostic procedures in other body regions), and control women. The comparison was performed using the Kruskal–Wallis test for unpaired samples with not normally distributed data.

Categorical data were reported as absolute numbers and percentages and compared between the three groups using the Chi square test.

In addition, women exposed to abdominal or lumbar IRs (Cohort A) were stratified according to the maximum fetal radiation doses (≤ 20 mSv, 20 to 50 mSv, ≥ 50 mSv), and pregnancy outcomes were compared among the three groups using the Kruskal–Wallis test in case of continuous outcome or the Fisher Exact test for categorical outcomes.

Crude and adjusted logistic regression models were used to estimate the odds ratios (ORs) and related 95% confidence interval of APO and SGA. Adjusted models included IRs exposure, maternal age, maternal occupation, BMI (body mass index), smoke (yes/no), folic acid intake, and previous APO. A *p*-value < 0.05 was considered as the significance level for all tests.

Results

Demographic and clinical characteristics

One hundred and thirty women exposed to abdominal or lumbar IRs (Cohort A), 415 women exposed to IRs in other body regions (Cohort B), and 1434 women unexposed to radio-diagnostic procedures during pregnancy (Control group) were enrolled (Table 1). The women for whom no follow-up data were available were nine in Cohort A and 22 in Cohort B; therefore, they were excluded from the analysis.

Maternal age and BMI were similar among the three groups. Women exposed to IRs (Cohort A and Cohort B) were more likely to be smokers as compared to the Control group (29.2% and 28.9% versus 16.6%, *p* < 0.001).

Furthermore, women exposed to IRs had a lower educational level as compared to the Control group; similarly, the type of occupation significantly differed among the three groups, and women exposed to IRs were more frequently housewives, housemaids or factory workers as compared to unexposed women.

Pregnancy history and information on current pregnancy

The occurrence of previous spontaneous miscarriages and previous stillbirths was comparable among the three groups (Table 2). Conversely, the proportion of women with history of TTOP was significantly higher (*p* = 0.027) among women exposed to IRs, both in abdominal or lumbar regions (12.3%) and in other regions (12.8%), compared to controls (8.7%). Moreover, mean values of gravidity and parity significantly differed (*p* < 0.001) among the three groups. In particular, gravidity values observed for Cohort A, B and for the Control group were 1.97, 2.18, and 1.86, respectively; whilst the values observed for parity in the same groups were 0.63, 0.75, and 0.55.

On the first contact with the Teratology Information Service, the median gestational age was comparable among the three groups (*p* = 0.622), being approximately 7 weeks from the last menstrual period. The number of women who did not take folic acid was significantly higher (*p* < 0.001) among women exposed to IRs, both in abdominal or lumbar

Table 1. Demographic and clinical characteristics.

	Cohort A N = 130 (%)	Cohort B N = 415 (%)	Controls N = 1434 (%)	p-value
Age (years), median (IQR)	33 (29–36)	34 (30–38)	34 (31–37)	0.077
Education				
Primary/secondary school	36 (27.7)	94 (22.6)	210 (14.6)	<0.001*
High school	66 (50.8)	202 (48.6)	651 (45.4)	
University degree	25 (19.2)	114 (27.5)	548 (38.2)	
Missing data	3 (2.3)	5 (1.2)	25 (1.7)	
Occupation				
Housewife	27 (20.8)	85 (20.4)	259 (18.1)	0.005*
Teacher/secretary/sales assistant	61 (46.9)	187 (45.1)	777 (54.2)	
Health professional	9 (6.9)	37 (8.9)	124 (8.7)	
Factory worker/housemaid	19 (14.6)	56 (13.5)	110 (7.7)	
Freelance professional	14 (10.8)	41 (9.9)	140 (9.8)	
Student	0	9 (2.2)	20 (1.4)	
Missing data	0	0	4 (0.3)	
BMI, median (IQR)	22 (20.2–25)	21.7 (19.9–24)	21.3 (19.9–23.5)	
\dot{y}	6 (4.6)	32 (7.7)	91 (6.4)	0.090
18.5–25 (normal)	89 (68.5)	312 (75.2)	1098 (76.6)	
25.1–30 (overweight)	23 (17.7)	44 (10.6)	178 (12.4)	
30.1–35 (obese)	4 (3.1)	16 (3.9)	34 (2.4)	
\dot{y}	3 (2.3)	5 (1.2)	13 (0.9)	
Missing data	5 (3.9)	6 (1.5)	20 (1.4)	
Smoke				
No	92 (70.8)	295 (71.1)	1196 (83.4)	<0.001*
Yes	38 (29.2)	120 (28.9)	238 (16.6)	

Cohort A: women exposed to abdominal or lumbar IRs; Cohort B: women exposed to IRs in other body regions. * $p < 0.05$.
BMI: body mass index; IQR: interquartile range; IRs: ionizing radiations.

Table 2. Pregnancy history and information on current pregnancy.

	Cohort A N = 130 (%)	Cohort B N = 415 (%)	Controls N = 1434 (%)	p Value
Pregnancy history				
Previous spontaneous miscarriages				
No	108 (83.1)	329 (79.3)	1189 (82.9)	0.225
Yes (1–2 events)	22 (16.9)	86 (20.7)	245 (17.1)	
Previous ETOP				
No	130 (100.0)	412 (99.3)	1418 (98.9)	0.392
Yes	0	3 (0.7)	16 (1.1)	
Previous TTOP				
No	114 (87.7)	362 (87.2)	1310 (91.4)	0.027*
Yes	16 (12.3)	53 (12.8)	124 (8.7)	
Previous stillbirth				
No	130 (100.0)	414 (99.8)	1430 (99.7)	0.831
Yes	0	1 (0.2)	4 (0.3)	
Previous living births				
None	66 (50.8)	182 (43.8)	806 (56.2)	<0.001*
1	48 (36.9)	167 (40.2)	493 (34.3)	
2+	16 (12.3)	66 (15.9)	136 (9.5)	
Gravidity, mean \pm SD	1.97 \pm 1.03	2.18 \pm 1.11	1.86 \pm 0.98	<0.001*
Parity, mean \pm SD	0.63 \pm 0.74	0.75 \pm 0.79	0.55 \pm 0.71	<0.001*
Current pregnancy				
Gestational days at time of enrolment, median (IQR)	46 (39–61)	47 (39–59)	47 (38–66)	0.622
Folic acid				
No	59 (45.4)	168 (40.5)	201 (14.0)	<0.001*
≥ 5 mg	47 (36.2)	176 (42.4)	837 (58.4)	
Missing data	23 (17.7)	69 (16.6)	395 (27.5)	
Gestational days at time of IRs exposure, median (IQR)	1 (0.8)	2 (0.5)	1 (0.1)	
mSv max, median (IQR)	23 (18–30)	25 (18–30)	–	0.488
	3.5 (1.5–8)	–	–	

Cohort A: women exposed to abdominal or lumbar IRs; Cohort B: women exposed to IRs in other body regions. * $p < 0.05$.

ETOP: elective termination of pregnancy; IQR: interquartile range; IRs: ionizing radiations; SD: standard deviation; TTOP: therapeutic termination of pregnancy.

regions (45.4%) and in other regions (40.5%) as compared to controls (14%).

The median gestational days from the last menstrual period to the time of exposure to radio-diagnostic procedures was comparable for Cohort A and B ($p = 0.488$).

Fetal and neonatal outcomes

A significantly higher rate of ETOP was found among women exposed to abdominal or lumbar IRs (10.8%), compared to the other two cohorts (5.1% and 3.3%, respectively) (Table 3). This higher rate for Cohort A was also confirmed

Table 3. Fetal and neonatal outcomes.

	Cohort A N = 130 (%)	Cohort B N = 415 (%)	Controls N = 1434 (%)	p-value
Pregnancy outcome				
Live birth	92 (70.8)	328 (79.0)	1105 (77.1)	0.001*
Spontaneous miscarriage	21 (16.2)	63 (15.2)	270 (18.8)	
ETOP	14 (10.8)	21 (5.1)	47 (3.3)	
TTOP	3 (2.3)	3 (0.7)	9 (0.6)	
Stillbirth	0	0	3 (0.2)	
Congenital abnormalities				
No	126 (96.9)	409 (98.6)	1410 (98.3)	0.445
Yes	4 (3.1)	6 (1.5)	24 (1.7)	
For women with live births	N = 92	N = 328	N = 1105	
Male	51 (55.4)	158 (48.2)	554 (50.1)	0.465
Female	41 (44.6)	170 (51.8)	551 (49.9)	
Gestational age at delivery (WOG), median (IQR)	39 (38–40)	40 (38–40)	39 (38–40)	0.063
Preterm delivery (<37 WOG)	14 (15.2)	31 (9.5)	136 (12.3)	0.221
Very preterm delivery (<34 WOG)	3 (3.3)	4 (1.2)	20 (1.8)	0.415
Birth weight (grams), median (IQR)	3360 (3000–3600)	3277.5 (3000–3620)	3260 (2980–3580)	0.650
HC at birth (cm), median (IQR)	34 (34–35)	34 (33.5–35)	34 (34–35)	0.942
1-min Apgar score, median (IQR)	9 (8–9)	9 (9–9)	9 (9–9)	0.757
5-min Apgar score, median (IQR)	10 (9–10)	10 (9–10)	10 (9–10)	0.844
Small for gestational age	N = 87	N = 323	N = 1092	
AGA	81 (93.1)	292 (90.4)	1030 (94.3)	0.116
aSGA	4 (4.6)	22 (6.8)	49 (4.5)	
sSGA	2 (2.3)	9 (2.8)	13 (1.2)	

Cohort A: women exposed to abdominal or lumbar IRs; Cohort B: women exposed to IRs in other body regions. * $p < 0.05$.

AGA: appropriate for gestational age; aSGA: asymmetric small for gestational age; ETOP: elective termination of pregnancy; IQR: interquartile range; HC: head circumference; IRs: ionizing radiations; sSGA: symmetric small for gestational age; TTOP: therapeutic termination of pregnancy; WOG: week of gestation.

by excluding from the analysis all women with a previous history of ETOP (*data not shown*). The number of women undergoing TTOP was higher in Cohort A (2.3%) as compared to the other groups (0.7% and 0.6%, respectively). Specifically, TTOP were related to 2 malformations in Cohort A and to 1 malformation and two cases of trisomy 21 in Cohort B (*data not shown*). In the Control group, TTOP were related to seven malformations, one case of trisomy 21 and one case of chromosome 13 alteration. Conversely, the highest proportion of miscarriages was found in the Control group (18.8%), as compared to Cohort A (16.2%) and Cohort B (15.2%). No statistically significant differences were found between the three groups in terms of occurrence of congenital abnormalities. Specifically, four cases of congenital malformations were reported in Cohort A (3.1%), six in Cohort B (1.5%), and 24 in the Control group (1.7%). In particular, among Cohort A we observed: (1) hypoplastic kidney, twisted foot bilateral, hydrocephalia umbilical artery; (2) left ventricular hyperplasia; (3) cardiac heteroplasia; (4) right megaureter. Among Cohort B we observed: (1) renal hypoplasia; (2) abnormal ureter exit in the bladder; (3) double renal pelvis; (4) congenital hypertrophic heart disease; (5) ventricular defect; (6) left renal agenesis. Finally, among Control group: three renal malformations; one ocular malformation; seven heart malformations; two spina bifida; five gastrointestinal malformations; four limb malformations; one acrania; one hydrocephalus.

No statistically significant differences were found between the three groups in terms of gestational age at birth, preterm (<37 WOG) or very preterm birth (<34 WOG). Auxological parameters analysis in live-born infants showed no significant differences among the three groups in terms of birth weight, and Apgar scores at 1 min and 5 minute.

Conversely, the proportion of infants with aSGA and sSGA was higher among women exposed to IRs as compared to

unexposed ones, although not at a significant level ($p = 0.116$). To explore differences in terms of occurrence of SGA according to the body area exposed to IRs, we further stratified women in Cohort B according to the area of exposure (i.e., head, neck, thorax, teeth, limb or breast) (**Supplementary Table 1**). The lowest proportion of SGA was observed in women exposed to limb IRs (3 cases out of 49, 6.1%), whereas the proportion of SGA in the other groups ranged from 9.9% (8/81) for thorax IRs to 14.3% (3/21) for head IRs, respectively. Women who underwent mammography had a significantly higher maternal age compared with other subgroups ($p < 0.001$), and all SGA babies in the mammography group were born from mother with age ≥ 40 years (*data not shown*).

Fetal and neonatal outcomes according to radiation dose

We further stratified pregnancy outcomes among women from Cohort A according to the calculated maximum fetal radiation dose (**Table 4**). Information on the fetal radiation dose could be calculated in 97 out of 133 women. Eighty women were exposed to a fetal radiation dose <20 mSv (range 0.05–20), 12 to a dose between 20 and 50 mSv, and 5 to a dose ≥ 50 mSv (max 92 mSv). Pregnancy outcomes significantly differed among the three groups. The proportion of live births was 77.5% among women exposed to <20 mSv, 41.7% among women exposed to 20–50 mSv, and 40% among women exposed to ≥ 50 mSv. Indeed, both spontaneous miscarriage and ETOP were more frequent among women exposed to ≥ 20 mSv as compared to women exposed to <20 mSv. One congenital anomaly was observed among women exposed to ≥ 50 mSv, and no case was observed among women in the other two groups. For the

Table 4. Fetal and neonatal outcomes among women from Cohort A according to the maximum fetal radiation dose.

	Cohort A			p Value
	mSv 0.05-20 N = 80	mSv 20-50 N = 12	mSv 50-92 N = 5	
Pregnancy outcome				
Live birth	62 (77.5)	5 (41.7)	2 (40.0)	<0.001*
Spontaneous miscarriage	10 (12.5)	5 (41.7)	1 (20.0)	
ETOP	8 (10.0)	2 (16.7)	1 (20.0)	
TTOP	0	0	1 (20.0)	
Stillbirth	0	0	0	
Congenital abnormalities				
No	80 (100.0)	12 (100.0)	4 (80.0)	–
Yes	0	0	1 (5.9)	
For women with live births	N = 62	N = 5	N = 2	
Gestational age at birth (WOG), median (IQR)	39 (38–40)	39 (37–41)	39 (38–40)	0.567
Preterm birth (≤ 37 WOG)	9 (14.5)	2 (40.0)	1 (50.0)	0.107
Very preterm delivery (≤ 34 WOG)	3 (4.8)	0	0	–
Birth weight (grams), median (IQR)	3340 (3000–3580)	3630 (2820–3650)	3270 (2990–3585)	0.851
Head circumference at birth (cm), median (IQR)	34 (34–35)	35 (33.5–35)	32.5 (30–35)	0.767
1-min Apgar score, median (IQR)	9 (9–9)	9 (8–9)	9 (9–9)	0.698
5-min Apgar score, median (IQR)	10 (9–10)	9 (9–10)	9 (9–9)	0.457
Small for gestational age	N = 58	N = 6	N = 2	
AGA	53 (86.2)	5 (83.3)	2 (50.0)	–
aSGA	4 (6.9)	–	–	
sSGA	1 (1.7)	1 (16.7)	–	

Cohort A: women exposed to abdominal or lumbar IRs. * $p < 0.05$.

AGA: appropriate for gestational age; aSGA: asymmetric small for gestational age; ETOP: elective termination of pregnancy; IQR: interquartile range; HC: head circumference; IRs: ionizing radiations; sSGA: symmetric small for gestational age; TTOP: therapeutic termination of pregnancy; WOG: week of gestation.

other three cases of congenital anomalies reported in Cohort A, information regarding the fetal radiation dose was not available. Regarding live-born infants, no statistically significant differences among the three groups in terms of gestational age at birth, occurrence of preterm or very preterm birth, birth weight, Apgar score, and aSGA or sSGA were reported.

Factors associated with the risk of adverse pregnancy outcomes

Univariate models showed that older women, smokers, and women with previous APO were at significantly higher risk of APO (Table 5), whereas women treated with folic acid were at significantly lower risk of APO. Multivariate analysis confirmed the negative association between age and APO (OR 1.08 [1.06–1.11]), and the protective role of folic acid (OR 0.24 [0.18–0.32] and 0.22 [0.16–0.31] for women treated with folic acid < 5 mg and ≥ 5 mg, respectively). In addition, multivariate analysis showed that women with IRs exposure in areas different from the abdominal/lumbar region were at lower risk of APO as compared to unexposed ones. In particular, women exposed to IRs in the head-trunk region or in the limbs had an OR of 0.54 [0.39–0.74] and of 0.37 [0.17–0.83] as compared to unexposed women, respectively.

Both crude and adjusted models showed that women with IRs exposure in the head-trunk region had a significantly increased risk of having an infant with SGA, as compared to unexposed women (OR of 1.81 [1.10–2.97]) (Table 6). Conversely, the risk of SGA was similar between women in Cohort A or exposed to radiations in the limbs, as compared to unexposed ones. Maternal age, occupation, smoke, treatment with folic acid, and history of previous APO, were not associated with the risk of SGA. As expected,

both crude and adjusted models showed that underweight women (BMI < 18.5) carried an increased risk of SGA as compared to normal-weight women (OR of 2.30 [1.21–4.36]).

No logistic regression models were fitted for the outcome “congenital abnormalities”, due to the small number of cases.

Discussion

This study evaluated pregnancy outcomes in a large cohort of women exposed to radio-diagnostic procedures during early pregnancy. Our results suggest that IRs exposure, either in the abdominal or lumbar region or in other body areas during early pregnancy was not associated with an increased rate of spontaneous miscarriage, stillbirth or congenital anomalies. Furthermore, according to previously reported data, exposure to radio-diagnostic procedures to the head, teeth or trunk may involve maternal thyroid and seems to be associated with an increased risk of SGA [17,18]. Conversely, women exposed to IRs more frequently underwent ETOP respect to unexposed ones.

In our study, the median gestational days from the last menstrual period to the time to IRs exposure was of 24 days. The majority of women did not know to be pregnant at the time of IRs exposure, being the pregnancy unplanned in most cases. Indeed, the proportion of patients assuming prophylactic folic acid was significantly lower among women exposed to IRs, as compared to control women.

At time of first contact with the Teratology Information Service, the median gestational age was of 46.5 days, as soon as pregnancy was confirmed. This is probably due to the fear of complications and fetal malformations and to the need of a rapid and reliable toxicological counselling with the aim of considering the ETOP. In Italy this procedure is permitted

Table 5. Crude and adjusted models for the risk of adverse pregnancy outcome.

	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p Value
Age	1.07 (1.05–1.10)	<0.001*	1.08 (1.06–1.11)	<0.001*
IRs exposure				
No exposure	Ref.		Ref.	
Abdominal/lumbar IRs	1.39 (0.93–2.07)	0.107	0.90 (0.58–1.39)	0.619
IRs in head-trunk	0.95 (0.72–1.25)	0.724	0.54 (0.39–0.74)	<0.001*
IRs in limbs	0.55 (0.26–1.17)	0.120	0.37 (0.17–0.83)	0.016*
Occupation				
Housewife	Ref.		Ref.	
Teacher/secretary/sales assistant	1.05 (0.79–1.40)	0.722	1.00 (0.73–1.36)	0.990
Health professional	1.14 (0.74–1.73)	0.555	1.01 (0.64–1.60)	0.975
Factory worker/housemaid	1.48 (0.99–2.20)	0.057(*)	1.23 (0.80–1.90)	0.341
Freelance professional	0.84 (0.54–1.30)	0.427	0.73 (0.46–1.16)	0.180
Student	0.93 (0.50–25.81)	0.886	1.42 (0.52–3.89)	0.490
BMI				
18.5–25 (normal)	Ref.		Ref.	
\ddot{y}	0.70 (0.43–1.12)	0.138	0.73 (0.45–1.22)	0.236
25.1–30 (overweight)	1.23 (0.90–1.67)	0.195	1.07 (0.77–1.49)	0.667
\ddot{y}	1.00 (0.57–1.73)	0.987	0.87 (0.47–1.59)	0.652
Smoke				
No	Ref.		Ref.	
Yes	1.30 (1.01–1.67)	0.044*	1.22 (0.93–1.61)	0.158
Folic acid				
No	Ref.		Ref.	
$\geq 5\text{mg}$	0.29 (0.22–0.37)	<0.001*	0.24 (0.18–0.32)	<0.001*
$\geq 5\text{mg}$	0.26 (0.19–0.35)	<0.001*	0.22 (0.16–0.31)	<0.001*
Previous APO**				
No	Ref.		Ref.	
Yes	1.41 (1.09–1.82)	0.008*	1.23 (0.94–1.62)	0.135

* $p < 0.05$. **Previous APO did not consider previous intentional termination of pregnancy.

APO: adverse pregnancy outcome; BMI: body mass index; IRs: ionizing radiations; OR: odd ratio.

Adjusted models included IRs exposure, maternal age, maternal occupation, BMI, smoke (yes/no), folic acid intake, and previous APO.

Table 6. Crude and adjusted models for the risk of small for gestational age (asymmetric and symmetric).

	Univariate OR (95% CI)	p Value	Multivariate OR (95% CI)	p Value
Age	1.02 (0.97–1.06)	0.471	1.02 (0.98 – 1.07)	0.367
IRs exposure				
No exposure	Ref.		Ref.	
Abdominal/lumbar IRs	1.52 (0.71–3.28)	0.282	1.62 (0.73–3.60)	0.235
IRs in head-trunk	1.78 (1.12–2.84)	0.014*	1.81 (1.10–2.97)	0.020*
IRs in limbs	1.04 (0.32–3.44)	0.944	1.11 (0.32–3.79)	0.870
Occupation				
Housewife	Ref.		Ref.	
Teacher/secretary/sales assistant	0.68 (0.41–1.14)	0.146	0.69 (0.40–1.17)	0.165
Health professional	1.35 (0.67–2.70)	0.398	1.34 (0.66–2.74)	0.418
Factory worker/housemaid	0.82 (0.37–1.81)	0.620	0.73 (0.33–1.66)	0.458
Freelance professional	0.67 (0.30–1.48)	0.321	0.60 (0.27–1.35)	0.220
Student	1.06 (0.23–4.78)	0.944	1.26 (0.27–5.93)	0.770
BMI				
18.5–25 (normal)	Ref.		Ref.	
\ddot{y}	2.11 (1.13–3.97)	0.019*	2.30 (1.21–4.36)	0.011*
25.1–30 (overweight)	1.09 (0.58–2.06)	0.782	1.05 (0.55–2.00)	0.876
\ddot{y}	0.84 (0.25–2.74)	0.766	0.76 (0.23–2.55)	0.660
Smoke				
No	Ref.		Ref.	
Yes	1.08 (0.66–1.77)	0.762	0.97 (0.57–1.63)	0.901
Folic acid				
No	Ref.		Ref.	
$\geq 5\text{mg}$	0.80 (0.46–1.37)	0.412	0.97 (0.54–1.73)	0.919
$\geq 5\text{mg}$	0.94 (0.52–1.71)	0.846	1.14 (0.60–2.17)	0.686
Previous APO**				
No	Ref.		Ref.	
Yes	0.98 (0.58–1.66)	0.941	0.93 (0.54–1.60)	0.791

* $p < 0.05$. **Previous APO did not consider previous intentional termination of pregnancy.

APO: adverse pregnancy outcome; BMI: body mass index; IRs: ionizing radiations; OR: odd ratio.

Adjusted models included IRs exposure, maternal age, maternal occupation, BMI, smoke (yes/no), folic acid intake, and previous APO.

only before the 90th day of gestation. It is widely described in literature that diagnostic procedures in pregnancy create a considerable state of maternal anxiety [1], that could be associated with negative pregnancy outcomes [19,20].

As mentioned above, our results confirm that exposure to IRs procedures during early pregnancy is not associated with an increased rate of spontaneous miscarriage or stillbirth. These results are comparable to those described by Choi and colleagues [21]. We found an increased rate of spontaneous miscarriages only in women exposed to a fetal radiation dose ≥ 20 mSv (Cohort A), however, the sample size of this subgroup was too small to draw reliable conclusions. Our results confirm other evidence from the literature, suggesting no increased risk of APO associated with early IRs exposure. According to a prospective observational cohort study evaluating pregnant women between 1987 and 2014, exposure to radio-diagnostic procedures, even in the abdominal or lumbar region, was not associated with a higher risk of malformations, spontaneous miscarriages, stillbirths or fetal growth restriction [22]. Conversely, we found that women exposed to IRs, particularly in abdominal or lumbar regions, more frequently underwent elective termination of pregnancy respect to unexposed women.

This result was confirmed also when excluding women with previous history of elective terminations of pregnancy, and may be explained by mother's fear of radiation effects to the fetus [1,19,20]. Notably, women exposed to IRs procedures had a lower educational level as compared to unexposed ones. Thus, the high rate of elective termination of pregnancy in this group might suggest difficulties in understanding or believing the information conveyed by the experts and claims the need for improving quality of communication during counselling [23].

Regarding congenital malformations, we found that the rate of major malformations was 3.1% (a total of four cases) among women exposed to IRs in the abdominal or lumbar regions, which is almost double compared to that observed in the control group or in women exposed to IRs in other body regions (1.7% and 1.5%, respectively). However, this difference did not reach statistical significance.

Unfortunately, technical parameters for the calculation of the fetal radiation dose were available only for one of the four cases of major malformations recorded in the group exposed to IRs in the abdominal or lumbar regions, and this woman had been exposed to a high fetal radiation dose (≥ 50 mSv after abdominal CT). Among other three women, two underwent abdomen radiography and one hysterosalpingography (all of them with an estimate predefined fetal dose of < 20 mSv). This finding is in line with previous literature studies, suggesting that exposure to radio-diagnostic procedures during early pregnancy with a fetal radiation dose level < 50 mSv, is not associated with an increased risk of major malformations of the fetus [4]. Of notice, to date clinicians can actually use 100 mSv as threshold according the National Council on Radiation Protection and Measurements Report 174. In fact, 100 mSv is a threshold below which no carcinogenic effects are expected [24]. Notably, within the control group, the rate of malformations was lower in respect

to what expected for the general population [25]. Indeed, our control group was highly selected, excluding women with major risk factors for pregnancy complications.

According to our study, a higher rate of SGA seems to be present in women who underwent radio-diagnostic procedures that involve maternal thyroid (i.e., head, teeth, neck, and thorax X-ray). The possible role of radiation involving maternal thyroid gland on the occurrence of SGA has been reported in previous studies, particularly among male newborns [1,26]. However, this association is still debated [17,18]. In fact, diagnostic radiological studies of the chest, head, neck or extremities are very unlikely to expose the embryo to a dose > 0.1 Gy. Therefore, there is no evidence of increased risk for birth defects, miscarriage, neurobehavioral effects, convulsive disorders, decreased IQ, or mental retardation for the offspring of women who have been exposed to the above-mentioned diagnostic radiological procedures during their pregnancy [24,27].

Moreover, we did not observe a negative association between smoke and SGA, even if smoke is a well-known cause of SGA [28]. Maybe, our analysis failed to confirm this association both due to the relative small number of women who declared to be smokers during the first contact with our Teratology Information Service, and to the fact that no information regarding the number of daily cigarettes consumed was available. In fact, in the analysis we could only consider the "smoke" as a dichotomous variable.

The major strength of our study relies on the fact that a large cohort of women without additional major risk factors for pregnancy complications was evaluated, thus limiting the influence of factors other than IRs exposure. Furthermore, we did not use predefined fetal doses as elsewhere [20], but we used tailored fetal radiation doses calculated on a case-by-case approach performed by health physicists, which allowed clinical toxicologists to provide a patient-specific clinical advice.

As for the limitations of our study, some of which are inherent to its observational nature, technical parameters for the calculation of the fetal radiation dose were retrospectively collected and were not always available for all patients. These parameters are not routinely collected as it would require radiologists and/or radiology technicians to consult and/or modify their standard operative protocols to retrieve this information. Another relevant limitation could be represented by the lack of information on maternal diseases associated to the diagnostic procedures during first trimester of pregnancy. In fact, this could also be a major cause of APO and/or SGA because women with more disease burden would require more than one radio-diagnostic procedure and this could be the reason for some of the birth outcomes observed both in Cohort A and Cohort B. Finally, no information regarding thyroid protection during the radio-diagnostic procedure was available. Thus, we could not assess either the effect of thyroid protection or that of nonprotection.

Conclusions

Despite the above-mentioned limitations, our study confirms that exposure to radio-diagnostic procedures that may

involve uterus at doses below 100 mSv does not increase the risk of deterministic effects and, although obtained on a small number of cases, that maternal thyroid radiation exposure in first trimester of pregnancy increases the risk of low birth weight infants.

Counselling women exposed to IRs during pregnancy should be more accurate. Clinicians should rely more often on clinical toxicologists, health physicists, radiologists and nuclear medicine specialists to have a tailored counselling based on the fetal absorbed dose specifically calculated for each patient.

Geolocation information

This study was conducted at Careggi University Hospital, Florence, Italy.

Disclosure statement

The authors report no conflict of interest.

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