



Original Article

Thyroid Hormone Levels in Mothers and Cord Blood at Delivery in Crude Oil Producing Community in Delta State, Nigeria



Mathias A. Emokpae*  and Lawrence Ogana

Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City, Nigeria

Received: October 18, 2023 | Revised: January 09, 2024 | Accepted: March 08, 2024 | Published online: May 29, 2024

Abstract

Background and objectives: Harm caused by crude oil spillage and its associated environmental toxicants manifests slowly. This study examined the impact of crude oil environmental toxicants on neonates' thyroid and cognitive functions in crude oil-producing communities.

Methods: The case-control study comprised 55 crude oil-exposed expectant mothers and 33 non-crude oil-exposed expectant mothers as controls. Serum Benzo Pyrene Dihydrodiol Epoxide (BPDE), triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) were assayed in expectant mothers and neonates. Intelligence quotient and APGAR scores were determined in the children using Fagan's test of infant intelligence.

Results: Serum TSH ($p < 0.05$) and BPDE ($p < 0.001$) were higher, while T3 and T3/T4 ratio were significantly lower ($p < 0.001$) in exposed pregnant women compared to the control. Cord blood TSH and T3/T4 ratio were lower ($p < 0.001$) while T4 and BDPE were higher ($p < 0.001$) in prenatally exposed neonates than prenatally non-exposed infants. Serum TSH correlated with BDPE ($R^2 = 0.080$, $p < 0.036$) and APGAR score ($R^2 = 0.341$, $p < 0.012$), while T3 and T4 were not associated with BDPE and APGAR score. TSH correlated with T3 ($R^2 = 0.082$, $p < 0.05$), T3 correlated with T4 ($R^2 = 0.111$, $p < 0.013$) and TSH ($R^2 = 0.082$, $p < 0.05$). Exactly 54.5% (30/55) of prenatally exposed neonates had a low intelligence quotient compared to 36.4% (12/33) in prenatally non-exposed neonates.

Conclusion: Crude oil and associated environmental pollutants might significantly affect the thyroid function. Environmental surveillance, biomonitoring and environmental cleanup are emphasized. Future research on the mechanisms of the observed toxicological effects on thyroid hormones and targeted protection of pregnant women and their offspring is suggested.

Introduction

Crude oil contains many compounds, primarily volatile and semi-volatile organic compounds, including some polycyclic aromatic hydrocarbons

(PAHs), as well as other sulfur and nitrogen containing compounds and metals. When oil is burned, additional PAHs can form as combustion by-products, along with inhalable fraction PM10 (particles measuring less than 10 microns), and respirable fraction PM2.5 (particles measuring less than 2.5 microns). Petroleum hydrocarbons differ with respect to their behavior in the environment and it is this behavior that defines whether they are more likely to be in air, water, soil, sediment, food or other media that people might come in contact with.¹

Crude oil exploration and exploitation generate environmental toxicants that are regarded as "slow poisons", because it may take several months or years for the harm they cause to manifest physically. The harmful effects of crude oil contamination on humans might not attract attention and it is difficult to fully recognize their contribution to acute and long-term effects on the health of persons living in oil-producing communities.² Even though a Post-Impact

Keywords: Petroleum; Polycyclic aromatic hydrocarbons; PAHs; Endocrine disruptors; Thyroid gland; Mothers; Nigeria; Thyroid hormones.

Abbreviations: Bap, Benzo(a)pyrene; BDPE, Benzo(a)pyrene diol epoxide; HRP, horseradish peroxidase; PAH, polycyclic aromatic hydrocarbons; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

*Correspondence to: Mathias A. Emokpae, Department of Medical Laboratory Science, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City 300001, Nigeria. ORCID: <https://orcid.org/0000-0002-6266-1774>. Tel: +234-8034511182, E-mail: mathias.emokpae@uniben.edu

How to cite this article: Emokpae MA, Ogana L. Thyroid Hormone Levels in Mothers and Cord Blood at Delivery in Crude Oil Producing Community in Delta State, Nigeria. *Explor Res Hypothesis Med* 2024;9(2):83–92. doi: 10.14218/ERHM.2023.00085.

Assessment is done every year in Nigeria, it does not sufficiently highlight the instant and persistent reproductive health consequences of the associated risk on the people living in the environment.

In a review of studies on “human health implications of crude oil spills in the Niger Delta, Nigeria”, it was reported that there was a comprehensive existence of components of crude oil in the environmental accessibility of the areas where crude oil exploration and exploitation occur. These crude toxicants such as PAHs, of which Benzo(a)pyrene (BaP) is one, are known reproductive health hazards and were found in both surface water and soil in these communities.³⁻⁵ Benzo(a)pyrene diol epoxide (BPDE) is an epoxide derived from hydride of a Benzo(a)pyrene. It is used as a surrogate of PAHs, which can be measured to provide valuable information on toxicological exposure and disease risk. The consumption of food, airborne and soil exposure have been reported to be predictive of PAHs accumulation in the circulation.⁴ According to the US Environmental Protection Agency guidelines, to adequately identify the source and harmful health effects associated with environmental exposure to PAHs, an assessment of an important priority list must be conducted.⁴ Previous studies have detected very high concentrations of PAHs in soil, air, water and crops in the Niger Delta region including Warri South.⁶⁻⁸ Although petroleum products are of low toxicity, local, systemic toxicity, and mutagenicity occur in mice at high doses.⁹ These toxic effects are attributed to the aromatic constituents of these substances. Some PAHs such as BaP can inhibit thyroid peroxidase, which is a rate-limiting enzyme in thyroid hormone biosynthesis. Increased expression of the enzyme is induced by thyroid stimulating hormone (TSH), and is responsible for the iodination of tyrosine to form mono, di, triiodothyronine and thyroxine.¹⁰ It has been hypothesized that prenatal exposure to chemicals that disrupt thyroid hormone, with iodine deficiency potentially exacerbating the situation, most likely contributes to increased incidence of neurodevelopmental diseases, and also to a hidden but socioeconomically consequential loss in IQ.^{11,12} An influence of iodine status on the relationship between PAHs and thyroid hormones has been observed in adolescents and adults.¹² Finally, untreated thyroid diseases during pregnancy, such as subclinical hypothyroidism or maternal hypothyroxinemia due to preconception iodine deficiency in the mother, are associated with a moderate delay in the child’s neurological development.^{13,14}

Prenatal exposure to crude oil toxicants is a great concern to public health practitioners and reproductive biologists. Therefore, monitoring exposure in pregnant women may be an acceptable substitute to evaluate the fetus’s exposure.⁹ The thyroid gland is a very important organ because of the influential roles it plays in growth, early development, and metabolism.¹⁵

Exposure to crude oil toxicants, especially during critical and sensitive developmental periods such as pregnancy, may lead to several health consequences that can manifest in both the pre-natal and post-natal life of individuals, and has the potential to be transmitted from one generation to another. Accordingly, the next generations are born “pre-polluted” owing to this preconception and pre-birth exposures.¹⁶⁻¹⁸ It is in the interest of citizens to know the impact crude oil contaminants have on the thyroid and cognitive functions of both mothers and neonates in crude oil-producing communities.

Methods

Ethical consideration

This study was conducted to conform to the ethics guidelines of the Helsinki Declaration (revised 2013) and approved by the Eth-

ics and Health Research Committee of the Central Hospital, Warri, Delta State (reference CHW/ECC VOL 1/168 dated October 9, 2018). Individuals who participated in this study gave informed consent. The purpose of the research was explained to those who could not read the participant information sheet. Absolute confidentiality of data was adhered to throughout the study.

Study participants

This is a case-control study conducted at the Central Hospitals, Warri and Asaba between July 2021 and June 2022. The participants were adult expectant mothers in their third trimester living permanently in Warri South Local Government area where there is active crude oil exploration and exploitation and Asaba town where there is no crude oil exploration/exploitation. Both regions are located in Delta state, Nigeria. A total of 55 healthy expectant mothers residing in Warri (cases) and 33 healthy expectant mothers residing in Asaba (controls) were recruited for the study.

Inclusion and exclusion criteria

Only healthy expectant mothers attending the ante-natal clinic for care, gave birth in the health care centers and those who had full-term deliveries were included in the study. Pregnant women who had lived for more than five years in Warri South where crude oil exploration and exploitation takes place were included while subjects who reside in Asaba and have never lived in Warri or any settlement where crude oil exploration and exploitation occurs were selected as controls. Pregnant women with chronic illness, thyroid dysfunction, hemoglobinopathies, or complicated obstetric conditions were excluded.

Questionnaire

Socio-anthropological data: age, lifestyle habits, educational status, medical history, and family history of hypothyroidism were obtained using an interview-administered questionnaire, Maternal health and obstetrical information, medication use, and the due date of delivery were obtained from the hospital records. The infant’s anthropometric measurements were determined using standard methods.

Sampling

The number of specimens required for the study was determined using the sample size determination formula for health studies $N = z^2pq/d^2$ and 3.83% prevalence of neonatal mortality due to crude oil spillage in the Niger Delta region of Nigeria.^{19,20}

Where n = Sample size, z = criteria value at 95% confidence level (1.96), p = prevalence, $q = 1-p$, and d = precision of 5% (0.05).

Calculation using these formulae: $n = z^2 pq/d^2 = (1.96)^2 \times 0.0383 \times (1 - 0.9617)/(0.05)^2 = 56.59$.

Therefore, 57 pregnant women were recruited for this study, but 55 completed the evaluation. The sample consisted of 55 maternal blood and 55 cord blood of crude oil-exposed participants (mother and child) and 33 crude oil non-exposed participants (mother and child).

Sample collection, processing, and storage

Approximately 5 mL of blood was obtained from the women during the third period of gestation and distributed into a plain container. This was allowed to clot at room temperature and then centrifuged after clot retraction at 1,000 g for 10 minutes. The serum was separated into a new plain container and stored at -80°C until analysis was done. Also, immediately after delivery, 5mL of cord

blood was obtained from the umbilical vein with the cord clamped at both ends and emptied into the plain container and labeled. After clot retraction, the cord blood was centrifuged for 15 mins at 2,500 rpm, and serum was separated and stored at -80°C until analyzed. The Fagan Test of Infant Intelligence was conducted weeks after birth.

Principle of Benzo(a)pyrene determination

The sandwich-ELISA technique that contains a strip plate pre-coated with an antibody specific to Benzo Pyrene Dihydrodiol Epoxide was used. When standards or serum are dispensed into appropriate microplate wells, the antigen reacts with the antibody. Thereafter, the horseradish peroxidase (HRP)-conjugate antibody distinct for Benzo pyrene dihydrodiol epoxide binds the antigen-antibody complex. The unbound components are washed away while the bound complex reacts with the Tetramethylbenzidine-substrate solution. When the stop solution is added, the color turns from yellow to blue. The absorbance is read spectrophotometrically at 450 nm. The concentration of Benzo pyrene dihydrodiol epoxide is extrapolated from the graph previously prepared from a series of Benzo(a)pyrene standards.

Serum triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were assayed using the competitive enzyme immunoassay technique with commercially available reagents.

Principle of thyroid hormone determination

Based on the competitive reaction between antigen in the serum or standard and enzyme-antigen conjugate for a few insoluble binding sites on the immobilized antigen. When the antibody-antigen complex is set apart from the unbound by washing, the enzyme in the complex reacts with the substrate to form a product. The amount of product formed corresponds to the concentration of antigen present in the serum. The concentration is extrapolated from the calibration curve previously plotted using a series of standards.

Cognitive function assessment using the Fagan test

Purpose

The objective of this test is to extricate potentially cognitively normal from potentially cognitively deficient infants who may be at risk for later intellectual deficit as a result of several prenatal or postnatal conditions.²¹

Principle

Fagan's check of toddler Intelligence was based on the idea that intelligence comprises a fixed of primary techniques for the obtainment of knowledge: tasks that are innate, incredibly automatic, dependent on neural integrity, and continuous with age. The pre-supposition is that the manner by which toddlers distribute their attention to new and formerly exposed stimuli is essentially the same procedure used by older youngsters and adults in resolving intelligence assessments. If infants vary within the rate with which they accomplish the fundamental tasks of understanding obtainment, then what is measured later measure on in an intelligence check, while a knowledge based totally solution is requested, is the continual result of the interplay of the price of extracting with the surroundings the child has been allowed to process.

The Fagan check of infant intelligence is accomplished at 67, 69, 79, and 92 of gestational age plus natal age in weeks. In order words, a time period toddler brought after 40 weeks of pregnancy is evaluated at 27, 29, 39, and 52 weeks thereafter. Also, a toddler delivered after only 32 weeks of being pregnant is evaluated at

35, 37, 47, and 60 weeks after delivery. The Fagan test of toddler Intelligence was performed within one week of the precise date the baby needed to be evaluated. A primary degree of extracting records is the potential of the little one to look longer at a brand-new target than at one formerly seen.²¹ Proof shows that toddlers' desire for novelty has shown that the abstraction of statistics is effective prevalence all through infancy.

Testing time required

The time needed for testing a selected toddler can also fluctuate due to the age of the child and the child's state. Overall, not more than 25 minutes is required for any test.

Conducting the test

The time that the child spends staring at the diverse photographs is the most essential feature of the Fagan check. Those are the statistics that ascertain if the infant is judged low-hazard, suspect, or excessive-hazard for later mental retardation. A similarly critical component of the test is that the photographs be offered exactly within the order as pre-arranged. The administrator of the Fagan takes a look to ensure correct recording of when, where, and how long the toddler looks at the photographs. The Fagan's test administrator is seated behind the stage after the parent and the toddler have settled down. The peephole is placed close to the baby to position the extent and distance for viewing are correct. Thereafter, the picture is placed in a comfortable and attainable position for testing. The stage is opened and the pictures are trusted one by one. The time it takes for the baby to stir on the photo is recorded. Then the level is closed quickly and gently nonetheless peering through the peephole. As soon as the stage is closed, watch whether or not he/she is still looking on the photos. How lengthy, and to which picture the infant focuses is recorded. The administrator needs to see a photo of the photo targeted over the pupil of the toddler's eye when the child is looking at the photograph. The picture is seen as a bright rectangle in the middle of the pupil. It is miles handiest while the photo is focused over the pupil that the time is recorded.

When the toddler looks at the picture to the left, it is recorded and when the baby looks at the image to the right, it is recorded. If the infant isn't always looking at both photos, it isn't always recorded. As the baby looks at the picture, time is recorded where and how long until you hear the tone signaling the end of that part of the test. Whilst the pre-set time tone sounds, the stage is quickly, but lightly opened and the next photo is inserted at the stage. This cycle is repeated till the check is completed.

The viable effects of the Fagan check of little one Intelligence are: If the suggested novelty is $>53.1 < 54.5$ the test result line reads: Suspect: repeat take a look at a Later Age. If the implied novelty is < 53.1 the test effects line reads hazard: Repeat at a later age. The test consequences are most effectively computed from a completely implied novelty rating. Aborted exams will produce data but not a Test Result outcome.

Statistical analysis

Data were scrutinized using Chi-square and independent Student's t-test while values were presented as mean \pm standard deviation. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 25 (IBM Corp, Cal, USA). Multivariate linear regression was performed with TSH, T3, and T4 concentrations as dependent variables against APGAR score and BDPE level as independent variables. A p -value < 0.05 was regarded as statistically significant.

Table 1. Socio-Demographic features of study participants

Characteristics	Variables	Exposed pregnant women	Non-exposed pregnant women	Chi-Square (X2)
		N (%)	N (%)	
Age of mothers	18–23 years	8 (14.5)	6 (18.2)	$p > 0.05$
	24–29 years	17 (30.9)	12 (36.4)	
	30–35 years	21 (38.2)	13 (39.4)	
	36–41 years	8 (14.5)	2 (6.1)	
	42–47 years	1 (1.8)	0 (0.0)	
Gravidae of mothers	First Pregnancy	4 (7.3)	5 (15.2)	$p > 0.05$
	Second Pregnancy	15 (27.3)	9 (27.3)	
	Multiple Pregnancy	36 (65.5)	19 (57.6)	
Parity of mothers	Primigravida	17 (30.9)	16 (48.5)	$p > 0.05$
	Multiparous	36 (65.5)	14 (42.4)	
	Nulliparous	2 (3.6)	3 (9.1)	
Educational status of mothers	Primary	4 (7.3)	2 (6.1)	$p > 0.05$
	Secondary	31 (56.4)	16 (48.5)	
	Tertiary	20 (36.4)	15 (45.5)	
Employment	Artisans	15 (27.3)	8 (24.2)	$p > 0.05$
	Students	1 (1.8)	0 (0.0)	
	Civil Servant	19 (34.5)	13 (39.4)	
	Traders	13 (23.6)	8 (24.2)	
	House Wives	5 (9.1)	4 (12.1)	
	Farmer	2 (3.6)	0 (0.0)	
Nature of birth of the women	Cesarean section	7 (12.7)	5 (15.2)	$p > 0.05$
	Vaginal delivery	48 (87.3)	28 (84.8)	

Results

The findings from the investigation are given in Tables 1–5. Table 1 details the socio-demographic data of subjects in exposed and non-exposed mothers. The comparison of age range, gravidae, parity, occupation, educational status, and nature of the birth of exposed mothers and non-exposed mothers were all statistically insignificant.

Table 2 shows the comparison of levels of measured thyroid hormones and BaP concentrations of exposed and non-exposed expectant mothers living in crude oil-producing communities. It shows that serum TSH ($p = 0.036$) and BPDE ($p < 0.001$) were considerably higher among the exposed expectant mothers than non-exposed expectant mothers. Also, serum T3 and T3/T4 ratio were considerably lower ($p < 0.001$) among exposed expectant mothers than non-exposed expectant mothers. There was no significant difference ($p > 0.05$) when the mean T4 concentration was compared between exposed and non-exposed pregnant women.

Table 3 illustrates the comparison of the serum levels of thyroid hormones and BDPE in cord blood of prenatally exposed neonates and non-exposed neonates. Cord blood TSH and T3/T4 ratio were significantly lower ($p < 0.001$) while T4 and BDPE were considerably higher ($p < 0.001$) among prenatally exposed neonates than prenatally non-exposed infants. Cord blood T3 was however not significantly different between the two groups ($p > 0.05$).

Table 4 shows Fagan's test of infant intelligence, APGAR score, and birth weight of the prenatally exposed and prenatally non-exposed neonates. The Fagan's test of intelligence quotient indicates that 30 (54.5%) of neonates prenatally exposed had low intelligence quotient versus 12 (36.4%) among the prenatally non-exposed neonates, while 25 (45.5%) in the exposed group had high intelligence quotient compared to 21 (63.6%) of the non-exposed neonates ($p = 0.040$).

Table 5 shows the multivariate regression between thyroid hormones, BDPE, and APGAR score. It indicates that TSH correlated with BDPE ($R^2 = 0.080$, $p < 0.036$) and APGAR score ($R^2 = 0.341$, $p < 0.012$), while T3 and T4 were not associated with BDPE concentration and APGAR score. Also, TSH correlated with T3 ($R^2 = 0.082$, $p < 0.05$), T3 correlated with T4 ($R^2 = 0.082$, $p < 0.05$). There was no association between BDPE and APGAR score.

Figure 1 is a map of Nigeria and Delta State where the study was conducted, while Figure 2 depicts a selection flow chart of study participants.

Discussion

Exposure to environmental contaminants during pregnancy is a potential risk to the healthy growth and well-being of the developing brain. Benzo(a)pyrene is widespread in the environment due

Table 2. Comparison of thyroid hormone levels and Benzo(a)pyrene concentration of exposed and non-exposed mothers to crude oil

Parameters	Exposed group (n = 55)	Non-exposed group	p-value
TSH ($\mu\text{IU/mL}$) (0.39–6.16 $\mu\text{IU/mL}$)	2.81 \pm 0.12	2.45 \pm 0.16	0.036
T3 (ng/dL) (5.2–18.5 ng/dL)	6.97 \pm 0.20	9.39 \pm 0.31	0.001
T4 ($\mu\text{g/dL}$) (4.8–11.6 $\mu\text{g/dL}$)	11.38 \pm 0.79	12.02 \pm 1.38	0.333
T3/T4 Ratio	0.60 \pm 0.02	0.78 \pm 0.001	0.001
BPDE (ng/g)	1,723.57 \pm 51.06	1,301.62 \pm 87.02	0.001

BPDE, Benzo(a)pyrene diol epoxide, reference ranges in parenthesis; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Table 3. Mean levels of thyroid hormones and Benzo(a)pyrene in cord blood of neonates prenatally exposed and prenatally non-exposed infants

Variables	Exposed (n = 55)	Non-exposed (n = 33)	p-Value
TSH ($\mu\text{IU/mL}$) (0.39–6.16 $\mu\text{IU/mL}$)	2.04 \pm 0.80	4.33 \pm 0.20	0.001
T3 (ng/dL) (5.2–18.5 ng/dL)	1.27 \pm 0.03	1.34 \pm 0.04	0.083
T4 ($\mu\text{g/dL}$) (4.8–11.6 $\mu\text{g/dL}$)	12.32 \pm 0.06	8.12 \pm 0.08	0.001
T3/T4 Ratio	0.103 \pm 0.001	0.165 \pm 0.001	0.001
BPDE (ng/g)	2,508.40 \pm 130.24	2,212.65 \pm 43.22	0.044

BPDE, Benzo(a)pyrene diol epoxide, reference ranges in parenthesis; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

to incomplete burning of organic matter, its presence in crude oil producing communities as a result spillage, exploration, and exploitation may be higher. Benzo(a)pyrene is a known neurotoxin, capable of causing neurobehavioral changes in experimental animals.²² Crude oil spillage is a constant occurrence in the Niger Delta region, and about 3.1 million barrels of crude oil has been spilled between 1976 to 2014 in this region. Therefore, individuals living in this region might be at risk of crude oil associated toxicants. Although oil exploration and exploitation have been going on in the Niger Delta of Nigeria, there is a dearth of information on the impact of prenatal exposure to crude-oil-associated toxicants on thyroid hormones and their possible effects on the neurodevelopment of prenatally exposed neonates and their mothers.

Prenatal exposure to toxicants and their hydroxylated metabolites may affect the thyroid hormones of the offspring.^{23,24} Even mild maternal thyroid dysfunction during pregnancy might adversely affect a child's neuropsychological development,¹¹ cognitive function, and decreased intelligence quotient.^{14,25} Low maternal tetraiodothyronine (T4) concentrations during gestation are associated with the impaired cognitive development of offspring as indicated by decreased Fagans or Bayleys Scores.²⁶ This study, therefore, is of public health importance and may provide valuable data that could be used in the formulation of reproductive health policies aimed at reducing the effects of neurotoxicants on infants.

Data from this study showed significant changes in thyroid hormone concentrations, association with BPDE as a marker of PAHs

Table 4. Fagan's test of intelligence and Apgar score of prenatally exposed and non-prenatally exposed neonates

Variables	Exposed	Non-exposed	χ^2	p-Value
	N (%)	N (%)		
Intelligence quotient				
Low	30 (54.5)	12 (36.4)	2.053	0.040
High	25 (45.5)	21 (63.6)		
APGAR Score of mothers				
Low	35 (63.6)	16 (48.5)	1.371	0.043
High	20 (36.4)	17 (51.5)		
Birth weight class				
Low Birth Weight	3 (5.5)	2 (6.1)	0.014	0.624
Normal Birth weight	52 (94.5)	31 (93.9)		
Sex				
F	32 (58.2)	16 (48.5)	0.440	0.253
M	23 (41.8)	17 (51.5)		

Table 5. Multivariate Regression between measured parameters

Variables	R Square	F-value	p-value
TSH			
BDPE	0.080	4.612	0.036
T3	0.082	4.061	0.05
T4	0.171	1.386	0.756
APGAR Score	0.341	3.467	0.012
T3			
T4	0.111	6.644	0.013
TSH	0.082	4.061	0.05
APGAR Score	0.171	1.386	0.765
BDPE	0.173	1.396	0.600
T4			
TSH	0.171	1.386	0.756
T3	0.111	6.644	0.013
APGAR Score	0.208	1.759	0.118
BDPE	0.184	1.990	0.098
BDPE			
T3	0.173	1.396	0.600
T4	0.111	1.386	0.760
TSH	0.080	4.612	0.036
APGAR Score	0.121	1.776	0.210

BPDE, Benzo(a)pyrene diol epoxide, reference ranges in parenthesis; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

during pregnancy and effects on the infants. Serum TSH was significantly higher while T3 and T3/T4 ratio were lower among exposed expectant mothers than non-exposed expectant mothers. Clinically, if the determination of serum T3 and T4 without fT3 and fT4 is done, it is difficult to identify the subtler but important imbalances in the T3 and T4 levels within the reference range. The calculation of the T3/T4 ratio may be very vital in this situation. A low T3/T4 ratio is a feature of levothyroxine treatment, as the subjects usually have a low T3 and higher T4 than healthy subjects. It has been observed that individuals at a higher risk of a T3 deficiency have less active thyroid tissue. Individuals with impaired functional thyroid glands have a low T3/T4 ratio. A low T3/T4 ratio is likely to cause metabolic syndrome, hyperinsulinemia, insulin resistance, impaired selenium, shorter life span, and other diseases.²⁷ During the onset of pregnancy, the fetus derives its thyroid hormones entirely from the mother until fetal thyroid gland function is matured (between the 18th–20th gestational week). The maternal source, however, remains a corresponding source of circulating thyroxine for the fetus until birth. Magnetic resonance imaging studies have indicated that children of women with overt hypothyroidism during pregnancy have abnormal morphology of the cortex, the hippocampal volume, and regions of the brain responsible for cognitive functions such as perception, analytical thinking, executive function, and memory.^{28–30} It is important to know that brain development starts almost immediately after conception, a process that occurs in a sequence of developmental events. This period corresponds to the time when the fetus is under increased environmental stressors. Therefore, expo-

sure of pregnant women to crude oil pollution may cause adverse health implications and outcomes for both mother and child. Our results are consistent with that of Kampouri *et al.*,²⁵ who reported that maternal thyroid hypofunction was linked with reduced offspring verbal and motor ability scores. During pregnancy, thyroid hormone homeostasis is essential for normal neural network development. Also, it was observed that there were significantly lower TSH and T3/T4 ratio as well as significantly higher T4 among prenatally exposed neonates than non-prenatally exposed neonates. Neonatal TSH concentrations were significantly associated with the cognitive outcomes of neonatal cord blood TSH concentration was associated with decreased points on general cognitive and executive function scores. Also, neonatal thyroid deficiency was associated with poor childhood cognitive outcomes, with cognitive hypothyroidism as the most common cause.³¹ The regression analysis indicated that TSH concentration may be the major predictive factor for BDPE level, APGAR score and a biological driver for T3 and T4. No association between BDPE concentration and APGAR score was detected (Table 5). Serum BPDE concentration correlated positively with T4 and negatively with TSH and T3/T4 ratio. This finding partially aligned with a previous study which reported an association between high PAHs levels and low thyroid function. An association was also reported between PAHs and lower concentrations of T3 and reduced expression of thyroid receptor genes in cell culture of rockfish embryos exposed to PAHs.³² Since the balance of thyroid hormones is important for growth, early development, and metabolism of pregnancy and fetal development, alterations caused by elevated BPDE could have adverse effects on birth outcomes. Conversely, some authors reported an association between PAHs and increased T3 and T3/T4 ratio, but not with TSH or T4 concentrations, which the authors suggested was a lack of negative feedback on TSH by T3 and increased thyroid activity. A positive association between high PAHs concentrations and risk for low IQ in childhood, low birth length, and attention deficit hyperactivity disorder has been reported.³³ The observed significantly higher levels of BaP in this study align with previous studies in the Niger Delta region of Nigeria,³⁴ which reported significantly higher levels of BaP on the surface sediments and waters of a flow station and its environs in the Niger Delta which was above the WHO recommended limits. Similarly, significantly higher amounts of BaP in the soil of Yenagoa town, Bayelsa State were recently reported.³⁵

The detection of significantly higher concentrations of BPDE among crude oil-exposed pregnant women and their offspring than in non-exposed groups was not surprising.³⁶ The significantly higher serum concentration of BPDE in pregnancy is consistent with the previous study, which reported that prenatal exposure to BaP brings about apoptotic germ cell death through activation of the intrinsic mitochondrial apoptotic pathway in mouse fetal gonad. Several PAHs present in crude oil, such as benzo(a)pyrene have been demonstrated to instigate developmental gonadotoxicity in males and females,^{37,38} but the contraption or mechanism of fetal gonadotoxicity of BaP remains unclear. It was recently observed that lifetime carcinogenic risk and BaP mutagenic potency were attributed to the exposure of adults and children to PAHs in the dust.³⁹ The detection of significantly higher BaP in the cord blood of neonates in the study participants may be evidence of transplacental transfer of BaP during pregnancy. This finding of significantly higher levels of BaP among prenatally exposed neonates is consistent with previous studies.^{37,38} It was observed that BaP-DNA adduct level in the cord blood of infants was associated with reductions in the developmental quotient scores at the age of 12 months.⁴⁰ In experimental animal studies, similar findings were reported, as exposure of experimental animals to PAHs dur-

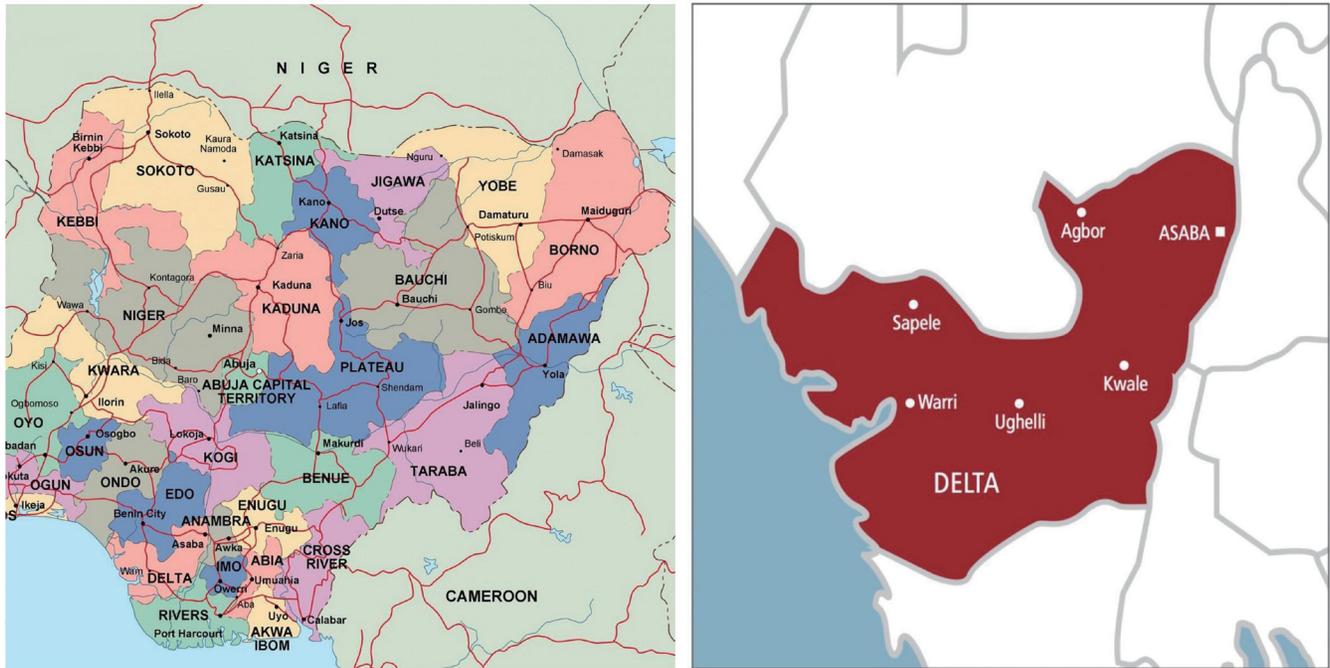


Fig. 1. Map of Nigeria and Delta State in Nigeria (Britannica.com; maps-nigeria.com)

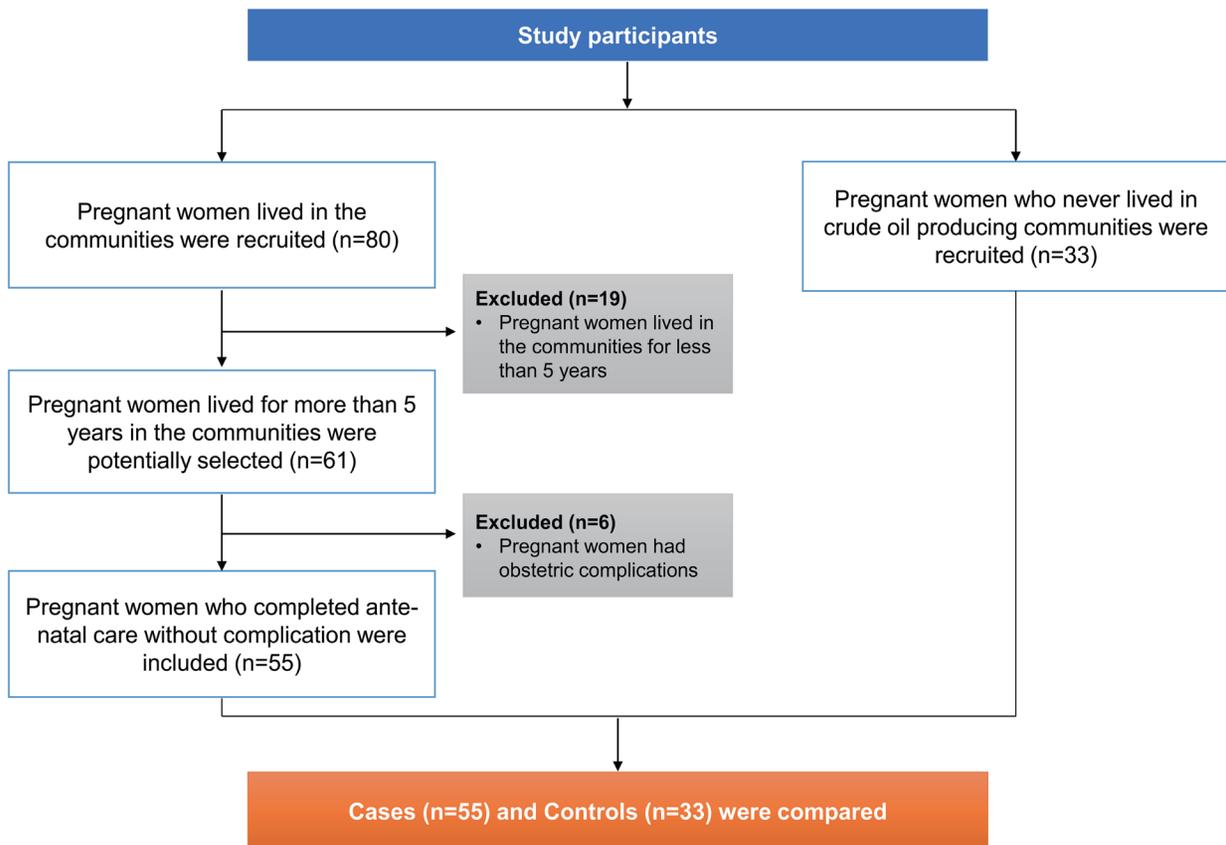


Fig. 2. Flow chart of the selection of study participants, inclusion and exclusion criteria. This flow diagram illustrates the number of pregnant women recruited from ante-natal clinics, and the number and reasons for excluding some of them based on the predetermined criteria. Following this process, fifty-five pregnant women and 33 controls who met the selection criteria were recruited in the study.

ing the prenatal period resulted in impaired memory and learning, anxiety, and depression behavior effects.^{41,42} Epidemiological studies conducted in the USA,⁴³ China,⁴⁴ and Poland indicated neurodevelopment effects among humans exposed to PAHs.⁴⁵ It has been established that prenatal exposure to PAHs may harm the neurodevelopment of children aged 2 to 8 years.⁴¹ Data on the effects of thyroid impairments on neurodegenerative disorders are conflicting. Some authors have suggested a link between thyroid impairments and neurocognitive disorders with improvement reported following treatment with T4. Others have suggested a non-reversible effect of thyroid hormonal deficiency on brain structures, particularly among subjects with overt hypothyroidism. However, neurocognitive disorder associated with overt hyperthyroidism can be reversed following treatment.^{46,47} The association between brain and thyroid hormones (especially T3) is well established. Thyroid hormones require network of transport systems to penetrate the blood brain barrier to reach their target cells. Any abnormality in these mechanisms can lead to disturbance of the thyroid dependent brain function irrespective of the blood hormonal levels. Thyroid hormones also require specific transporters to cross the blood brain barrier, and the most important is the monocarboxylate transporter 8 (MCT8), which has high affinity for T3. An aberrant *MCT8* gene can lead to mental retardation and kinetic disorders. Changes in the concentration of neurotransmitters of specific sections of the brain can cause cognitive and behavioral symptoms of thyroid dysfunction.⁴⁸ In this respect, it should also be taken into account that endocrine disruptors such as PAHs exacerbate this effect in the presence of iodine deficiency. Iodine supplementation before and during pregnancy would help improve iodine status in pregnancy.⁴⁹

Limitations of this study

This study has several limitations. Apart from the small sample size, the iodine status of the pregnant women was not recorded. Despite the introduction of universal salt iodization more than two decades ago in Nigeria, about 60% of pregnant women are still iodine deficient.⁴⁹ Apparently, a high prevalence of inadequate iodized salt consumption is responsible for iodine deficiency in pregnant women in Nigeria. Furthermore, despite the Universal Salt Iodisation (USI) program, high cassava consumption leads to hypothyroidism and increased goiter formation.^{49–52} WHO recommends iodine supplementation in pregnancy in regions where USI coverage is less than 90%, for more than 2 years and expanding the USI program.⁵³ Therefore, iodine supplementation before and during pregnancy is necessary to improve iodine status in pregnancy.^{49,53} Incorporating iodine nutritional assessment into national demographic surveys will help identify populations and geographic locations that may be in need of iodine supplementation, as well as regular monitoring of the effectiveness of national iodization programs.⁴⁷ In addition to environmental factors, lifestyle factors such as body mass index, smoking, physical activity and diet can also influence thyroid function and therefore should be taken into account.^{54,55}

The main sources of PAHs in urban dust, generated by the combustion of biomass, wood and charcoal, as well as vehicle traffic, should also be taken into account for women in the control group in the city of Asaba.³³ Furthermore, the Fagan tests are not specific but are accepted as a hint for further intelligence development study. Despite the limitations listed above, this study is novel. Oil spills in the Niger Delta are well known, however, there is little information on the effects of prenatal exposure to crude oil-related

toxicants on thyroid hormones and their possible effects on the neurological development of prenatally exposed newborns and their mothers. To the best of our knowledge, this is the first study on the effects of prenatal exposure to crude oil toxicants and their impact on thyroid hormone levels in Niger Delta, Nigeria.

Future directions

Crude oil spillage and environmental pollution should be minimized. Regulatory agencies and governments should ensure that environmental surveillance and bio-monitoring are regularly conducted in these communities. Also, basic social amenities and training should be provided to the inhabitants to minimize their contact with these toxicants.

Conclusions

The data from this study indicated that expectant mothers residing in crude oil producing communities and their newborn infants are significantly affected by crude oil and associated environmental pollutants. Further studies with a larger number of subjects are still required to confirm these preliminary results. It is recommended that safe and clean food, including water, be made available to the population particularly the pregnant women and children who are more vulnerable to the adverse effects of oil pollution in oil-contaminated communities. Future research should investigate the mechanisms of the observed toxicological effects on thyroid hormones and target the protection of pregnant women and their offspring in oil-contaminated communities.

Acknowledgments

The authors appreciate the contributions of the Clinicians, Nurses, Medical Laboratory Scientists, and Research Assistants involved in the completion of this study.

Funding

No source of funding

Conflict of interest

This is part of a PhD research data conducted by LO and supervised by MAE.

Author contributions

Study concept and design (MAE, LO); acquisition of data (LO); analysis and interpretation of data (MAE, LO); drafting of the manuscript (MAE, LO); critical revision of the manuscript for important intellectual content (MAE, LO); administrative, technical, or material support (MAE, LO); study supervision (MAE). All authors have made a significant contribution to this study and have approved the final manuscript.

Data sharing statement

The data used are derived from a PhD thesis and other data sources used in supporting the findings of this study are adequately cited in the article.

Ethics statement

This study was conducted to conform to the ethics guidelines of the Helsinki Declaration (revised 2013) and approved by the Ethics and Health Research Committee of the Central Hospital, Warri, Delta State (reference CHW/ECC VOL 1/168 dated October 9, 2018). Individuals who participated in this study gave informed consent.

References

- [1] United Nations Environment Programme. Environmental Assessment of Ogoni land. Nairobi: UNE; 2011:P8–17.
- [2] Ordiniho B, Brisibe S. The human health implications of crude oil spills in the Niger delta, Nigeria: An interpretation of published studies. *Niger Med J* 2013;54(1):10–16. doi:10.4103/0300-1652.108887, PMID:23661893.
- [3] Bolden AL, Rochester JR, Schultz K, Kwiatkowski CF. Polycyclic aromatic hydrocarbons and female reproductive health: A scoping review. *Reprod Toxicol* 2017;73:61–74. doi:10.1016/j.reprotox.2017.07.012, PMID:28739294.
- [4] Ramesh A, Harris KJ, Archibong AE. Chapter 38—Reproductive toxicity of polycyclic aromatic hydrocarbons. In: Gupta RC (ed). *Reproductive and Developmental Toxicology*. 3rd ed. Cambridge (MA): Academic Press; 2022:759–778. doi:10.1016/B978-0-323-89773-0.00038-2.
- [5] Ibor OR, Nnadozie P, Ogarekpe DM, Idogho O, Anyanti J, Aizobu D, *et al*. Public health implications of endocrine disrupting chemicals in drinking water and aquatic food resources in Nigeria: A state-of-the-science review. *Sci Total Environ* 2023;858(Pt 2):159835. doi:10.1016/j.scitotenv.2022.159835, PMID:36334666.
- [6] Ogbuagu DH, Njoku JD, Uzoije AP, Nwachukwu JI, Ebe TE. Correlates in groundwater quality parameters and textural classes of soils in a peri-industrial district of the Nigerian delta region. *J Environ Earth Sci* 2012;2:40–51.
- [7] Amangabara GT, Njoku JD. Assessing groundwater vulnerability to the activities of artisanal refining in Bolo and environs, Ogu/Bolo Local Government Area of Rivers State, Nigeria. *British J Environ Clim Chang* 2012;2:28–36. doi:10.9734/BJECC/2012/1088.
- [8] Dehghani S, Fararouei M, Rafiee A, Hoepner L, Oskoei V, Hoseini M. Prenatal exposure to polycyclic aromatic hydrocarbons and effects on neonatal anthropometric indices and thyroid-stimulating hormone in a Middle Eastern population. *Chemosphere* 2022;286(Pt 1):131605. doi:10.1016/j.chemosphere.2021.131605.
- [9] Kuang H, Zhou W, Zeng Y, Xu D, Zhu W, Lin S, *et al*. Dose makes poison: Insights into the neurotoxicity of perinatal and juvenile exposure to environmental doses of 16 priority-controlled PAHs. *Chemosphere* 2022;298:134201. doi:10.1016/j.chemosphere.2022.134201.
- [10] Rurale G, Gentile I, Carbonero C, Persani L, Marelli F. Short-Term Exposure Effects of the Environmental Endocrine Disruptor Benzo(a)Pyrene on Thyroid Axis Function in Zebrafish. *Int J Mol Sci* 2022;23(10):5833. doi:10.3390/ijms23105833, PMID:35628645.
- [11] Demeneix BA. Evidence for Prenatal Exposure to Thyroid Disruptors and Adverse Effects on Brain Development. *Eur Thyroid J* 2019;8(6):283–292. doi:10.1159/000504668, PMID:31934553.
- [12] Yang S, Sun J, Wang S, E L, Zhang S, Jiang X. Association of exposure to polycyclic aromatic hydrocarbons with thyroid hormones in adolescents and adults, and the influence of the iodine status. *Environ Sci Process Impacts* 2023;25(9):1449–1463. doi:10.1039/d3em00135k, PMID:37555279.
- [13] Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. *JAMA Pediatr* 2015;169(9):838–45. doi:10.1001/jamapediatrics.2015.0498, PMID:26146876.
- [14] Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Fornis J, Garcia-Esteban R, *et al*. Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 2013;24(1):150–157. doi:10.1097/EDE.0b013e318276ccd3, PMID:23232616.
- [15] Bernal J. Thyroid Hormones in Brain Development and Function. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, *et al* (eds). *Endotext*. South Dartmouth (MA): MDText.com, Inc; 2000. PMID:25905404.
- [16] Van Cauwenbergh O, Di Serafino A, Tytgat J, Soubry A. Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: a systematic review on research in mammals. *Clin Epigenetics* 2020;12(1):65. doi:10.1186/s13148-020-00845-1, PMID:32398147.
- [17] Bautista NM, Crespel A, Crossley J, Padilla P, Burggren W. Parental transgenerational epigenetic inheritance related to dietary crude oil exposure in Danio rerio. *J Exp Biol* 2020;223(Pt 16):jeb222224. doi:10.1242/jeb.222224, PMID:32620709.
- [18] Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. *Reprod Toxicol* 2011;31(3):363–373. doi:10.1016/j.reprotox.2010.12.055, PMID:21256208.
- [19] Lwanga SK, Lemeshow S. Sample size determination in health studies; a practical manual. Geneva: World Health Organization; 1991.
- [20] Bruederle A, Hodler R. Effect of oil spills on infant mortality in Nigeria. *Proc Natl Acad Sci USA* 2019;116(12):5467–5471. doi:10.1073/pnas.1818303116, PMID:30837310.
- [21] Fagan JF. The relationship of novelty preferences during infancy to later intelligence and later recognition memory. *Intelligence* 1984;8(4):339–346. doi:10.1016/0160-2896(84)90016-3.
- [22] Gbotolorun SC, Ezeife CC, Ogunlade B. Prenatal exposure of bonny light crude oil induces embryotoxicity, impaired cognitive functions and cortico-hippocampal neurodegeneration on fetal outcomes of pregnant sprague-dawley rats. *Drug Chem Toxicol* 2022;45(5):1978–1985. doi:10.1080/01480545.2021.1894721, PMID:33719803.
- [23] Zhang Y, Yang Y, Zhang Q, Cui J, Rahaman A, Huang XR, *et al*. Effect of Benzo[a]pyrene-DNA Adduct in Cord Blood on the Neurodevelopment of 12-Month-Old Infants in Qingdao City. *Neuropsychiatr Dis Treat* 2019;15:3351–3357. doi:10.2147/NDT.S219244, PMID:31819460.
- [24] Nie J, Li J, Cheng L, Deng Y, Li Y, Yan Z, *et al*. Prenatal polycyclic aromatic hydrocarbons metabolites, cord blood telomere length, and neonatal neurobehavioral development. *Environ Res* 2019;174:105–113. doi:10.1016/j.envres.2019.04.024, PMID:31055168.
- [25] Kampouri M, Margetaki K, Koutra K, Kyriklaki A, Karakosta P, Sarri K, *et al*. Maternal mild thyroid dysfunction and child behavioral and emotional difficulties at 4 and 6 years of age: The Rhea mother-child cohort study, Crete, Greece. *Horm Behav* 2019;116:104585. doi:10.1016/j.yhbeh.2019.104585, PMID:31476313.
- [26] Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, *et al*. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 1999;50(2):149–55. doi:10.1046/j.1365-2265.1999.00639.x, PMID:10396355.
- [27] Farasat T, Cheema AM, Khan MN. Hyperinsulinemia and insulin resistance is associated with low T₃/T₄ ratio in pre diabetic euthyroid Pakistani subjects. *J Diabetes Complications* 2012;26(6):522–5. doi:10.1016/j.jdiacomp.2012.05.017 2012, PMID:22795338.
- [28] Lischinsky JE, Skocic J, Clairman H, Rovet J. Preliminary Findings Show Maternal Hypothyroidism May Contribute to Abnormal Cortical Morphology in Offspring. *Front Endocrinol (Lausanne)* 2016;7:16. doi:10.3389/fendo.2016.00016, PMID:26941710.
- [29] Jansen TA, Korevaar TIM, Mulder TA, White T, Muetzel RL, Peeters RP, *et al*. Maternal thyroid function during pregnancy and child brain morphology: a time window-specific analysis of a prospective cohort. *Lancet Diabetes Endocrinol* 2019;7(8):629–637. doi:10.1016/S2213-8587(19)30153-6, PMID:31262704.
- [30] Hernandez-Castillo C, Shuck SC, Termini J. DNA Adducts as Biomarkers in Toxicology. In: Patel VB, Preedy VR, Rajendram R (eds). *Biomarkers in Toxicology. Biomarkers in Toxicology. Biomarkers in Disease: Methods, Discoveries and Applications*. Cham: Springer; 2023. doi:10.1007/978-3-031-07392-2-21.
- [31] Lain SJ, Rifas-Shiman SL, Pearce EN, Nassar N, Oken E. Neonatal Thyroxine, Maternal Thyroid Function, and Cognition in Mid-childhood in a US Cohort. *Matern Child Health J* 2020;24(4):503–513. doi:10.1007/s10995-019-02867-5, PMID:31897929.
- [32] Hansen BH, Salaberria I, Read KE, Wold PA, Hammer KM, Olsen AJ, *et al*. Developmental effects in fish embryos exposed to oil dispersions—The impact of crude oil micro-droplets. *Mar Environ Res* 2019;150:104753. doi:10.1016/j.marenvres.2019.104753, PMID:31284099.

- [33] Yang L, Shang L, Wang S, Yang W, Huang L, Qi C, *et al*. The association between prenatal exposure to polycyclic aromatic hydrocarbons and birth weight: A meta-analysis. *PLoS One* 2020;15(8):e0236708. doi:10.1371/journal.pone.0236708, PMID:32790684.
- [34] Howard IC, Briggs AO, Nduka JO. Prevalence of Benzo (a) pyrene (BaP) in the surface sediments and waters of a flow station and its environs in the Niger Delta. *J. Niger Environ Soc* 2014;1(1):82–87.
- [35] Leizou KE. Distribution and the use of diagnostic ratios for source investigation in urban soils of the Yenagoa City, Bayelsa State, Nigeria. *International Conference on Energy and Sustainable Environment. IOP Conf Ser Earth Environ Sci* 2021;665:012076. doi:10.1088/1755-1315/665/1/012076.
- [36] Jedrychowski WA, Perera FP, Tang D, Rauh V, Majewska R, Mroz E, *et al*. The relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts in cord blood. *J Expo Sci Environ Epidemiol* 2013;Jul23(4):371–7. doi:10.1038/jes.2012.117, PMID:23299301.
- [37] Nakamura BN, Mohar I, Lawson GW, Cortés MM, Hoang YD, Ortiz L, *et al*. Increased sensitivity to testicular toxicity of transplacental benzo[a]pyrene exposure in male glutamate cysteine ligase modifier subunit knockout (Gclm^{-/-}) mice. *Toxicol Sci* 2012;126(1):227–241. doi:10.1093/toxsci/kfs017, PMID:22253057.
- [38] Lim J, Kong W, Lu M, Luderer U. The Mouse Fetal Ovary Has Greater Sensitivity Than the Fetal Testis to Benzo[a]pyrene-Induced Germ Cell Death. *Toxicol Sci* 2016;152(2):372–381. doi:10.1093/toxsci/kfw083, PMID:27208085.
- [39] Iwegbue CMA, Kekeke EF, Tesi GO, Olisha C, Egobueze FE, Chukwu-Madu E. Impact of Land-Use Types on the Distribution and Exposure Risk of Polycyclic Aromatic Hydrocarbons in Dusts from Benin City, Nigeria. *Arch Environ Contam Toxicol* 2021;81(2):210–226. doi:10.1007/s00244-021-00861-z, PMID:34254149.
- [40] Perera FP, Tang D, Rauh V, Tu YH, Tsai WY, Becker M, *et al*. Relationship between polycyclic aromatic hydrocarbon-DNA adducts, environmental tobacco smoke, and child development in the World Trade Center cohort. *Environ Health Perspect* 2007;115(10):1497–1502. doi:10.1289/ehp.10144, PMID:17938742.
- [41] Saunders CR, Das SK, Ramesh A, Shockley DC, Mukherjee S. Benzo(a) pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. *J Appl Toxicol* 2006;26(5):427–438. doi:10.1002/jat.1157, PMID:16858674.
- [42] Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, *et al*. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6–7 years. *Environ Health Perspect* 2012;120(6):921–926. doi:10.1289/ehp.1104315, PMID:22440811.
- [43] Perera FP, Wang S, Vishnevetsky J, Zhang B, Cole KJ, Tang D, *et al*. Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. *Environ Health Perspect* 2011;119(8):1176–1181. doi:10.1289/ehp.1002705, PMID:21486719.
- [44] Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, *et al*. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics* 2009;124(2):e195–e202. doi:10.1542/peds.2008-3506, PMID:19620194.
- [45] Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, *et al*. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. *Environ Health Perspect* 2010;118(9):1326–1331. doi:10.1289/ehp.0901070, PMID:20406721.
- [46] Kramer CK, von Mühlen D, Kritz-Silverstein D, Barrett-Connor E. Treated hypothyroidism, cognitive function, and depressed mood in old age: the Rancho Bernardo Study. *Eur J Endocrinol* 2009;161(6):917–921. doi:10.1530/EJE-09-0606, PMID:19755406.
- [47] Smith CD, Grondin R, LeMaster W, Martin B, Gold BT, Ain KB. Reversible cognitive, motor, and driving impairments in severe hypothyroidism. *Thyroid* 2015;25(1):28–36. doi:10.1089/thy.2014.0371, PMID:25381990.
- [48] Eslami-Amirabadi M, Sajjadi SA. The relation between thyroid dysregulation and impaired cognition/behaviour: An integrative review. *J Neuroendocrinol* 2021;33(3):e12948. doi:10.1111/jne.12948, PMID:33655583.
- [49] Kayode OO, Odeniyi IA, Olopade OB, Iwuala SO, Odokoya OO, Fasanmade OA. Iodine status in pregnant Nigerian women; Does gestational age matters? *J Clin Sci* 2019;16:20–25. doi:10.4103/jcls.jcls_3_18.
- [50] John OC, Otoide OA, Omoruyi SA. Assessing the trend of iodine deficiency among antenatal patients of the university of Port Harcourt teaching hospital. *IJSRA* 2020;07:123–129.
- [51] Mwadzombo S, Chimbevo L, Oshule P, Essuman S, Wambura F. A Relationship Between Goitre Prevalence and Cassava (*Manihot esculenta* Crantz) Consumption in Kilifi County, Coast Province of Kenya. *Sci J Public Health* 2019;7(6):206–213.
- [52] Musa AH, Mshelia DS, Sakina HA, Gali RM, Mamza PY. Urinary iodine excretion among pregnant women attending antenatal clinic at university of Maiduguri teaching hospital, Maiduguri, north-eastern Nigeria: A pilot study. *EJPMR* 2016;3:8–12.
- [53] Kareem YO, Ameyaw EK, Amoah RM, Adegboye OA, Yaya S. An assessment of individual, community and state-level factors associated with inadequate iodised salt consumption among pregnant and lactating women in Nigeria. *BMC Pregnancy Childbirth* 2023;23(1):524. doi:10.1186/s12884-023-05833-w, PMID:37464273.
- [54] Businge CB, Musarurwa HT, Longo-Mbenza B, Kengne AP. The prevalence of insufficient iodine intake in pregnancy in Africa: a systematic review and meta-analysis. *Syst Rev* 2022;11(1):231. doi:10.1186/s13643-022-02072-6, PMID:36303220.
- [55] Babić Leko M, Gunjača I, Pleić N, Zemunik T. Environmental Factors Affecting Thyroid-Stimulating Hormone and Thyroid Hormone Levels. *Int J Mol Sci* 2021;22(12):6521. doi:10.3390/ijms22126521, PMID:34204586.