

Pregnancy outcome after first trimester exposure to ionizing radiations

Lucie Guilbaud, Delphine Beghin, Ferdinand Dhombres, Eléonore Blondiaux, Stéphanie Friszer, Hubert Ducou Le Pointe, Elisabeth Elefant, Jean-Marie Jouannic

► **To cite this version:**

Lucie Guilbaud, Delphine Beghin, Ferdinand Dhombres, Eléonore Blondiaux, Stéphanie Friszer, et al.. Pregnancy outcome after first trimester exposure to ionizing radiations. European Journal of Obstetrics and Gynecology and Reproductive Biology, Elsevier, 2019, 232, pp.18-21. 10.1016/j.ejogrb.2018.11.001 . hal-02314031

HAL Id: hal-02314031

<https://hal.sorbonne-universite.fr/hal-02314031>

Submitted on 11 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Full length article

Pregnancy outcome after first trimester exposure to ionizing radiations

Lucie Guilbaud^{a,*}

lucie.guilbaud@gmail.com

Delphine Beghin^b

Ferdinand Dhombres^c

Eléonore Blondiaux^c

Stéphanie Friszer^a

Hubert Ducou Le Pointe^c

Elisabeth Eléfant^c

Jean-Marie Jouannic^a

^aDepartment of Fetal Medicine, Armand Trousseau Hospital, APHP, Sorbonne University, UPMC Paris 6 University, Paris, France

^bCentre de Référence sur les Agents Tératogènes, Armand Trousseau Hospital, APHP, Paris, France

^cDepartment of Radiology, Armand Trousseau Hospital, APHP, Sorbonne University, UPMC Paris 6 University, Paris, France

*Corresponding author at: Service de Médecine Fœtale, Hôpital Armand Trousseau, 26 avenue du Docteur Arnold Netter, 75012 Paris, France.

Abstract

Objective

To evaluate the effects of ionizing radiation exposure during the first trimester of pregnancy in usual clinical situations.

Study design

We conducted a prospective observational cohort study using data collected between 1987 and 2014. This database was authorized by the French "Commission Nationale de l'Informatique et des Libertés". The exposed group consisted of 319 pregnant women exposed to sub diaphragmatic ionizing radiations for diagnostic purposes, during the first trimester of pregnancy, and the control group consisted of 319 pregnant women without any exposure or exposed to non-teratogenic agents. Data on maternal history and radiations exposure were collected on first contact, and pregnancy outcomes were documented at follow-up. An univariate analysis was performed to compare both groups for the main outcomes.

Results

Exposure to sub diaphragmatic ionizing radiation for diagnosis purpose (median fetal dose of 3.1 mGy [0.2–130.0]) during the first trimester of pregnancy was not significantly associated with an increased risk of malformations (1.5% vs 1.8%, $p = 1.00$), miscarriage (7.8% vs 7.2%, $p = 0.88$), *in utero* fetal death (0.3% vs 0%, $p = 1.00$) or fetal growth restriction (5.4% vs 3.5%, $p = 0.62$).

Conclusion

Pregnant women exposed to irradiant diagnostic procedures do not present a higher risk of malformations, miscarriage, *in utero* fetal death or fetal growth restriction and should be reassured, even if the examination focused on the pelvis.

Keywords: Pregnancy; Diagnostic radiations; Fetal exposure; Teratogenesis; Ionizing radiations

Introduction

Exposure to ionizing radiations during pregnancy generally induces anxiety for both the patients and the physicians. Thus, erroneous information to the couple may result in unjustified terminations of pregnancy [1].

The effects of radiation exposures can be classified as deterministic and stochastic. The deterministic effects occur principally above a threshold dose, reflecting cell death. During the pregnancy, these deterministic effects include miscarriages, fetal malformations, fetal growth restriction and mental retardation. The stochastic effects occur sometimes after exposure and are mainly represented by radiation-induced cancer. Whereas many data on stochastic effects are available from epidemiological studies [2–4], little is known on the deterministic effects of ionizing radiations during the pregnancy. Furthermore, almost all the data available on deterministic effects are based on experimental studies or on the human survivors of atomic bombings and nuclear accidents follow-up. According to these studies, prenatal exposure to radiations may lead to different complications, depending on the gestational age at exposure [5–15].

Based on animal studies, it is accepted that a radiation exposure during the pre-implantation stage, before 4 weeks of gestation (i.e. weeks from the first day of last menstrual periods), leads to an « all or none » phenomena. Given the omnipotential nature of embryonic cells, the effects of radiation exposure may lead either to a miscarriage or no consequences [6–8]. The period between 4 and 10 weeks of gestation is extremely sensitive to the teratogenic effect of ionizing radiations and several cases of microcephaly, cataract and microphtalmia have been reported [9–12]. From 10 weeks of gestation, the main reported risks of an exposure to ionizing radiations seems to be fetal growth restriction and mental retardation [13,14]. However, most of these results are based on the prenatal exposure to much higher doses than those delivered in case of diagnostic irradiant examinations.

The objective of our study was to compare pregnancy outcomes in women with and without first trimester exposure to diagnostic sub diaphragmatic ionizing radiations.

Materials and Methods

We conducted a cohort study using data prospectively collected by our National Teratology Information Service between January 1st, 1987 and December 31st, 2014. The database used for the purpose of this study was authorized by the French Commission Nationale de l'Informatique et des Libertés (CNIL).

The exposed group consisted of pregnant women exposed to sub diaphragmatic irradiant examinations for diagnostic purposes between 2 and 15 weeks of gestation. The irradiant examinations included abdomen X-ray, lumbar spine X-ray and pelvis X-ray examinations, hysterosalpingography, intravenous urogram, abdomen and pelvis computerized tomography scan (CT scan), lumbar spine CT scan, cholangiography and abdominal scopic examinations.

The control group consisted of pregnant women without irradiant exposure during the pregnancy. These cases consisted of pregnant women for whom physicians called the National Teratology Information Service to report exposures with no known teratogenic risk (e.g. acetaminophen, penicillin, oral contraceptive stopped before 6 weeks, non-live vaccines, topical preparations with negligible systemic absorption, cosmetics) between 2 and 15 weeks of gestation. Unexposed patients were matched to the exposed ones for the calendar month of the first call to the center.

The exclusion criteria for both groups were an occupational exposure to ionizing radiations, radiotherapy or a concomitant use of a teratogenic drug (e.g. carbamazepine, carbimazole, cyclophosphamide, lithium, methotrexate, misoprostol, mycophenolate, phenobarbital, retinoids, thalidomide, valproic acid and vitamin K antagonists).

Data collection was performed using structured questionnaires at the first phone contact with the patient's physician, and after birth, sending questionnaires to the same physician. In all cases, data were recorded prospectively with no knowledge about the outcome of the pregnancy at the time of the first call. Recorded data were: maternal demographic characteristics, personal and familial medical history, current and previous obstetrical history, smoking, alcohol consumption and prescription and non-prescription drugs use. Details about radiation exposures included the type of examination, its indication and the gestational age at exposure. The fetal dose exposure was recorded when the data was available, or was estimated according to the International Commission on Radiological Protection publication number 84 [16]. Prospective follow-up was conducted within two months after the expected date of delivery with emphasis on pregnancy complications, gestational age at delivery, birth weight, congenital malformations and neonatal complications. An induced abortion before 14 weeks for personal reasons was defined as a voluntary termination of pregnancy, and a termination of pregnancy for a medical reason was defined as an elective termination of pregnancy.

The primary outcome of interest was the risk of major malformations after ionizing radiation exposure during the first trimester of pregnancy. Minor malformations were also recorded. Congenital malformations were classified as either major or minor in accordance with the European Surveillance of Congenital Anomalies (EUROCAT) guide [17]. The secondary outcomes were the risk of miscarriage (spontaneous abortion before 22 weeks of gestation), stillbirth (intrauterine fetal death after 22 weeks of gestation) and fetal growth restriction defined as a birthweight lower than the 5th percentile, due to this exposure.

Statistics

Continuous end points were expressed as means \pm standard deviations (SD) and compared using the Student's ~~F-test~~-test. Categorical end points were expressed as rates and compared between these groups using the chi-square test, or Fisher's exact test when the assumptions for the chi-square test were not met. A P-value less than 0.05 was considered significant. Statistical analyses were performed using R 3.3.2 Statistical Software.

Results

During the 28 years of the study, the National Teratology Information Service received 319 calls from physicians for a sub-diaphragmatic exposure to ionizing radiations during the first trimester of pregnancy. The pregnancy outcome of these 319 exposed women

was compared with those of the 319 women of the control group. The two groups did not differ for maternal characteristics and for their initial risk of fetal malformations (familial history of congenital malformation, smoking, alcohol) (Table 1).

Table 1 Patient characteristics.

alt-text: Table 1

Characteristic	Radiations N = 319 mean \pm SD n (%)	Control group N = 319 mean \pm SD n (%)	<i>p</i>
Maternal age (years)	30.4 \pm 0.7	30.8 \pm 1.4	0.47
Primiparous	183 (57.5%)	206 (64.6%)	0.08
Significant disease before pregnancy^a	1 (0.3%)	3 (0.9%)	0.62
History of congenital malformation	2 (0.6%)	2 (0.6%)	1.00
Teratogenic drugs exposure^b	0	0	1.00
Smoke during pregnancy	9 (2.8%)	12 (3.8%)	0.66
Alcohol during pregnancy	4 (1.3%)	0	0.12
Multiple pregnancies	2 (0.6%)	1 (0.3%)	1.00

^a defined as a risk factor for miscarriage, fetal growth retardation, in utero fetal death, chromosomal aberrations or congenital malformation.

^b e.g. acitretin, antivitamin K, isotretinoin, methotrexate, mycophenolate, or sodium valproate.

The characteristics of ionizing radiations exposures are summarized in Table 2. The irradiant examinations were performed at a mean gestational age of 4.5 weeks (minimum: 3.4, maximum: 5.3) and the women did not know about their condition of pregnancy in all cases. Among the 319 women of the radiations group, 194 (60.8%) were exposed to two examinations or more, on the same day. Most of the patients who had abdominal CT scan or lumbar spine CT scan, had first an abdomen X-ray or a lumbar spine X-ray examination. The median calculated dose received by the fetus was 3.1 mGy with a minimum of 0.2 mGy and a maximum of 130 mGy. All fetuses received a dose below 200 mGy, with a dose lower than 50 mGy for 311 fetuses (97.5%), and lower than 100 mGy for 317/319 fetuses (99.4%). For 66 patients from the radiations group (20.7%), we recorded a concomitant medication exposure, represented by analgesics and antibiotics prescription but with no associated risk for fetal anomaly or teratogenicity.

Table 2 Radiations exposures.

alt-text: Table 2

Examination	Number of patients n (%)	Common indication	Term of exposure (weeks) mean \pm SD
Abdomen X-ray	105 (32.9%)	Abdominal pain	5.0 \pm 2.6
Abdomen/pelvis CT scan	72 (22.6%)	Abdominal pain	4.9 \pm 2.6
Lumbar spine X-ray	66 (20.7%)	Lumbar spine pain	4.0 \pm 1.0
Pelvis X-ray	54 (16.9%)	Pelvis pain	3.4 \pm 2.1
Hysterosalpingography	38 (11.9%)	Infertility investigation	4.9 \pm 1.7
Intravenous urogram	32 (10.0%)	Suspicion of urolithiasis	4.4 \pm 2.3
Lumbar spine CT scan	27 (8.5%)	Lumbar spine pain	3.8 \pm 1.5
Fluoroscopy	21 (6.6%)	Installation of a double J catheter	4.4 \pm 1.7
Cholangiography	12 (3.8%)	Intra-operative cholangiography during cholecystectomy	5.3 \pm 1.8

Pregnancy outcomes in both groups are presented in [Table 3](#). No significant differences were observed for the rate of miscarriage before 22 weeks and intrauterine fetal death after 22 weeks. In the radiations group, the rate of voluntary termination of pregnancy was significantly higher than in the control group (7.8% and 3.1%, $p = 0.02$). No elective termination of pregnancy was recorded in the control group whereas 7 (2.2%) were performed in the radiations group. The overall live birth rate was significantly lower in the radiations group (81.8% vs 89.0%, $p = 0.01$). Among the two cases exposed to an irradiation dose higher than 100 mGy, there was one case of voluntary termination of pregnancy. The other pregnancy was continued and no anomalies were observed after at birth in the neonate.

Table 3 Pregnancy and neonatal outcomes

Outcome	Radiations N = 319 mean \pm SD n (%)	Control group N = 319 mean \pm SD n (%)	<i>p</i>
Miscarriage before 22 weeks	25 (7.8%)	23 (7.2%)	0.88
VTP	25 (7.8%)	10 (3.1%)	0.02
ETOP	7 (2.2%)	0	0.02
Ectopic pregnancy	1 (0.3%)	1 (0.3%)	1.00
IUFD after 22 weeks	1 (0.3%)	0	1.00
Live birth	261 (81.8%)	284 (89.0%)	0.01
Gestational age at birth^a (weeks)	39.2 \pm 0.3	39.5 \pm 0.2	0.26
Birth weight^a (g)	3288.7 \pm 68.5	3328.7 \pm 51.5	0.66
Birth weight < 5th percentile^a	14 (5.4%)	11 (3.5%)	0.62
Major malformations^a	0	0	1.00
Minor malformations^a	4 (1.5%)	5 (1.8%)	1.00
Chromosomal aberration	6 (1.9%)	0	0.03

VTP: Voluntary termination of pregnancy, ETOP: *Elective termination of pregnancy*, IUFD: *intrauterine fetal death*^a[among live births](#).

^a [among live births](#).

Indications for elective termination of pregnancy were chromosomal aberrations (Down syndrom: n = 2, trisomy 13: n = 2; trisomy 18: n = 1) and maternal conditions (psychiatric disorder: n = 1, severe ulcerative colitis: n = 1). Among the women who had elective termination of pregnancy for chromosomal anomalies, the median age was 33 \pm 2 years old. Their irradiation exposures were represented by a pelvis X-ray and a lumbar spine X-ray at 5 weeks (Down syndrome, n = 1, and trisomy 13, n = 1), a pelvis X-ray alone at 4 weeks (Down syndrome, n = 1), an intravenous urogram at 5 weeks (trisomy 13, n = 1) and a hysterosalpingography at 3 weeks and 4 days (trisomy 18, n = 1). The elective termination of pregnancy were performed at a mean term of 16⁺4 weeks with a mean delay of 12 weeks between the exposure and the elective termination of pregnancy.

Exposure to ionizing radiations was not associated with a lower birth weight, and there were no differences between the groups regarding the rate of fetal growth restriction. In both groups, no major malformations were observed. In the radiation group, among 261 newborns, we recorded 4 cases (1.5%) of minor malformations (two cases with moderate hydronephrosis, one angioma, one gastroesophageal reflux). In the control group, among 284 newborns, 5 cases (1.8%) of minor malformations were observed (one moderate hydronephrosis, one unilateral foot malposition, one cervical cyst, one gastroesophageal reflux, one ectopic kidney). In the radiation group, additionally to the 5 chromosomal aberrations resulting in an elective termination of pregnancy, one newborn presented a tetralogy of Fallot associated with a 22q1.1 deletion. The chromosomal anomaly rate was significantly higher in the exposed group with no cases in the control group ($p = 0.03$).

Discussion

This observational prospective cohort study indicates that exposure to diagnostic subdiaphragmatic ionizing radiations during the first trimester of pregnancy is not associated with an increased risk of major malformations, miscarriages, intrauterine fetal deaths or fetal growth restrictions.

Experimental studies with rodents and observation of nuclear accidents' victims found no increased risk of miscarriages with radiation doses under 200 mGy [7], a threshold dose of 100 mGy for teratogenic effects [9,18] and of 250 mGy for fetal growth restriction [18]. Osei et al. reported an observational study on the deterministic effects of prenatal radiation exposure for maternal diagnosis purpose, on a total of 50 pregnancies [19]. In this study, fetuses could be exposed at any time of the pregnancy, including second trimester, and the radiations exposures did not focus on the sub diaphragmatic area only. Furthermore, no comparison was made with a control group. In spite of these limitations, they concluded that prenatal radiation exposure in case of mother diagnostic examinations did not result in any deterministic effects. Our controlled study confirmed that prenatal exposure to sub diaphragmatic radiations with doses lower than 50 mGy does not increase the risk of congenital malformation, miscarriage, fetal growth restriction and intrauterine fetal death. Our results are consistent with the recent systematic review of Gomes et al. and provide additional clinical arguments to support patients reassurance [20].

In our study, we observed a relatively higher rate of voluntary termination of pregnancy in the exposed group. It is tempting to speculate that this higher rate of voluntary termination of pregnancy may reflect maternal anxiety caused by irradiation during pregnancy. We believe our results should make physicians more comfortable in their prenatal counselling to alleviate the maternal anxiety in case of prenatal exposition to diagnostic subdiaphragmatic ionizing radiations during the first trimester. Elective termination of pregnancy's rate was also significantly higher in the radiation group, but directly related to the chromosomal aberrations presented in this group. This high rate of chromosomal aberrations is difficult to explain, except as a selection bias.

This study included 319 women exposed to diagnosis ionizing radiations during early pregnancy, and is, to our knowledge, the only continuous prospective study with a control group to focus on the deterministic effects of ionizing radiations exposure during the first trimester of pregnancy. Moreover, we only focused on radiations exposure related to diagnosis purposes, which are minor exposures and are the most relevant for an analysis of factual clinical cases. Lastly, sub diaphragmatic radiations exposure during pregnancy represents the worst-case scenario because the fetus is located within the ionizing radiation field. If this kind of radiation is safe for the fetus, we can speculate that irradiation of other parts of the pregnant woman's body should be safer than sub diaphragmatic ones.

This study presents some limitations. We did not observe any major malformation in the two groups, nor the usual baseline prevalence of 1–3% of congenital birth defect, which could be explained by the size of this cohort. All cases were managed at national level, by the National Teratology Information Service, in direct collaboration with clinical physicians, and we have no reason to believe that there was a selection bias in any of our two groups. Also, although the patients of the control group have not been exposed to radiations during their pregnancy, their selection from the National Teratology Information Service database necessarily implies a drug exposure during their pregnancy (non-teratogenic drug). Unfortunately, we were not able to find a more suitable cohort due to the very long period of time on which this study is based. However, as many pregnant women are on medication during their pregnancy, we considered that this control group was consistent with reality [21]. Lastly, because children follow-up does not exceed two months, we are not able to provide data about mental retardation risk or carcinogenic risk. In this setting, the effect of prenatal exposure to low doses could not be studied.

In conclusion, prenatal exposure to diagnostic irradiant examination during the first trimester does not increase the risk of major or minor malformations, miscarriage, fetal death and fetal growth restriction. Therefore, appropriate counselling to women inadvertently exposed to radiations at early stages of pregnancy should be reassuring. Moreover, this kind of exposure should not be an indication for an elective termination of pregnancy, even if the radiological examination focuses on the pelvis. Overall, a relevant diagnostic procedure necessary for a woman's health should not be contraindicated in case of pregnancy. However, non-irradiant diagnosis procedures (ultrasound or magnetic resonance imaging) should be preferred in case of pregnancy [15]. Consequently, the diagnosis of pregnancy should be excluded in all women of childbearing age, before any irradiant procedure.

References

- [1] S. [Ratnapalan](#), [N. Bona](#), [K. Chandra](#) and G. Koren, Physicians' perceptions of teratogenic risk associated with radiography and CT during early pregnancy, *AJR Am J Roentgenol* **182** (5), 2004, 1107–9.
- [2] J.F. [Bithell](#) and [A.M. Stewart](#), Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey, *Br J Cancer* **31** (3), 1975, 271–287.
- [3] Y. Yoshimoto, Cancer risk among children of atomic bomb survivors. A review of RERF epidemiologic studies. Radiation [Effects Research Foundation](#)[JAMA-effects research foundation](#), *JAMA* **264** (5), 1990, 596–600.
- [4] D.L. [Preston](#), [H. Cullings](#), [A. Suyama](#), et al., Solid cancer incidence in atomic bomb survivors exposed in utero or as young children, *J Natl Cancer Inst* **100** (6), 2008, 428–436.
- [5] Committee on Obstetric Practice, Committee [Opinion No. 723: Guidelines for Diagnostic Imaging During Pregnancy and Lactation](#), *Obstet Gynecol* **130** (October (4)), 2017, e210–e216.
- [6] D.M. [Schlesinger](#) and [R.L. Brent](#), Effects of X irradiation during preimplantation stages of gestation on cell viability and embryo survival in the mouse, *Radiat Res* **75** (1), 1978, 202–216.
- [7] [R.L. Brent](#), Saving lives and changing family histories: appropriate counseling of pregnant women and men and women of reproductive age, concerning the risk of diagnostic radiation exposures during and before pregnancy, *Am J Obstet Gynecol* **201** (1), 2009, 4–24.
- [8] M.C. [Haeusler](#), [A. Berghold](#), [W. Schoell](#), [P. Hofer](#) and M. Schaffer, The influence of the post-Chernobyl fallout on birth defects and abortion rates in Austria, *Am J Obstet Gynecol* **167** (4 Pt 1), 1992, 1025–1031.
- [9] P.U. [Devi](#), [R. Baskar](#) and [M.P. Hande](#), Effect of exposure to low-dose gamma radiation during late organogenesis in the mouse fetus, *Radiat Res* **138** (1), 1994, 133–138.
- [10] P.U. Devi and R. Baskar, Influence of gestational age at exposure on the prenatal effects of gamma-radiation, *Int J Radiat Biol* **70** (1), 1996, 45–52.

- [11] M. Otake and W.J. Schull, Radiation-related small head sizes among prenatally exposed A-bomb survivors, *Int J Radiat Biol* **63** (2), 1993, 255–270.
- [12] R. Rugh, L. Duhamel, A. Chandler and A. Varma, Cataract development after embryonic and fetal x-irradiation, *Radiat Res* **22**, 1964, 519–534.
- [13] M. Otake, W.J. Schull and S. Lee, Threshold for radiation-related severe mental retardation in prenatally exposed A-bomb survivors: a re-analysis, *Int J Radiat Biol* **70** (6), 1996, 755–763.
- [14] W.J. Schull and M. Otake, Cognitive function and prenatal exposure to ionizing radiation, *Teratology* **59** (4), 1999, 222–226.
- [15] Committee ~~Opinion No. 723 Summary: Guidelines for Diagnostic Imaging During Pregnancy and~~ ~~Opinion No. 723 summary: guidelines for diagnostic imaging during pregnancy and~~ Lactation, *Obstet Gynecol* **130** (Oct (4)), 2017, 933–934.
- [16] International ~~Commission on Radiological P~~ ~~commission on radiological p~~rotection. Pregnancy and medical radiation, *Ann ICRP* **30** (1), 2000, iii - viii, 1-43.
- [17] EUROCAT Guide, available at http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4.
- [18] M. De Santis, E. Di Gianantonio, G. Straface, et al., Ionizing radiations in pregnancy and teratogenesis: a review of literature, *Reprod Toxicol Elmsford N* **20** (3), 2005, 323–329.
- [19] E.K. Osei and K. Faulkner, Fetal doses from radiological examinations, *Br J Radiol* **72** (860), 1999, 773–780.
- [20] M. Gomes, A. Matias and F. Macedo, Risks to the fetus from diagnostic imaging during pregnancy: review and proposal of a clinical protocol, *Pediatr Radiol* **45** (December (13)), 2015, 1916–1929.
- [21] I. Lacroix, C. Damase-Michel, M. Lapeyre-Mestre and J.L. Montastruc, Prescription of drugs during pregnancy in France, *Lancet* **356** (9243), 2000, 1735–1736.

Queries and Answers

Query: Your article is registered as a regular item and is being processed for inclusion in a regular issue of the journal. If this is NOT correct and your article belongs to a Special Issue/Collection please contact I.lovheim@elsevier.com immediately prior to returning your corrections.

Answer: ok

Query: The author names have been tagged as given names and surnames (surnames are highlighted in teal color). Please confirm if they have been identified correctly.

Answer: Yes

Query: Please confirm that the provided email is the correct address for official communication, else provide an alternate e-mail address to replace the existing one, because private e-mail addresses should not be used in articles as the address for communication.

Answer: ok

Query: Please check the hierarchy of the section headings and correct if necessary.

Answer: ok

Query: Correctly acknowledging the primary funders and grant IDs of your research is important to ensure compliance with funder policies. We could not find any acknowledgement of funding sources in your text. Is this correct?

Answer: Yes

Query: Please note that as per the journal style, if there are more than six authors, the first six author names are listed followed by 'et al.'; please provide names of first six authors followed by 'et al.' for Refs. [4,18].

Answer: ok