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Effects of maternal exposure to ^{131}I used for treatment of Graves' disease during childbearing age on chromosomal aberration and intellectual development of offspring

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► ***Original article***

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ABSTRACT

Background: Although radioiodine-131 (^{131}I) has been widely used for the treatment of Graves' disease (GD), radiation is a potential risk factor for mutagenic abnormalities. This retrospective clinical study mainly aimed to investigate the influence of maternal exposure to 131I used for the treatment of GD prior to pregnancy on chromosomal aberration and intellectual development of offspring in China. ***Materials and Methods:*** In total, 69 children whose mothers received ^{131}I for the treatment of GD during childbearing age were included. Data on the obstetric history, medical records, and the birth characteristics of the children were obtained. The thyroid function, thyroid ultrasound, chromosomal structure, and somatic and intellectual development of the children were measured. ***Results:*** In all 66 women, the range of the administered ^{131}I was within 228.2 ± 70.3 MBq. The height and weight of all children were within the normal ranges, and one child was confirmed as having subclinical hypothyroidism. Two children were diagnosed with benign thyroid nodules, one child was diagnosed with thyroid cysts, and one child was confirmed as having several anechoic areas in both lobes of the thyroid gland. Chromosomal aberration was observed in one child. None of the children showed any abnormalities in somatic and/or intellectual development. ***Conclusion:*** This is the first study to confirm that ^{131}I used for the treatment of GD prior to pregnancy does not significantly increase the risk of chromosomal aberration or impair the intellectual development of offspring.

INTRODUCTION

Graves' disease (GD) is an autoimmune thyroid disorder in which inappropriate stimulation of the thyroid gland results in unregulated synthesis and secretion of thyroid hormones, leading to hyperthyroidism [1]. Hyperthyroidism-related complications affect approximately 0.1%–0.4% of pregnancies and GD accounts for 85% of these cases [2, 3]. The incidence of GD peaks in the third to fourth decade of life (child-bearing age). Therapeutic options for GD include antithyroid drugs, radioiodine -131 (^{131}I) treatment, or, occasionally, surgery (near-total thyroidectomy) [4, 5]. Some women with GD may receive definitive therapy with ^{131}I treatment prior to pregnancy to avoid potential fetal malformations caused by antithyroid drugs during pregnancy [6].

Although ^{131}I treatment is an inexpensive, safe, and effective treatment for GD [7], it may cause potential detrimental side effects, such as ophthalmopathy, hypothyroidism, thyroiditis, sialadenitis, bone marrow depression, pulmonary fibrosis, or even a second primary malignancy [8, 9]. In addition, ^{131}I treatment could impair the gonads, leading to transient or chronic hypospermia, early onset of menopause, and menstrual cycle abnormalities; hence, radioactive treatments are not suitable for fertile women owing to the potential genetic damages to the offspring [10-13]. Moreover, maternal exposure to ^{131}I may increase the risk of the offspring developing thyroid cancer since ^{131}I preferentially accumulates in the thyroid gland after

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transferring across the placenta [14]. Fear of potential adverse reactions has restricted the application of ^{131}I therapy in young women of childbearing age with GD. To the best of our knowledge, no study has reported on the chromosomal aberration or health status of offspring born to mothers who received 131I treatment for GD before pregnancy.

This retrospective clinical study mainly aimed to investigate the influence of maternal exposure to ^{131}I used for the treatment of GD prior to pregnancy on chromosomal aberration and intellectual development of offspring in China. Women who received ^{131}I treatment for GD during reproductive age and their children born several years after the treatment were included. The obstetric history of the mothers, their medical records, and the birth characteristics of the children were collected. Further, the thyroid function, chromosome structure, ultrasound screening of the thyroid, and somatic and intellectual development of the children were measured. The findings of the present study will help determine whether the administration of ^{131}I treatment for GD prior to pregnancy exerts adverse effects on the offspring. To the best of our knowledge, this is the first study to confirm that ^{131}I used for the treatment of GD prior to pregnancy does not significantly increase the risk of chromosomal aberration or impair the intellectual development of offspring.

MATERIALS AND METHODS

Study subjects

From September 1995 to July 2017, 328 fertile women with GD who received ^{131}I treatment in the Department of Endocrinology of the Fifth Medical Center, Chinese PLA General Hospital (Former 307th Hospital of the PLA) were identified using medical records. Among the 328 patients, 113 women decided to conceive as they had normal thyroid function for pregnancy, at least 6 months after ^{131}I treatment. Thyroid function is considered normal if the level of the thyroid-stimulating hormone (TSH) is less than 2.5 mU/L in the first trimester and less than 3 mU/L in later pregnancy. These women included those with euthyroidism, hypothyroidism (in whom normal thyroid function was maintained during pregnancy via levothyroxine replacement therapy), and mild hyperthyroidism (who were treated with low-dose propylthiouracil or methimazole to maintain normal thyroid function). Thyroid function was monitored early in the first trimester and every 4 to 6 weeks thereafter. Forty-seven patients were excluded: 35 patients refused to participate, and the children of 12 patients were less than 6 months old at the time of follow-up and thus, unable to cooperate with the trial items. Ultimately, 66 women, together with their 69 children, fulfilled the study criteria and provided written informed consent to participate in our study.

Data collection

The 66 women were interviewed to obtain data regarding their medical history of GD and regarding the ^{131}I treatment that they had received. Birth outcomes and any adverse events related to the births of the children were documented. Further, the thyroid function, thyroid ultrasonography screening, and somatic and intellectual development of the children were evaluated, and chromosomal aberrations, if any, were detected.

Thyroid function

The commercially available Thyroid Assay Menu kits (including serum triiodothyronine (T3), thyroxine (T4), free T3, free T4, TSH, thyroglobulin antibody (TG-Ab) and thyroperoxidase antibody (TPO-Ab)) were obtained from ADVIA Centaur, Siemens Healthcare Diagnostics Inc. Serum T3, T4, free T3, free T4, TSH, TG-Ab, and TPO-Ab levels were measured using ADVIA Centaur XP Analyzer (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) using original reagents, and the operational procedures were performed according to the manufacturers' instructions. Thyroid-stimulating hormone receptor (*TSHR)* antibody levels were analyzed by *Elecsys Anti-TSHR* assay (Roche Diagnostics, Mannheim, Germany) in a Cobase601 analyzer (Roche Diagnostics).

Thyroid ultrasound

Thyroid ultrasound was performed using the SIEMENS ACUSON Sequoia 512 Color Doppler ultrasound diagnostic instrument (Siemens Medical Solutions, Mountain View, CA, USA). The size, morphology, parenchymal echogenicity, blood flow and vascularity of the thyroid gland, ectopic thyroid tissue (if any) and the number, size, and shape of the boundary surrounding the acoustic halo, internal echo, calcification, and internal and peripheral blood supply of the thyroid nodule (if any) were examined.

Chromosomal analyses

Cultured peripheral lymphocytes obtained from the children were subjected to standard chromosomal analyses following standard procedures (R-banding after heat denaturation and Giemsa staining). About 0.2 mL of whole blood was added to 5 mL of RPMI 1640 medium (without phytohemagglutinin). Blood cells were cultured for 24 hours in an incubator at 37°C, and then treated with colchicine 1 h before the end of the incubation period (final concentration =0.05 μg/mL). Subsequently, the cells were centrifuged and suspended in a preheated hypotonic solution of 0.1 mol/L KCl. Thereafter, the cells were centrifuged again, the supernatant was removed, and the cells were fixed by a drop-wise addition of 1 mL of a fixative (ice-cold methanol: acetic acid, 3:1) and

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stained by R-banding after heat denaturation and Giemsa staining. In total, 20 metaphase spreads were analyzed and photographed under the Zeiss Axio Imager Z2 microscope (Zeiss, Oberkochen, Germany). Karyotype analysis was performed using a MetaSystems image analysis system (MetaSystems, Altlussheim, Germany) according to the International System of Human Cytogenetic Nomenclature.

Physical examination

The height and weight of the offspring were measured by two trained clinical researchers, and the average of the values obtained by the two researchers was considered. If the difference between the two measurements was more than 10%, a third measurement was obtained, and the average value of the three measurements was considered.

Developmental quotient or intelligence quotient assessment

The intellectual and motor development of all children under 6 years of age was assessed using a diagnostic kit to assess intelligence (supervised by the Capital Institute of Pediatrics, China). The results of the evaluation were expressed in terms of developmental quotient (DQ). A DQ ≤75, 75<DQ<85, and DQ≥85 indicated low, marginal, and normal intellectual and motor development, respectively.

The intelligence quotient (IQ) of children aged over 6 years was evaluated through standardized neuropsychological examinations (Chinese Revision of Wechsler Intelligence Scale for Children, C-WISC, revised by Lin Chuanding and Zhang Houcan, 6–16 years). Full scale IQ included six verbal IQ subtests and six performance IQ subtests. The score of every branch scale and the total IQ score was calculated, and the results were expressed as IQ. An IQ score of ≤70, 70<IQ≤80, 80<IQ≤90, 90<IQ≤110, 110<IQ≤120, 120<IQ≤130, and IQ>130 exhibited mental deficiency, critical state, lower (dull) intelligence, medium intelligence, upper middle intelligence (intelligent), excellent intelligence, and very excellent intelligence, respectively.

Statistical analysis

All data analyses were performed using SPSS 18.0 software. Continuous variables were expressed as mean±standard error of mean. The distributions of continuous variables were estimated using Kolmogorov–Smirnov Z test. If the data was in normal distribution, Student's t test was used to compare the differences between two groups; otherwise, the Mann–Whitney U test was used. The categorical variables were recorded as case number and percentage, and the chi-square test was used for comparisons between groups. All tests were two tailed, and a P value <0.05 was considered statistically significant.

RESULTS

General information of interviewed women and offspring

In total, 66 eligible fertile women (average age, 34.33±4.96 years) who received ^{131}I treatment for GD from September 1995 to July 2017 were retrospectively investigated. These women, who had conceived at least 6 months after stopping ^{131}I treatment, and their 69 children were interviewed. The mean age of the patients at the first ^{131}I treatment was 27.46±5.76 years. The dose of ^{131}I administered within 228.2±70.3 MBq. In total, 52 (78.79%) women received one ^{131}I treatment, 11 (16.67%) women received two ^{131}I treatments, and 3 (4.54%) women received three ^{131}I treatments. The thyroid levels of all women progressively decreased after ^{131}I treatment (figure 1). In total, 44 (66.67%) women developed hypothyroidism or subclinical hypothyroidism after treatment and were administered levothyroxine (12.5–175 μg/d). Six (9.10%) women were diagnosed with hyperthyroidism or subclinical hyperthyroidism during pregnancy; 2 of these received propylthiouracil 12.5 mg/d and 100 mg/d), 2 received methimazole (10 mg/d and 20 mg/d), and 2 received no antithyroid treatment during pregnancy. Moreover, 16 (24.24%) women with euthyroidism were also clinically followed (table 1).

Table 1. Baseline characteristics of the included women.

Characteristics	No. (%)
Total case number	66
Age (years, mean ± SD)	34.33 ± 4.96
Age at first 131I treatment (years, mean ± SD)	27.46 ± 5.76
Number of treatments	
1	52 (78.79)
2	11 (16.67)
3	3 (4.54)
Interval between treatment and pregnancy (years)	
≤ 1	7 (10.61)
1–2	14 (21.21)
2–3	14 (21.21)
≥ 3	31 (46.97)
Thyroid function during pregnancy	
Hypothyroidism	44 (66.67)
Hyperthyroidism	6 (9.10)
Normal	16 (24.24)
Average dose of Euthyrox for hypothyroidism cases (μg, mean ± SD)	77.42 ± 30.89

^{131}I: radioiodine-131; SD: standard deviation

Baseline characteristics of offspring

Among the 66 women, 63 had a single birth after ^{131}I treatment, and 3 women had two pregnancies. Sixty-seven (97.10%) babies were born at full term, whereas 2 (2.90%) were born prematurely (at 28 and 34 weeks, with birth weights of 3,200 g and 2,800 g, respectively). The proportion of eutocia: cesarean section delivery was 30:39. No neonate was considered a low-birth-weight infant (weighing <2.5

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kg); five of the infants (7.25%) had high birth weight (>4 kg). However, the birth weights of all the infants were within the normal range. One child, each, had a history of asphyxia, amniotic fluid inhalation, and premature rupture of membranes, and no child had a history of meconium aspiration. None of the 69 neonates showed excess of embryo arrest, stillbirths, congenital malformations, or cancer (table 2).

Table 2. Characteristics of the children at birth.

Characteristics	No. (%)
Total number	69
Delivery method	
Natural childbirth	30 (43.48)
Cesarean section	39 (56.52)
Gender	
Male	39 (56.52)
Female	30 (43.48)
Gestational age at birth (weeks)	
< 37	2 (2.90)
37	4 (5.80)
37–40	53 (76.81)
≥ 40	10 (14.49)
Birth weight (g, mean ± SD)	3,331.52 ± 384.04
Low birth weight	0 (0)
Normal birth weight	64 (72.75)
High birth weight	5 (7.25)
Adverse events	
History of asphyxia	1 (1.45)
History of amniotic fluid inhalation	1 (1.45)
History of meconium aspiration	0 (0.00)
History of premature rupture of membranes	1 (1.45)

SD: standard deviation

Thyroid function evaluation and thyroid ultrasound of offspring

All 69 children were subjected to thyroid function tests. A 16-month-old boy did not cooperate in the blood tests, so his tests could not be completed. A 15-year-old boy with subclinical hypothyroidism (TSH 7.46 uIU/mL) showed elevated TPO-Ab/TG-Ab titers (TPO-Ab 447.7 IU/mL, TG-Ab 730.2 IU/mL) and positive thyroid ultrasound findings for autoimmune thyroiditis. He was subsequently diagnosed with subclinical hypothyroidism and autoimmune thyroiditis. Thyroid ultrasound also detected benign thyroid nodules in two children, thyroid cysts involving both thyroid lobes in one child, and several anechoic areas in both lobes of the thyroid gland in one child (table 3).

Chromosomal aberrations

Karyotype analysis was performed using the R-banding technique to measure DNA damages in circulating peripheral blood lymphocytes of the children. All children showed normal karyotype, except one child who showed the (46, XX) karyotype, with one aberrant cell, which was possibly ectopic (figure 2). However, the child's parents declined further examinations.

Estimation of somatic and intellectual development

Evaluation of the physical development of the children at different developmental stages showed no detectable abnormalities. The parents of four children refused DQ or IQ examination for their children, and only stated that their children showed an excellent academic performance. Overall, among 51 children aged within 6 years, the adaptability score of one child was ≤75, the adaptability scores of two children were between 75 and 85, the gross motor function score of one child was between 75 and 85, the fine motor function score of one child was ≤75, the verbal assessment scale score of one child was ≤75 and those of three children were between 75 and 85, and the social competence score of one child was ≤75 and that of one child was between 75 and 85 (table 4). The IQ of all 14 children aged more than 6 years was >90, which was higher than the level of lower or dull intelligence. Table 4 presents the data on the IQ of the 14 children.

Table 3. Thyroid function and thyroid ultrasonography screening of the children at follow-up.

Indexes	No. (%)
Age (months)	median: 47.13, range: 12–180
Thyroid function of mothers during pregnancy	
Hypothyroidism	46 (66.67)
Hyperthyroidism	6 (8.69)
Normal	17 (24.64)
Thyroid function of the children	
Hypothyroidism with elevated TPO-Ab/TG-Ab	1 (1.45)
Hyperthyroidism	0 (0)
Normal	67 (97.10)
Invalid data	1 (1.45)
T3 (nmol/L, mean ± SD)	2.36 ± 0.32
T4 (nmol/L, mean ± SD)	118.86 ± 20.11
FT3 (pmol/L, mean ± SD)	6.42 ± 0.74
FT4 (pmol/L, mean ± SD)	16.82 ± 1.76
TSH (mU/L, mean ± SD)	3.01 ± 1.31
TPO-Ab (IU/mL)	median: 10.80, range: 5.40–447.70
TG-Ab (IU/mL)	median: 12.80, range: 10.10–730.20
TR-Ab (IU/mL, mean ± SD)	0.49 ± 0.15
Chromosome karyotype analysis	
Normal	66 (95.65)
Abnormal	1 (1.45)
Invalid data	2 (2.90)
Thyroid ultrasound	
Normal	63 (91.30)
Autoimmune thyroiditis	1 (1.45)
Benign thyroid nodule	2 (2.90)
Thyroid cysts	1 (1.45)
Anechoic areas in both lobes of the thyroid	1 (1.45)
Invalid data	1 (1.45)

SD: standard deviation; T3: triiodothyronine; T4: thyroxine; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; TPO-Ab: thyroperoxidase antibody; TG-Ab: thyroglobulin antibody; TR-Ab: thyroid-stimulating hormone receptor antibody

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Table 4. Somatic and intellectual development of the children during the follow-up.

Index	No. (%)/Mean ± SD
Age < 6 years	
Number of children	51
Adaptability score	99.86 ± 11.34
≤ 75	1 (1.96)
75–85	2 (3.92)
≥ 85	48 (94.12)
Gross motor function score	103.47 ± 10.02
≤ 75	0 (0.00)
75–85	1 (1.96)
≥ 85	50 (98.04)
Fine motor function score	104.12 ± 13.13
≤ 75	1 (1.96)
75–85	0 (0.00)
≥ 85	50 (98.04)
Verbal assessment scale	99.71 ± 12.06
≤ 75	1 (1.96)
75–85	3 (5.88)
≥ 85	47 (92.16)
Social competence score	106.78 ± 14.41
≤ 75	1 (1.96)
75–85	1 (1.96)
≥ 85	49 (96.08)
Age ≥ 6 years	
Number of children	14
Verbal intelligence quotient	114.21 ± 12.10
≤ (lower)	0 (0.00)
90 < IQ ≤ 110 (medium)	5 (35.71)
110 < IQ ≤ 120 (upper middle or intelligent)	6 (42.86)
120 < IQ ≤ 130 (excellent)	2 (14.29)
> 130 (extremely excellent)	1 (7.14)
Performance intelligence quotient	115.79 ± 15.27
≤ (lower)	0 (0.00)
90 < IQ ≤ 110 (medium)	6 (42.86)
110 < IQ ≤ 120 (upper middle or intelligent)	4 (28.57)
120 < IQ ≤ 130 (excellent)	2 (14.29)
> 130 (extremely excellent)	2 (14.29)
Full intelligence quotient	116.64 ± 13.96
≤ (lower)	0 (0.00)
90 < IQ ≤ 110 (medium)	6 (42.86)
110 < IQ ≤ 120 (upper middle or intelligent)	3 (21.43)
120 < IQ ≤ 130 (excellent)	3 (21.43)
> 130 (extremely excellent)	2 (14.29)

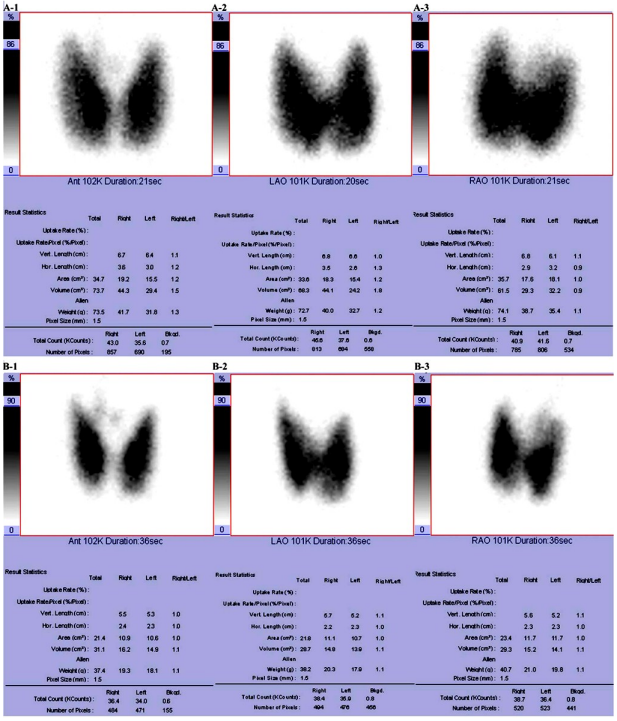

Figure 1. Thyroid scan image before and after radioiodine-131 (131I) treatment. (A1–A3) Initial image showing Graves' disease, estimated weight 75 g (Before treatment); (B1–B3) Images after 131I treatment, estimated weight 30 g. Ant: anterior; LAO: left anterior oblique; RAO: right anterior oblique.

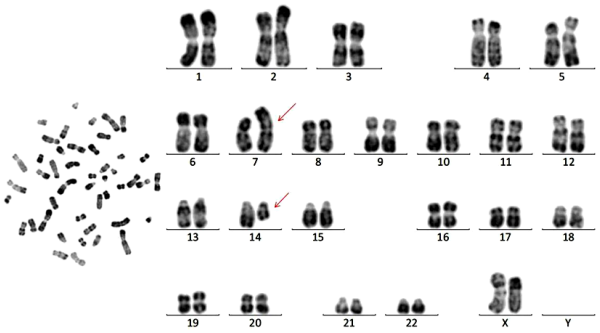

Figure 2. One child showed the (46, XX) karyotype, with one aberrant cell, which was possibly ectopic.

DISCUSSION

Radioiodine-131 treatment has generally been recommended as a relatively safe, simple, and effective therapy for GD. However, caution should be exercised when using this treatment for women of childbearing age, due to the potential complications such as fetal hypothyroidism, solid cancers, mental retardation, etc. [15, 16]. Basbug *et al.* reported the first case of fetal hypothyroidism, wherein the mother had received a single dose of 5 mCi ^{131}I at 16 weeks of gestation [17]. Prinsen *et al.* retrospectively analyzed three women who received 131I treatment for GD during pregnancy, and only one woman who had received ^{131}I treatment at 14 weeks of gestation delivered an infant diagnosed with hypothyroidism ascribed to radioiodine [18]. Likewise, our study included 66 women along with their 69 children. All the women were treated with ^{131}I for GD before pregnancy, and only one child was diagnosed with hypothyroidism. In a retrospective cohort study of the database of the Department of Pediatric Endocrinology in Portugal, 50 newborns born to 46 women with GD were included, among which three were confirmed as having hypothyroidism in the neonatal period [19]. The results revealed that maternal exposure to ^{131}I for treatment of GD prior to pregnancy may not increase the risk of fetal hypothyroidism. However, given the relatively small sample size in the mentioned studies, the conclusion should be confirmed by further studies with a larger sample size.

Radioactive iodine treatment may induce malignancies. A significantly increased incidence of

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thyroid cancer was observed in children born after the Chernobyl accident, indicating a possible link between childhood thyroid cancer and radioactive iodine exposure [20]. Even worse, the organ-absorbed doses were modestly positively associated with the risk of death from solid cancer among patients with hyperthyroidism receiving radioactive iodine treatment [21]. However, some studies reported conflicting results. In the study by Read *et al*., 116 patients with GD who had been treated with ^{131}I under 20 years of age were followed up for 36 years. The results revealed that none of the patients developed thyroid cancer or leukemia, and none of the pregnancies resulted in an unusual number of congenital anomalies in the child, or spontaneous abortions [22]. Radioiodine-131 treatment might be safe and effective for young women with GD. A cohort study including 16,637 patients, with 123,166 person -years of follow-up, demonstrated that radioiodine treatment for hyperthyroidism did not alter the risk of solid cancers such as thyroid cancer, leukemia, lung cancer, breast cancer, etc. [23]. Similarly, none of the children in our study were confirmed to have thyroid cancer based on thyroid ultrasound. Radioiodine-131 treatment prior to pregnancy might have no significant influence on thyroid function of the offspring and the morbidity of fetal cancers. The side effects induced by radiation treatment on the embryo/fetus are closely dependent on the pregnancy stage, delivered radiation dose, and pathological alterations [24]. Therefore, the potential influences should be taken into consideration when administering 131I treatment to women of childbearing age.

Fetal mental retardation is another important focus of maternal exposure to radioactive iodine [25]. It has been reported that during the 8th and 15th week of gestation, the risk of fetal mental retardation resulting from radiation exposure might be up to 40%/Sv [26]. In our study, all the eligible women received ^{131}I treatment at least 6 months before pregnancy. No abnormalities were detected in the physical development of the children at different developmental stages. Thus, ^{131}I treatment prior to pregnancy might not significantly influence fetal mental development. This finding was in line with those of other published articles. Zhang *et al.* investigated the effects of ^{131}I treatment on pregnancy outcomes among patients who received ^{131}I treatment in their reproductive age for Graves' hyperthyroidism. The results showed that all patients for whom the ^{131}I treatment was ceased at least 6 months before conception had normal deliveries and, notably, their pregnancy outcomes did not show significant differences from those of healthy women [27]. Guan *et al.* reported that infants born to 69 women who were treated with ^{131}I prior to pregnancy had normal birth weights, and they were observed to grow and develop normally [28]. Thus, ^{131}I treatment prior to pregnancy might have no detrimental effects on the health status and mental development of the infants.

The current study has several limitations. Firstly, the retrospective nature of this study might cause a selection bias in the final results. Secondly, the relatively small sample size reduced the statistical power of our results. In addition, there was no matched control group in our study. The control group was necessary to enhance the statistical power of our analysis. Therefore, further prospective studies with larger sample sizes are warranted to verify and improve our results.

In conclusion, maternal exposure to ^{131}I treatment for GD prior to pregnancy does not significantly influence the birth outcomes, thyroid function, or somatic and intellectual development of the offspring.

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***Conflict of interest*:** None of the authors have any potential conflicts of interest associated with this research.

***Ethical consideration*:** The study was approved by the Institutional Ethics Committee of The Fifth Medical Center, Chinese PLA General Hospital (Former 307th Hospital of the PLA).

***Author contributions*:** J.Z. analyzed the data and wrote the paper. J.W., Q.G., and Y.H. analyzed the data. Q. L. and J. L. performed the developmental quotient or intelligence quotient assessment. B.Y. performed chromosomal analyses. D.Z., Q.F., and Z.L. performed data collection. F.C. provided Figure 1. J.X. and Y.F. contributed to conceptualization, funding acquisition, resources, supervision, and writing - review & editing. All authors read and approved the final manuscript.

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