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Artificial Neural Network for Predicting Iodine Deficiency in the First Trimester of Pregnancy in Healthy Women

Maria Teresa Murillo-Llorente,[1] Carmen Fajardo-Montañana[1] and Marcelino Perez-Bermejo[1]

[1]School of Medicine and Health Sciences, Catholic University of Valencia San Vicente Mártir, Valencia, Spain

Iodine deficiency in Spain is a persisting public health problem and the prescription of potassium iodide is recommended during pregnancy. The purpose of this study was to develop an Artificial Neural Network (ANN) to predict the risk factors of iodine deficiency during pregnancy, and compare the results obtained with a logistic regression model. Two hundred forty-four healthy pregnant women were included in a descriptive and prospective study in their first trimester of pregnancy. The women enrolled were asked specifically about their use of supplements containing potassium iodide, iron, folic acid and/or multivitamins during pregnancy. The consumption of iodine-rich foods was assessed through a food frequency questionnaire. A median UIC of 57.4 μg/L (IQR 32.8-99.3) was obtained, with 89.3% < 150 μg/L, the minimum recommended ioduria level by the WHO. There was no correlation between urinary iodine concentrations and maternal age, BMI or gestation week at recruitment. The urinary iodine concentrations were significantly higher in women who reported taking iodized supplements and/or iodized salt than those who did not. Number of gestations, age, body mass index, and intake of iodized supplements and iodized salt were the most important predictors of iodine deficiency. Based on Receiver Operating Characteristic analysis, the diagnostic performance of the ANN model was superior to the logistic regression model. The ANN model, with variables on pregnancy and the intake of iodine rich foods, iodized supplement and iodized salt may be useful for predicting iodine deficiency in the early pregnancy.

Keywords: Artificial Neural Network; gestation; iodine deficiency; iodized salt; logistic regression model
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Introduction

Iodine deficiency during pregnancy is associated with an increased risk for pregnancy complications and a 13.5 decrease in intelligence quotient (IQ) in exposed offspring (Zimmermann 2012; Lazarus 2015).

American Thyroid Association (ATA) indicates that universal screening should be performed in iodine-deficient areas (Alexander et al. 2017). Low to moderate iodine deficiencies have been found in many European regions, especially in south and eastern Europe (Gutekunst and Scriba 1989). Spain is a country with food production with low iodine content (Sociedad Española de Endocrinología y Nutrición and Grupo de Trabajo de trastornos por déficit de Yodo 2004), which causes a deficient intake of iodine in a mild/moderate way (Velasco 2007). For this reason, in our country the explicit recommendation of the prescription of potassium iodide (IK) is maintained before pregnancy and, if possible, during pregnancy and in the lactation period (Donnay et al. 2014). In the pregnant population, the situation in our country is that iodine deficiency persists taking into account the criteria determined by international organizations (Donnay et al. 2014; Fundación Española de Dietistas y Nutricionistas 2017)

At present, it is difficult to predict when an individual patient will have iodine deficiency. Bartosch-Harlid et al. (2008) suggested that Artificial Neural Network (ANN) is potentially more successful than conventional multivariant statistical techniques at predicting clinical outcomes when the relationship between the variables that determine the prognosis is multidimensional and non-linear. For this reason, we decided to develop an ANN to predict the risk factors of iodine deficiency during pregnancy and compare the results obtained with a logistic regression model. Some

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Correspondence: Maria Teresa Murillo-Llorente, School of Medicine and Health Sciences, Catholic University of Valencia San Vicente Mártir, C/Quevedo, 2. E46001 Valencia, Spain.
e-mail: mt.murillo@ucv.es

studies show that Artificial Neural Networks can be successfully used to help in the diagnosis of thyroid disease (Ozyilmaz and Yildirim 2002; Temurtas 2009; Nazari Kousarrizi et al. 2012) or other areas of endocrinology (Kupusinac et al. 2014; Sangi et al. 2015; Zhu et al. 2013), but ANNs have always been used for different classifications in various pathologies or mortality studies; however, they have rarely been used to analyze risk factors.

In most of the previous studies, the factors used for iodine deficiency classification were socio-demographic ones, the use of iodized salt and the presence of goiter (Gur et al. 2003; Pouessel et al. 2003). In this study, in addition, intake of food supplements, and consumption of iodine-rich foods were used as predictors of iodine deficiency.

Methods

Study subjects

We conducted a cross-sectional study on 244 healthy Caucasian women at the Hospital Universitario de La Ribera (HULR), Valencia (Spain), at their first antenatal visit (gestational weeks 6-12), from September 2014 to January 2015.

The study was approved by the Clinical Research Ethics Committee of the HULR (accepted on December 13th, 2013) and written informed consent was obtained from all the participants. This work complies with the principles laid down in the Declaration of Helsinki.

All participants underwent an obstetric examination to exclude maternal and/or fetal risk factors. The inclusion criteria were women aged 16 or older, gestational age up to and including 12 weeks of amenorrhea.

Refusal to participate, gestational age out of first trimester, high risk pregnancies, personal history of thyroid or any other endocrine disorders, and/or use of drugs which interfere with iodine metabolism were deemed exclusion criteria.

From an initial sample of 275 women, 31 subjects (11.27%) were excluded from the study after application of the inclusion and exclusion criteria. The reasons for exclusion were non Caucasian (n = 17; 6.18%), hypothyroidism (n = 4; 1.45%), hyperthyroidism (n = 1; 0.36%), thyroid autoimmunity (n = 2; 0.72%), abortion (n = 2; 0.72%), being under 16 years (n = 1; 0.36%), blood or urine tests from another Institution (n = 2; 0.72%), more than 12-week gestation period (n = 1; 0.36%), and an outlier (n = 1; 0.36%).

Women enrolled were specifically asked about their use of supplements containing potassium iodide, iron, folic acid and/or multivitamins during their pregnancy. The consumption of iodine-rich foods was assessed through a food frequency questionnaire (FFQ) previously validated in the Spanish population (Vila et al. 2016).

Laboratory procedures

All the pregnant women provided an aliquot of non-first void urine sample (first-void samples may underestimate iodine levels (Konig et al. 2011)) collected in sterile plastic bottles for determinations of urinary iodine. All urine samples were taken from 08.00 a.m. to 10.00 a.m. and stored at −20ºC until analysis in the iodine laboratory. Values of urinary iodine concentration were measured by the Dunn colorimetric technique (Dunn et al. 1993) and the results are expressed in mg/L.

Statistical analysis

The quantitative variables were measured as the mean ± standard deviation or mean (interquartile range (IQR)) and the qualitative variables as percentages. The contrast hypothesis for two samples was evaluated with Student's t-test for quantitative variables and the Chi-squared test (or Fisher's exact test as appropriate) in case of categorical ones. If the variables were not within normality limits, a Mann-Whitney or Kruskall-Wallis test was performed. For the adjustment of the model for other variables, two- or multi-way analysis of variance (ANOVA) was designed, introducing the continuous variables as covariates. The correlation between variables was determined using the Spearman test, designing multiple regression models in cases in which prediction of the variance adjusted for other variables was desired, besides the main variable. In all cases the rejection level for a null hypothesis was $\alpha < 0.05$.

For the multivariate analysis, we decided to use the Urinary Iodine Concentration (UIC) as a determinant, since it is a good indicator to assess iodine deficiency in a population (Donnay 2004), being normally considered the best biochemical indicator of the nutritional status of iodine when it is determined in an appropriate sample and with the appropriate technology (Espada Sáenz-Torre 2008).

In our work we use an Artificial Neural Network Multilayer Perceptron (MLP) with a hidden layer, as it is the most used today, mainly because it is capable of acting as a universal approximator of functions. Furthermore, together with the backpropagation algorithm, it is capable of learning any type of continuous function between a group of input and output variables, minimizing the error. Thus, an exploratory three-layer multiplayer perceptron ANN model with a backpropagation algorithm was built.

For the input layer, those that were significantly related to the presence of iodine deficiency, according to the results of the univariate analyzes, were selected as input variables. The final ANN model was developed, with 12 input variables, one hidden layer (with 8 nodes) and one output variable, transformed to range from 0-1 (see Fig. 3). Iodine deficiency was predicted if the output was greater than or equal to 0.5.

Sensitivity analysis (importance analysis) was performed to determine the optimal variables for the construction of the final ANN model (Garson 1991; Goh 1995). This analysis identifies the relative importance (weight of the association) that the input variables have over the output (iodine deficiency).

The data were randomly divided into a training sample (202 cases, 82.8%) and a test sample (42 cases, 17.2%) for network training.

A logistic regression (LR) analysis was performed to develop a logistic regression function for comparison. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the performance of the ANN and LR models. Statistical analyses were performed using IBM SPSS Statistics v.23 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of participants are shown in Table 1. Of the 244 participants, 167 (68.4%) reported taking iodized supplements before pregnancy with 150-200 μg iodine as a daily dose; 111 (45.5%) women were taking iodized salt daily.

Median (IQR) urinary iodine concentrations and potential confounders are shown in Table 2.

In our study, most of the women studied were in a situation of iodine deficiency, taking into account the results of UIC obtained (median 57.4 μg/L (32.8-99.3)). In fact, 75.4% were < 100 μg/L (minimum iodine level recommended by ICCIDD, International Council for Control of Iodine Deficiency Disorders (2007), and 89.3% < 150 μg/L (minimum recommended ioduria level by the World Health Organization (WHO)) (Abalovich et al. 2007; Alexander et al. 2017) (Fig. 1).

There was no correlation between UIC and maternal age, body mass index (BMI), age, place of residence, number of gestations or gestation week at recruitment (Table 2). There was a statistically significant difference in UIC between women who reported taking iodized supplements and those who did not; equally, there was difference in UIC between women who reported taking iodized salt and those who did not (Table 2).

Univariate and multivariate analyses

Twelve variables considered relevant to the presence of iodine deficiency were tested using univariate and multivariate analyses. Multivariate analysis by logistic regression identified the following three independent variables as predictive of iodine deficiency: number of gestations ($p = 0.01$); iodized supplements intake ($p < 0.000$); and iodized salt intake ($p < 0.000$) (Table 3). The probability of iodine deficiency decreases with increasing intake of iodized salt and iodized supplements, as well as with increasing number of pregnancies. The equation that predicts iodine deficiency is: 1.516 − 0.377 gestations − 1.098 iodized supplement intake − 1.004 iodized salt intake.

ANN analysis

As shown in Fig. 2, the number of gestations, age, BMI, intake of iodized supplements and iodized salt were the most important predictors of iodine deficiency by sensitivity analysis. Fig. 3 represents the final ANN model developed and trained in the sample. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio of the ANN was 56.0%, 85.0%, 3.73 and 0.52, respectively. The ROC curves for the ANN model and LR model for predicting iodine deficiency are shown in Fig. 4. The AUC of the ANN model (AUC = 0.798 ± 0.028) was significantly higher than the AUC of the LR model (AUC = 0.672 ± 0.034) ($p < 0.000$), which indicates that the ANN model is more precise in the classification of the dependent variable than the logistic regression model.

Discussion

Due to an increased demand of iodine during gestation, pregnant woman are particularly at high risk of iodine deficiency, which is the leading cause of preventable mental retardation and brain damage worldwide (Vermiglio et al. 1999; de Escobar et al. 2007; Murcia et al. 2011; Hynes et al. 2013; Lazarus 2015). Our observations show that there is a high prevalence of iodine deficiency in the analyzed population, and thus it is a highly suitable population for detecting the risk factors that cause such iodine deficiency.

This study uses UIC to classify pregnant women as being sufficient (≥ 150 μg/L) or deficient (< 150 μg/L) in iodine (ICCIDD et al. 2007; Alexander et al. 2017). The results of this study show that the number of previous gestations, iodized supplements intake, age, iodized salt intake and folic acid intake were the most important predictors of iodine deficiency. Most of the studies investigate the predictive factors of UIC and, therefore, a contribution of both dietary and supplementary iodine intake. Andersen et al. (2013) conclude that pregnant women may be inclined to take an iodine supplement if they have a greater knowledge of their increased iodine needs during pregnancy.

In most of the previous studies, the factors used for iodine deficiency classification were socio-demographic ones, the use of iodized salt and the presence of goiter (Gur et al. 2003; Pouessel et al. 2003; Kshatri et al. 2017). In this study, in addition, intake of food supplements and consumption of iodine-rich foods were used as predictors of iodine deficiency.

The use of ANN in the context of iodine deficiency has not been explored. To our knowledge, this is the first study that applies an ANN model to analyze the risk factors of iodine deficiency. We do not wish to claim that neural net-

Table 1. Baseline Characteristics for total cohort (n = 244).

Characteristics	Value
Age*	30.96 (5.00)
BMI (Kg/m^2)**	23 (15-37)
Gestations (week)**	6 (4-12)
Iodized supplement intake	167 (68.4%)
Iodized salt intake	111 (45.5%)

*mean (SD); **median (IQR) or (n) %.

Table 2. Adjusted urinary iodine values.

UIC μg/L	n	Median	IQR	p
Cohort	n = 244	57.4	32.8-99.3	
Iodized supplement intake	Yes (n = 167)	64.6	40.8-111.0	**0.000***
	No (n = 77)	35.8	24.2-79.9	
Iodized salt intake	Yes (n = 111)	67.1	39.6-106.2	**0.011***
	No (n = 133)	48.6	27.8-94.7	
BMI	Underweight (n = 14)	35.2	21.9-67.7	0.367**
	Normal range (n = 148)	61.6	34.6-107.7	
	Overweight class I (n = 30)	57.3	28.7-96.0	
	Overweight class II (n = 23)	52.5	35.9-85.6	
	Obese class I (n = 20)	51.4	23.8-97.9	
	Obese class II (n = 9)	57.0	21.5-75.5	
Place of residence	Coast (n = 46)	56.7	30.8-112.7	0.871*
	Inland (n = 198)	57.9	33.0-99.2	
Week of gestation	Week 2 (n = 1)	126.6	-	0.662**
	Week 3 (n = 2)	81.2	70.6-81.2	
	Week 4 (n = 21)	78.1	34.7-133.3	
	Week 5 (n = 45)	63.0	30.3-106,7	
	Week 6 (n = 70)	57.6	35.1-105.7	
	Week 7 (n = 40)	47.5	28.0-107.9	
	Week 8 (n = 31)	47.9	33.8-80.5	
	Week 9 (n = 21)	58.0	28.2-82.6	
	Week 10 (n = 8)	49.3	35.6-98.9	
	Week 11 (n = 2)	127.1	99.4-127.1	
	Week 12 (n = 3)	23.7	14.7-23.7	
Gestations	1st Gestation (n = 107)	57.8	29.4-85.1	0.381**
	2nd Gestation (n = 87)	69.2	35.8-111,0	
	3rd Gestation (n = 38)	47.0	26.8-87.0	
	4th Gestation (n = 4)	85.1	23.6-158.2	
	5th Gestation (n = 6)	36.7	21.9-90.3	
	> 5th Gestation (n = 2)	46.3	37.6-46.3	
Nº abortions	0 (n = 181)	59.0	34.7-97.1	0.223**
	1 (n = 49)	52.5	28.2-116.9	
	2 (n = 10)	30.5	20.9-79.6	
	3 (n = 3)	81.8	45.5-81.8	
	4 (n = 1)	133.0	-	
Age (years)	≤ 17 (n = 1)	14.7	-	0.143**
	18-19 (n = 4)	52.0	30.4-62.1	
	20-34 (n = 179)	57.8	33.8-101.9	
	35-39 (n = 55)	59.9	27.8-106.2	
	≥ 40 (n = 5)	23.7	17.8-52.0	

*Mann-Whitney *U*-test; **Kruskal-Wallis test.

works are the answer to all complex data analysis, but based on ROC analysis, the diagnostic performance of the ANN model was superior to the LR model. We have simply shown that a neural network can discover a useful predictive relation between the risk factors analyzed and iodine deficiency during pregnancy. Therefore, ANNs often include parameters that may not reach significance using conventional statistics, as evidenced by the fact that only number of gestations, iodized supplement intake and iodized salt intake were significant in the logistic regression analysis.

Our work has some limitations. First, as usual in any observational study, confounding or non-measured factors may compromise the scope or accuracy of the model. Second, external validity was not tested for either logistic regression or ANN. Independent and external validation

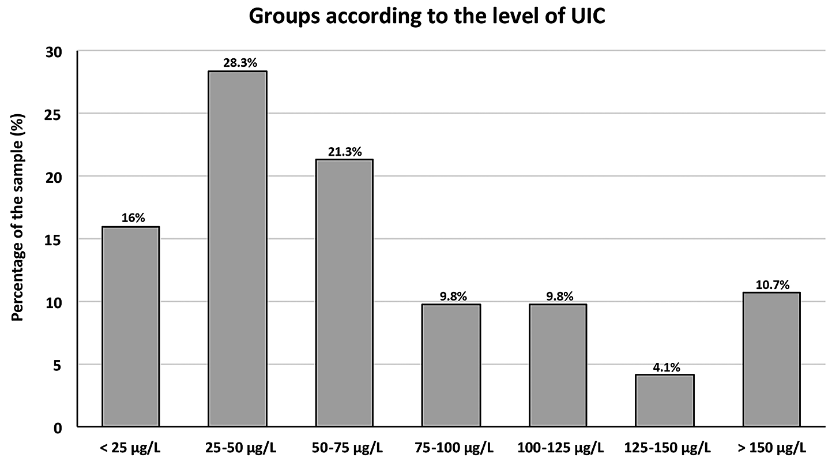

Fig. 1. Distribution of the sample according to the level of Urinary Iodine Concentration.

Table 3. Logistic regression analyses predicting iodine deficiency.

Factors	Coefficient	OR	95% CI	p value
Gestations	−0.377	0.686	0.514-0.915	**0.010**
Age	−0.008	0.992	0.938-1.049	0.782
Iodized supplement intake	−1.098	0.334	0.184-0.604	**< 0.000**
BMI	−0.007	0.993	0.935-1.055	0.833
Iodized salt intake	−1.004	0.366	0.211-0.635	**< 0.000**
Milk consumption	−0.176	0.838	0.366-1.920	0.676
Fish consumption	−0.165	0.848	0.362-1.982	0.703
Crustaceans consumption	−0.447	0.640	0.358-1.244	0.132
Molluscs consumption	0.208	1.231	0.583-2.599	0.586
Seaweed consumption	−0.269	0.764	0.190-3.071	0.704
Place of residence	−0.325	0.723	0.351-1.488	0.378
Folic acid intake	0.624	1.866	0.871-4.000	0.103
Constant	1.516	4.553	-	-

OR, odds ratio; CI, confidence interval.

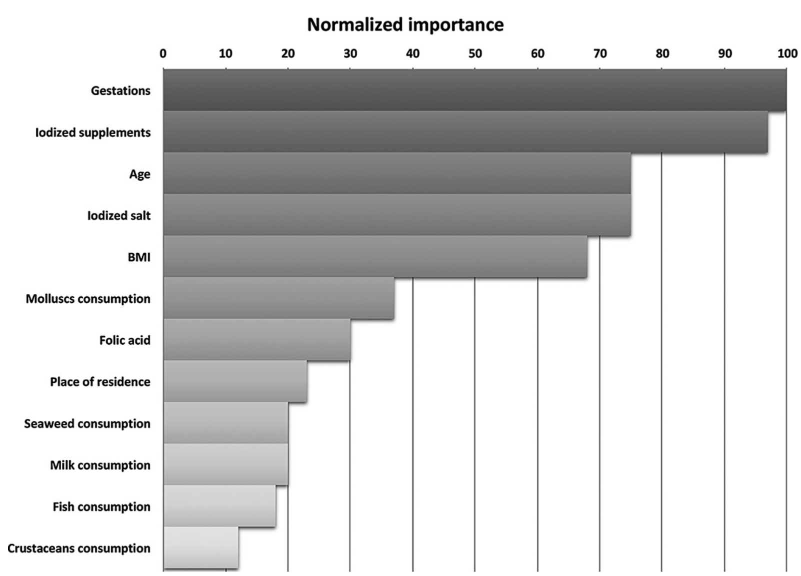

Fig. 2. Sensitivity Analysis of the input variables.
The value shown for each input variable is a measure of its relative importance in the classification of iodine deficiency.

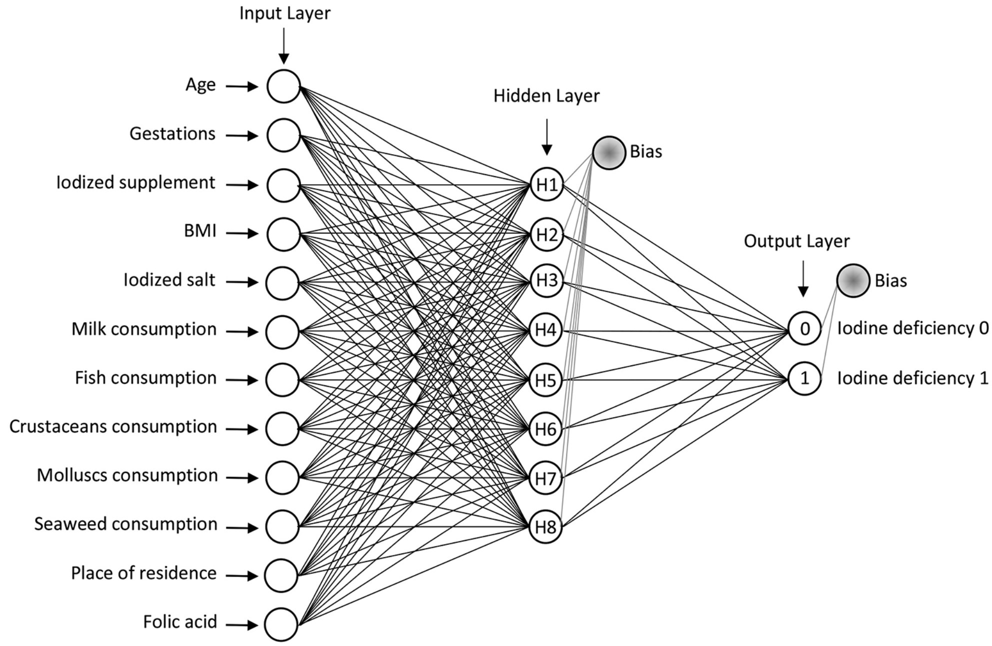

Fig. 3. Artificial Neural Network Model for the prediction of iodine deficiency.
It consists of twelve input variables, a hidden layer with eight nodes, and one output variable. Number 1 corresponds to iodine deficiency and 0 to non-iodine deficiency.

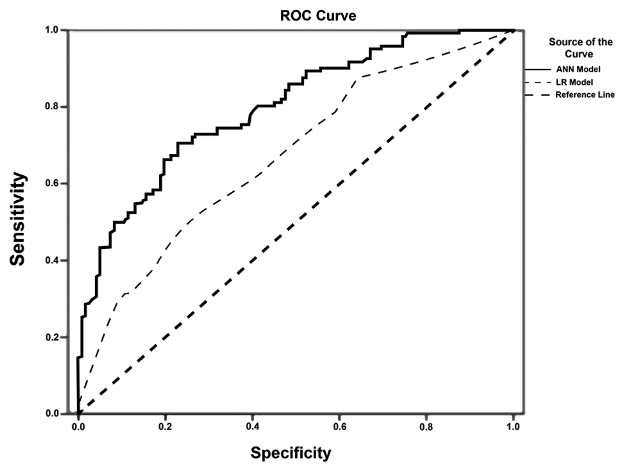

Fig. 4. Receiver Operating Characteristic curves for the Artificial Neural Network model and Logistic Regression model.
The Area Under the Curve of the Artificial Neural Network model (solid line) was significantly higher than the Area Under the Curve of the Logistic Regression model (dash line) ($p < 0.000$).

would be necessary in a different population. Therefore, a new cohort study would be desirable before any potential clinical use could be considered. On the other hand, since it is a study on risk factors for iodine deficiency, the levels of thyroid hormones have not been added, and it is also part of a larger study in which the thyroid function of pregnant women was analyzed in the first gestation trimester (Murillo-Llorente et al. 2020).

In conclusion, the number of gestations, age, BMI, and intake of iodized supplements and iodized salt were the most important predictors of iodine deficiency. Based on Receiver Operating Characteristic analysis, the diagnostic performance of the ANN model was superior to the logistic regression model, and this type of models could be used to help experts make their diagnosis. Thus, an artificial neural network model with variables on pregnancy and the intake of iodized supplement and iodized salt may be useful for predicting iodine deficiency in the early pregnancy.

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Conflict of Interest

The authors declare no conflict of interest.

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