



The role of placental iodine storage in the neonatal thyroid stimulating hormone surge: iodine as a driving force to adapt the terrestrial life

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Abstract

Purpose Iodine plays a pivotal role in adaptation during the transition from intrauterine to extrauterine life. Although it is well known that the placenta plays a role in iodine storage, a relationship between the neonatal thyroid stimulating hormone (TSH) peak and placental iodine concentration has not been established. This study focuses on the role of placental iodine concentration in the TSH surge after delivery.

Materials and methods This study included 42 mothers and their newborns, none of whom had perinatal risk factors. The following samples were collected to analyze iodine: placental tissue, amniotic fluid (AF), and 24-h maternal urine. Blood was drawn from the umbilical cord (uc), newborns (at the 1st–24th hours), and mothers (at 1st hour) to analyze the following hormones: TSH, freeT4/T3 (fT4/fT3), human chorionic gonadotrophin (hCG), prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), and cortisol.

Results The mean iodine levels of placental tissue, AF, and 24-h maternal urine were as follows: 29.06 ± 45.88 µg/kg, 182.80 ± 446.51 µg/L, and 498.35 ± 708.34 µg/L, respectively. The mean TSH and hCG values were 32.41 ± 13.96 mIU/ml and 30.66 ± 18.55 mIU/ml, respectively, at the 1st hour. Placental iodine had strong, very strong, and weak negative correlations with TSH, hCG, and PRL, respectively ($r_{\text{TSH}} = -0.763$, $p < 0.001$; $r_{\text{hCG}} = -0.919$, $p < 0.001$; $r_{\text{PRL}} = -0.312$, $p = 0.044$).

Conclusion This study showed that the placental iodine level was inversely correlated with neonatal TSH, hCG, and PRL. It indicates that placental iodine concentration is an efficient driving force shaping the dynamic pattern of the neonatal TSH peak in addition to hCG and PRL surges, which reflects the adaptive effort in the transition from intrauterine to extrauterine life.

Keywords Placental iodine · Neonatal TSH surge · Perinatal factors

Introduction

The neonatal thyroid stimulating hormone (TSH) surge occurs immediately after birth. Thyroid hormones (TH) are master molecules that play a pivotal role in adaptation to ecological transitions and metamorphosis events through

fast and effective responses to environmental signs [1]. One of the main tasks of THs is to store iodine [2]. As an iodine reservoir, THs play a critical role in the hormonal regulation of metabolic activities required to adapt during the transition from aquatic to terrestrial life. Ontogenetically, the neonatal TSH surge after delivery is an evolutionary trait, which reflects the adaptive effort of ecological transition [3].

Foetal TH synthesis undergoes dynamic changes during intrauterine life. During the first gestational weeks, placental hormones including human chorionic gonadotrophin (hCG) that has a thyrotropic (TSH stimulating) effect. TH synthesis and iodine supply, while fetal TSH begins to stimulate its downstream hormones in the second half of pregnancy [4]. Placenta, which is an interface between mother and fetus, not only plays a role in the uptake and transport of maternal iodine sources to the fetus, but is also the most important

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extrathyroidal iodine reservoir organ throughout the pregnancy [5]. The placenta also provides iodine regulation varying depending on the requirement of the developing fetus, who is extremely sensitive to iodine fluctuations. Therefore, fetal iodine regulation is associated with a functional placenta rather than maternal dietary iodine intake [6]. It has a compensatory role for the fetus as an iodine reservoir organ [5]. Postnatal iodine delivery to the newborn from the placenta is suddenly interrupted following the cutting of the umbilical cord.

After birth, neonatal TSH increases dramatically within minutes and decreases within days, physiologically. There are many well-known perinatal factors such as maternal age, gestational week, mode of delivery, order of birth, perinatal asphyxia, duration of labour, seasonality, gestational diseases, and iodine deficiency affecting the neonatal TSH surge [7]. These factors pose the challenge to distinguish the physiological pattern of the neonatal TSH from congenital hypothyroidism. Many previous studies have reported inconsistent results regarding the relationship between neonatal TSH surge and perinatal factors [8–10]. Some of these studies were conducted, retrospectively, and the data were obtained from medical records. Moreover, the reports do not seem to sufficiently explain causality. Although it is well known that the placenta plays a pivotal role in iodine metabolism to synthesize foetal THs, the relationship between the neonatal TSH peak and placental iodine concentration is unclear [6].

It can be predicted that postpartum removal of the placenta, which plays a compensatory role for the fetus as an iodine reservoir, may have a remarkable effect on the neonatal TSH pattern. This study focused on the potential relationship between the neonatal TSH peak, which emerged as an adaptation mechanism in the transition from intrauterine to extrauterine life, and the placental iodine level as a driving force of TH synthesis.

Materials and methods

This is a prospective, single-center study conducted between March 2019 and February 2020. The participants included 42 mothers, aged from 18 to 41 years, and their newborns; the mothers gave birth by elective cesarean section following uncomplicated pregnancies at 38 to 42 weeks of gestation. The following variables were registered: birth history, exposure to perinatal asphyxia, Apgar scores, and the newborn's length and weight at birth. The exclusion criteria were as follows: twin pregnancy, newborn with perinatal asphyxia, gestational diabetes, newborn who was <37 or >42 weeks of gestational age, eclampsia/pre-eclampsia, intrauterine growth retardation, birth weight less than 2600 g (gm), vaginal delivery, maternal smoking or drug use, maternal

thyroid disease, diagnosis of congenital hypothyroidism by heel-stick screening, maternal thyroid-stimulating hormone (TSH) higher than 8 IU/mL, emergency cesarean section, newborn with isolated or multiple anomalies, and Apgar score < 8 points at five minutes. Informed consent was obtained from all mothers for the study.

The samples collected and assays studied are as follows: iodine in placental tissue, amniotic fluid (AF), and maternal urine. Blood was drawn for the following hormone assays from the umbilical cords (*uc*) (within 10 min), the mothers (at the first hour), and the newborns (postnatal first and 24th hours after birth): TSH, free T4 and T3 (fT4 and fT3), human chorionic gonadotrophin (hCG), prolactin hormone (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), and cortisol. Hormone results at the first or 24th hours will be presented by adding "1" and "24" to the end of the abbreviations (TSH1/TSH24, etc.). Within 10 min of the birth, 5 cubic centimeters (cc) of blood was drawn from the umbilical vein. After delivery, 5 cc of blood was taken from the newborn (at the first and 24th hours) and from the mother (at the first hour). The sera that were separated after the blood samples were centrifuged. Hormone analysis was performed on the Beckman Coulter Inc. UniCelDxI800 Access Immunoassay System (U.S.A.). All hormone assays were analyzed through the chemiluminescence immunoassay method using TSH;3rd IS, total β -HCG;5th IS. The newborns were divided into three groups according to serum TSH levels at the first hour. The groups were determined based on cut-off values from previous screening programs, which are 1-low: 0–9.9 mIU/mL, 2-moderate: 20–39.9 mIU/mL, and 3-high: ≥ 40 mIU/mL [11].

Iodine analysis in samples

Placental tissue collection for iodine analysis

All placentas ($n=42$) were obtained from pregnant women who had undergone elective cesarean section delivery. Within 10 min of the time the following umbilical cord had been cut, biopsies were performed from placental tissue by applying the principles determined by Kristof Y et al. [12]. Placental biopsies were obtained from three cotyledons located in the front, right, and left of the larger umbilical artery lines (Fig. 1). Placental tissues measuring 2 × 2 centimeters (cm) were cut at distances of 2 cm from the umbilical cord. The tissue pieces were rubbed and dried with filter paper to purify them from wet and bloody content and then placed in plastic tubes. An average of 1 gm of each sample was obtained from three tissue pieces for analysis. The samples were placed in glass Petri dishes and dried for 24 h in an oven at 105°Celsius (C). The pieces were weighed and recorded a second time after drying and were prepared for iodine analysis. Iodine measurements of placental tissues

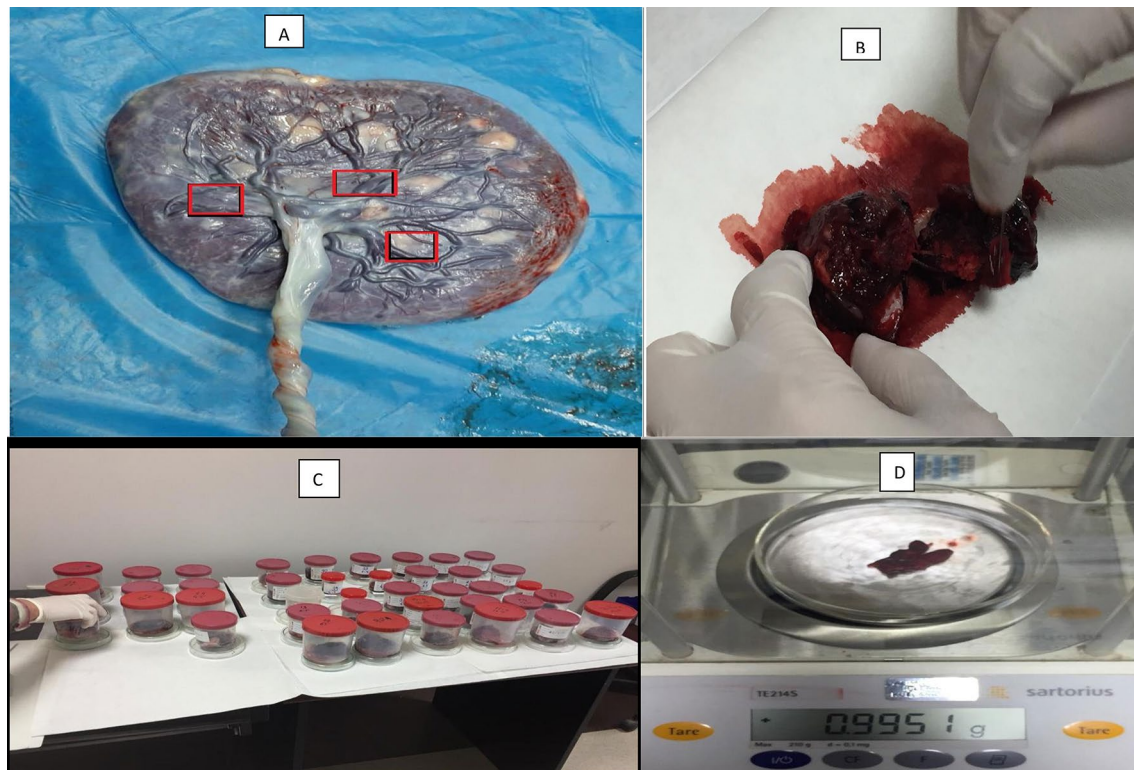


Fig. 1 Collection of placental tissue to iodine analyze: **a** biopsy site, **b** drying by filter paper, **c** keeping in plastic tube, **d** weighing

were analyzed using the inductively coupled plasma-mass spectrometry (ICP–MS) method. Measurements were determined in micrograms per kilogram ($\mu\text{g}/\text{kg}$).

Iodine analysis in amniotic fluid and urine

5 cc of amniotic fluid were withdrawn and placed in plastic tubes. After delivery, urine was collected every 24 h from the mothers and placed in plastic tubes. Iodine measurements in both samples were analyzed through the ICP-MS method. Measurements were determined in $\mu\text{g}/\text{liter}$ (L). The samples were kept in a freezer at -80°C until analysis.

Results

All newborns (with birth weights of 2.600 to 3.900 gr) who were not exposed to perinatal asphyxia. The mean maternal age was 27.23 ± 6.25 years. Table 1 presents the mean values for possible perinatal factors associated with the newborn TSH peaks. The mean iodine levels of the placental tissue were found to be $29.06 \pm 45.88 \mu\text{g}/\text{kg}$ (5.58–276.01) (Table 2). The AF and 24-h maternal urine iodine levels were $182.80 \pm 446.51 \mu\text{g}/\text{liter}$ (16.87–2658.55) and 498.35 ± 708.34 (37.38–3652.7), respectively. The mean value of TSH1 (at the first hour) was $32.41 \pm 13.96 \text{ mIU}/\text{mL}$

Table 1 Variables affecting perinatal factors neonatal thyroid stimulating hormone surge

Variable	<i>n</i>	Mean \pm SD	Range
Maternal			
Maternal age (year)		27.23 ± 6.25	18–41
Height (cm)		160.71 ± 6.91	142–173
Weight (kg)		78.07 ± 13.35	51–113
BMI at delivery (kg/m^2)		30.41 ± 4.73	20.76–41.50
Placental weight (gr)		516.21 ± 80.71	330–780
Placental volume (cm^3)		509.34 ± 82.35	320–780
Dried placenta tissue (gr)		0.21 ± 0.10	0.09–0.739
Delivery			
Apgar score at 1 min		7.02 ± 0.56	8–10
Apgar score at 5 min		9.66 ± 0.61	6–10
Neonatal			
Gestational age (week)		38.24 ± 0.53	38–41
Birth weight (gr)		3135.47 ± 354.31	2600–3900
Birth height (cm)		49.09 ± 1.09	48–54
Girl/Boy	20/22		
Birth order (<i>n</i>)			
First	8		
Second	14		
Third or later	20		

\pm SD standard deviation *BMI* body mass index

Table 2 Mean iodine and hormone levels in samples

Variable	Maternal/Neonatal	Sampling site	Mean \pm SD	Range
Iodine	Maternal		29.06 \pm 45.88	5.58–276.01
		Amnion fluid (μ L)	182.80 \pm 446.51	16.87–2658.55
		Urine (μ L)	498.35 \pm 708.34	37.38–3652.7
TSH (mIU/L)	Neonatal	Blood at first hour	32.41 \pm 13.96	3.02–58.34
		Blood after 24 h	8.46 \pm 5.37	1.6–24.98
	Maternal	Umbilical cord	4.84 \pm 1.61	1.96–9.63
		Blood	2.1 \pm 1.58	0.83–8.91
fT4 (ng/dL)	Neonatal	Blood at first hour	1.59 \pm 0.27	1.2–2.48
		Blood after 24 h	2.20 \pm 0.44	1.3–3.16
	Maternal	Umbilical cord	1.23 \pm 0.23	0.85–1.79
		Blood	0.88 \pm 0.22	0.88–1.99
fT3 (pg/dL)	Neonatal	Blood at first hour	3.68 \pm 0.73	1.59–4.96
		Blood after 24 h	3.62 \pm 0.79	0.59–5.19
	Maternal	Umbilical cord	1.80 \pm 0.40	1.36–3.55
		Blood	3.01 \pm 0.42	2.32–4.96
HCG (mIU/mL)	Neonatal	Blood at first hour	30.66 \pm 18.55	3.80–80.95
		Blood after 24 h	13.43 \pm 10.88	1.53–38.94
	Maternal	Umbilical cord	30.48 \pm 30.81	4.89–190.69
		Blood	11,999.50 \pm 10,143	125.4–36.745
LH (mU/mL)	Neonatal	Blood at first hour	0.56 \pm 0.40	0.0–1.65
		Blood after 24 h	0.27 \pm 0.28	0.0–1.38
	Maternal	Umbilical cord	0.37 \pm 0.60	0.0–3.36
		Blood	0.19 \pm 0.14	0.0–0.78
FSH (mU/mL)	Neonatal	Blood at first hour	0.42 \pm 0.23	0.04–1.37
		Blood after 24 h	0.32 \pm 0.24	0.0–1.18
	Maternal	Umbilical cord	0.23 \pm 0.20	0.0–0.86
		Blood	0.09 \pm 0.34	0.0–2.1
PRL (ng/mL)	Neonatal	Blood at first hour	351.16 \pm 97.60	118.23–566.54
		Blood after 24 h	385.49 \pm 175.48	127.86–1332.12
	Maternal	Umbilical cord	349.29 \pm 121.81	101.23–567.37
		Blood	222.67 \pm 163.49	45.34–630.65
Cortisol (μ dL)	Neonatal	Blood at first hour	17.17 \pm 5.80	3.10–29.32
		Blood after 24 h	8.00 \pm 3.72	1.14–16.1
	Maternal	Umbilical cord	5.02 \pm 1.92	1.45–13.36
		Blood	23.92 \pm 8.47	3.31–39.32

\pm SD standart deviation *TSH* thyrois stimulating hormone, *HCG* human chorionic gonadotropin hormone, *LH* luteinizing hormone, *FSH* follicule stimulating hormone, *PRL* prolactin

(3.02–58.34). The mean value of neonatal HCG1 (at the first hour) was found to be 30.66 \pm 18.55 mIU/mL. Table 2 also provides the iodine and hormonal values in all samples.

None of the perinatal factors including maternal weight, height, placental weight, Apgar scores, birth length, birth weight, and birth order had a significant association with the TSH1 peaks in three groups according to TSH1 levels (Table 3). There was a weak correlation of the TSH1 peaks with birth order, placental weight, and maternal urine iodine levels ($r=0.310$, $p=0.394$; $r=0.313$, $p=0.648$).

There was a significant difference between the three groups (low, moderate, and high TSH surge levels)

regarding neonatal TSH1, HCG1, and placental iodine levels ($p < 0.001$ for each variable) (Table 4). The mean values between the three groups (low, moderate, and high groups according to TSH1 levels, respectively) were, for TSH1: 12.09 \pm 7.86 mIU/mL (5.3–19.2), 30.46 \pm 5.47 mIU/mL (23.5–38.7), and 48.06 \pm 5.71 mIU/mL (40.45–58.3), for HCG1: 11.28 \pm 5.17 mIU/mL (3.8–18.3), 29.75 \pm 14.56 mIU/mL (7.89–67.1), and 44.07 \pm 18.99 mIU/mL (5.12–80.95), for and placental iodine: 82.30 \pm 87.00 μ g/kg (49.01–276.03), 20.10 \pm 13.6188 μ g/kg (6.85–69.48), and 10.75 \pm 8.7988 μ g/kg (5.58–38.85) (Fig. 2). Figure 3 shows the comparisons of each group to

Table 3 Perinatal factors in three groups according to TSH peak level at first hour

Variable	TSH (Mean \pm SD)			<i>p</i>
	0–19.9 (<i>n</i> = 8)	20–39.9 (<i>n</i> = 21)	≥ 40 (<i>n</i> = 13)	
Maternal				
Age (year)	26.5 \pm 5.20	27.9 \pm 7.00	26.5 \pm 5.86	0.769
Height (cm)	161.37 \pm 7.13	158.80 \pm 6.93	161.76 \pm 7.04	0.434
Weight (kg)	82.87 \pm 10.09	79.61 \pm 15.01	72.61 \pm 11.08	0.177
BMI (kg/m ²)	31.97 \pm 4.54	31.45 \pm 4.74	27.76 \pm 3.98	0.05
Placental				
Weight (gr)	493.75 \pm 59.76	524.04 \pm	517.69 \pm 93.80	0.680
Volume (cm ³)	480.00 \pm 64.36	515.23 \pm 64.90	517.45 \pm 70.96	0.544
Neonatal				
Girl/Boy (<i>n</i>)	3/5	12/9	5/8	0.652
Weight (kg)	3087.50 \pm 396.18	3133.33 \pm 344.24	3168.46 \pm 324.31	0.883
Length (cm)	49.62 \pm 1.18	49.76 \pm 0.99	50.38 \pm 1.12	0.186
Birth order (<i>n</i>)				
First	0	4	3	0.105
Second or later	4	6	4	0.740
Third or later	4	11	6	0.156
Apgar score at 1minute	7.02 \pm 0.56	7.05 \pm 0.43	7.06 \pm 0.02	0.789
Apgar score at 5minute	9.56 \pm 0.66	9.44 \pm 0.67	9.21 \pm 0.73	0.682

Kruskal–Wallis test and chi square tests were used depend on variable. *p* value is significant at $p < 0.05$
TSH level mIU/mL, *BMI* body mass index

the others (low–moderate, low–high, and moderate–high) and the differences between the means of the TSH1, HCG1, and placental iodine.

One of the study's most important findings is that there is an inverse relationship between the TSH1 peak and placental iodine levels ($r = -0.763$, $p < 0.001$) (Fig. 4, Table 5). There was no correlation between the mean levels of the AF and urine iodine and the mean TSH1 peaks ($r = -0.133$, $p = 0.696$, $r = -0.036$, $p = 0.816$, respectively). While TSH1 peaks were not correlated with umbilical cord TSH ($r_{\text{umbilicalTSH}} = 0.151$, $p = 0.339$), it was correlated with neonatal and umbilical PRL levels ($r_{\text{neonatalPRL}} = 0.282$, $p = 0.092$; $r_{\text{umbilicalPRL}} = 0.455$, $p = 0.011$) (Table 5).

Another important finding of the study is that there is a correlation between placental iodine levels and neonatal HCG1 levels (Fig. 5). A very strong inverse correlation was found between the mean levels of neonatal HCG1 and placental iodine ($r_{\text{HCG-pliodine}} = -0.919$, $p < 0.001$) (Fig. 5) (Table 5). There is a similar relationship between both neonatal TSH1 and HCG1 levels and other variables (with iodine and PRL levels) (Table 5).

Neonatal PRLs had a weak but positive correlation with levels of TSH1 and HCG1 ($r_{\text{PRL-TSH1}} = 0.282$, $p = 0.890$ and $r_{\text{PRL-HCG}} = 0.340$, $p = 0.027$), and there were positive moderate correlations between the mean TSH1–TSH24 and HCG1–HCG24 levels ($r_{\text{TSH1-TSH24}} = 0.552$ versus $r_{\text{HCG1-HCG24}} = 0.583$, respectively).

Discussion

This study focused on the pivotal role of placental iodine content as a driving force in remarkable surges in TSH levels that reflect the efforts to adapt in the transition from intrauterine to extrauterine life after birth. It has been shown that thyroid glands and hormones have throughout the course of history pursued an evolutionary pathway that contributes to the adaptation to the transition from iodine-rich aquatic life to iodine-deficient terrestrial life in terms of structure and function [2]. The results of this study suggest that the dynamic fluctuation in TSH levels during the perinatal period reflects the ontogenetic heritage from evolutionary processes that have emerged for iodine regulation.

The present study was established by designing a homogeneous population, as much as was possible, with regard to potential perinatal factors associated with neonatal TSH to measure iodine influence. All newborns had birth weights of 2600–3900 gm and none were exposed to perinatal asphyxia. In this study, no difference was found in terms of perinatal factors in the three groups classified by the TSH peak levels. Previous studies have reported contradictory results in terms of perinatal factors [7–9]. To our knowledge, there has been no previous report investigating the relationship between placental iodine levels and neonatal TSH peaks. Therefore, it is still unclear from previous studies that found a relationship between perinatal risk factors, including perinatal asphyxia and neonatal TSH peaks, whether the placental

Table 4 Comparison of maternal derived-iodine levels and pregnancy-related hormone peak levels at the first hour after delivery according to the neonatal TSH peak levels

Variable	Maternal/Neonatal	Sampling localization	TSH peak level (IU/ml)			<i>p</i>
			Low 0–19.9 (<i>n</i> = 8)	Moderate 20–39.9 (<i>n</i> = 21)	High ≥ 40 (<i>n</i> = 13)	
Iodine	Maternal	Placenta	82.30 ± 87.00	20.10 ± 13.61	10.75 ± 8.79	< 0.001
		Amnion fluid	224.07 ± 296.63	127.09 ± 236.49	247.08 ± 725.01	0.727
		Urine	442.17 ± 495.48	352.13 ± 282.02	768.42 ± 1148.25	0.247
TSH	Neonatal	Blood after 24 h	12.09 ± 7.86	30.46 ± 5.47	48.06 ± 5.71	< 0.001
	Maternal	Umbilical cord	3.53 ± 1.08	4.93 ± 1.14	5.51 ± 2.09	0.019
fT4	Neonatal	Blood	2.61 ± 2.59	1.97 ± 1.49	2.02 ± 0.80	0.612
		Blood at first hour	1.56 ± 0.22	1.64 ± 0.26	1.52 ± 0.30	0.392
		Blood after 24 h	2.26 ± 0.59	2.31 ± 0.40	1.98 ± 0.34	0.106
fT3	Maternal	Umbilical cord	1.39 ± 0.21	1.19 ± 0.23	1.18 ± 0.23	0.084
		Blood	0.93 ± 0.12	0.88 ± 0.30	0.84 ± 0.09	0.678
		Blood at first hour	3.42 ± 0.79	3.89 ± 0.69	3.51 ± 0.72	0.185
hCG	Neonatal	Blood after 24 h	3.64 ± 0.91	3.55 ± 0.84	3.72 ± 0.67	0.840
		Blood	1.75 ± 0.18	1.74 ± 0.18	1.93 ± 0.69	0.412
		Blood at first hour	3.00 ± 0.30	3.03 ± 0.51	2.97 ± 0.25	0.902
LH	Maternal	Umbilical cord	11.28 ± 5.17	29.75 ± 14.56	44.07 ± 18.99	< 0.001
		Blood	7.40 ± 2.70	11.29 ± 8.03	20.61 ± 13.26	0.005
		Blood after 24 h	26.93 ± 19.62	25.45 ± 19.36	40.72 ± 47.86	0.359
FSH	Neonatal	Umbilical cord	12,540 ± 11,690	11,954 ± 8875	11,739 ± 11,844	0.985
		Blood	0.65 ± 0.38	0.47 ± 0.39	0.67 ± 0.42	0.309
		Blood after 24 h	0.35 ± 0.30	0.26 ± 0.32	0.22 ± 0.21	0.620
PRL	Maternal	Umbilical cord	0.24 ± 0.56	0.26 ± 0.75	0.16 ± 0.15	0.464
		Blood	0.17 ± 0.10	0.18 ± 0.13	0.23 ± 0.19	0.564
		Blood at first hour	0.571 ± 0.34	0.345 ± 0.18	0.461 ± 0.19	0.056
Cortisol	Neonatal	Blood after 24 h	0.561 ± 0.01	0.363 ± 0.21	0.302 ± 0.14	0.032
		Blood	0.24 ± 0.22	0.26 ± 0.24	0.16 ± 0.15	0.464
		Blood at first hour	0.02 ± 0.02	0.05 ± 0.10	0.19 ± 0.54	0.378
Cortisol	Neonatal	Blood at first hour	310.00 ± 38.23	352.47 ± 113.34	372.76 ± 92.95	0.363
		Blood after 24 h	433.62 ± 368.75	366.19 ± 80.61	387.06 ± 113.41	0.662
		Umbilical cord	269.40 ± 105.39	357.05 ± 125.30	385.92 ± 110.63	0.093
Cortisol	Maternal	Blood	330.99 ± 185.48	220.44 ± 167.71	159.61 ± 110.60	0.06
		Blood at first hour	13.40 ± 5.89	18.78 ± 6.03	16.92 ± 4.48	0.07
		Blood after 24 h	6.11 ± 3.80	8.78 ± 3.42	7.89 ± 3.99	0.228
Cortisol	Maternal	Umbilical cord	251.18 ± 1.55	357.05 ± 1.39	366.25 ± 2.72	0.07
		Blood	24.26 ± 9.68	21.73 ± 8.40	27.27 ± 7.24	0.180

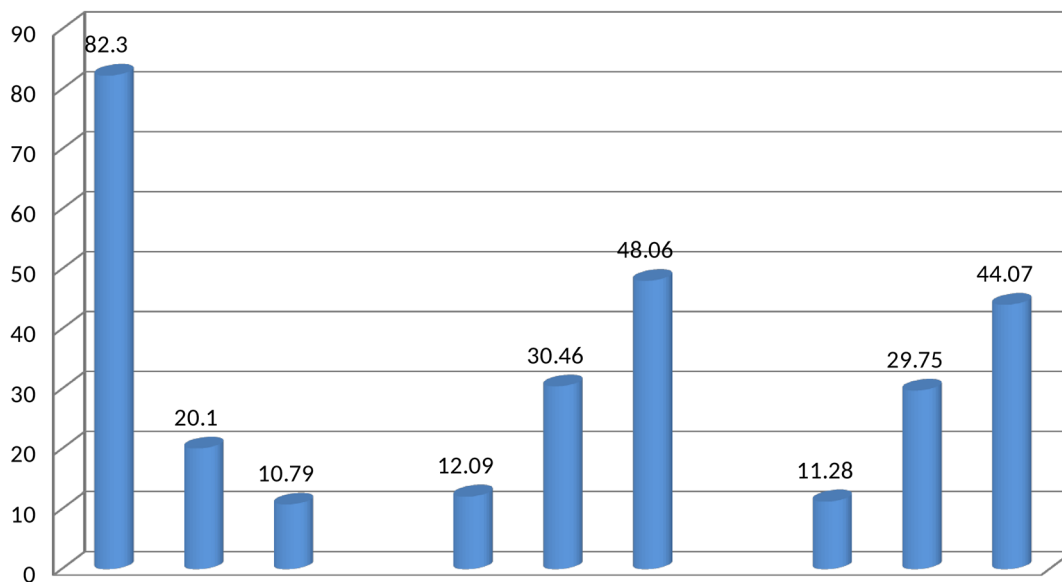
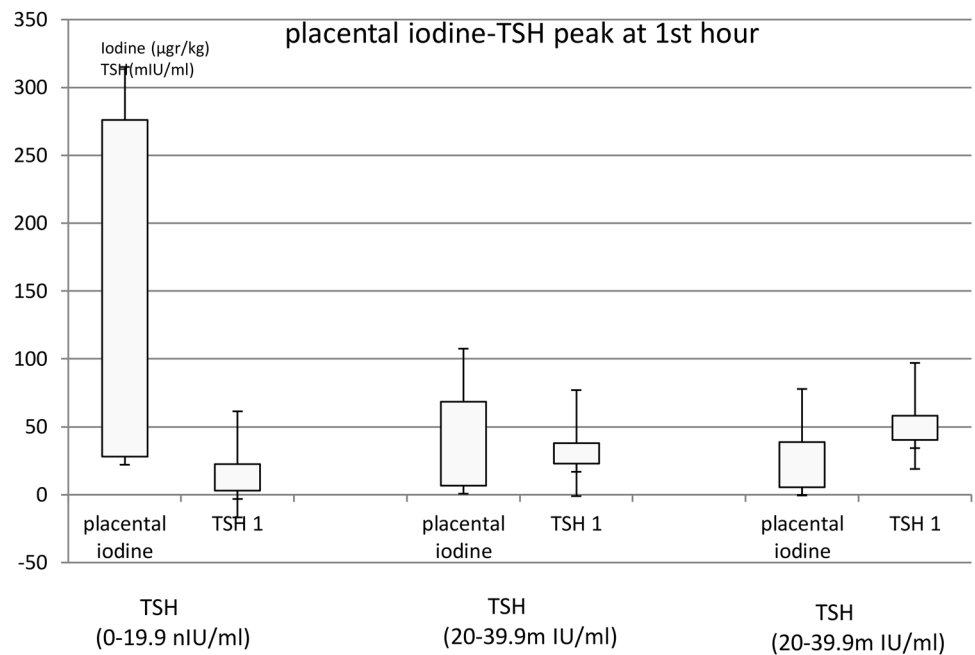
mean ± SD standard deviation

Kruskal Wallis test was used $p < 0.05$ is significant

iodine reserve had an influence on these results. Moreover, perinatal asphyxia leads to changes in placental iodine storage [13]. Oxygen acts as a signal for iodine regulation. Similarly, when mothers smoke, this causes changes in placental iodine regulation [14]. These findings suggest that the interaction between perinatal factors and neonatal TSH can be carried out through placental iodine regulation. When all perinatal factors in the groups were compared, there was

no difference between the three groups (low, moderate, and high). However, significant differences were found between the levels of the mean placental iodine, neonatal TSH1, and *ucTSH* and the neonatal HCG1 levels in each group. While neonatal TSH1 levels correlated with HCG1 levels in the same direction, TSH1 levels were found to have an inverse correlation with levels of placental iodine. This finding indicates that the neonatal TSH peak levels can be determined

Fig. 2 Mean levels of placental iodine and TSH surge according to TSH peak groups



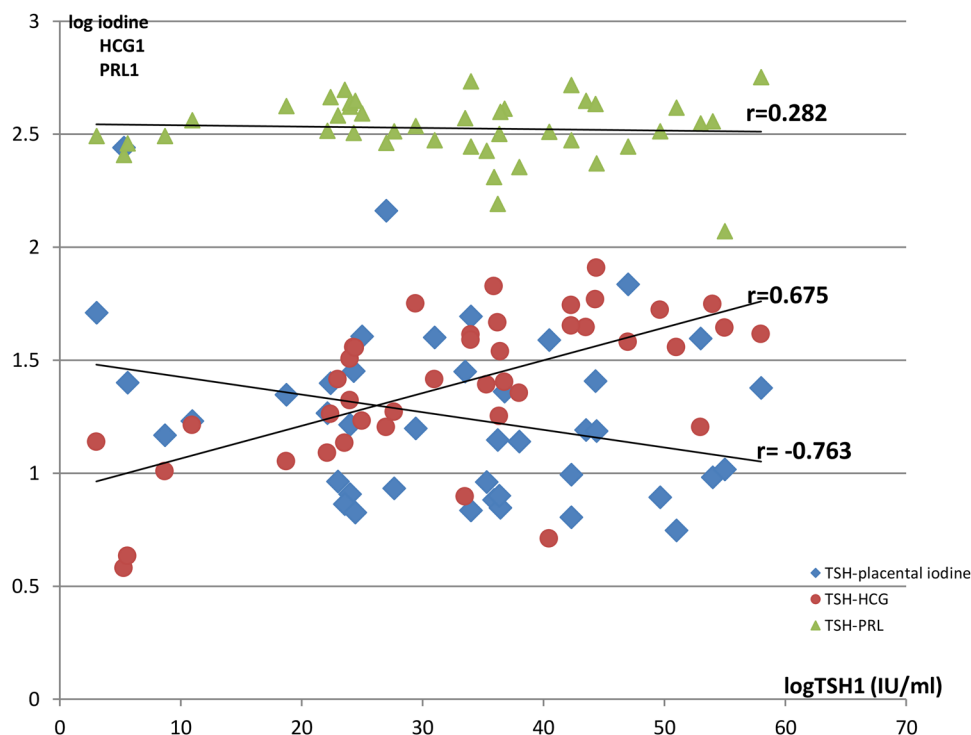
TSH peak level	P value		
Intergroup comparison	Placental iodine	TSH at 1st hour	HCG at 1st hour
Low/ Moderate	0.04	<0.001	<0.001
Low/High	0.01	<0.001	<0.001
Moderate/High	0.02	<0.001	0.003

Mann-Whitney U test was used. $p < 0.05$ is significant TSH (mIU/ml): thyroid stimulating hormone (low group: $TSH < 19.9$; moderate group $TSH: 20-39.9$; high group $TSH \geq 40$)

Figure 3: The mean of placental iodine, TSH and HCG levels between three groups according to TSH peak level at 1st hour

Fig. 3 Mean of placental iodine, TSH and HCG levels between three groups according to TSH peak level at 1st hour

Fig. 4 TSH correlations with placental iodine, HCG, and PRL at first minute after delivery. TSH1, HCG1, PRL1: at 1st hour



by placental iodine levels under conditions, where there are no perinatal risk factors.

One of the perinatal factors affecting neonatal TSH levels is the mode of delivery [15]. It is generally known that TSH levels in newborns delivered by cesarean section are lower than those delivered by normal vaginal delivery [16]. However, there are some previous studies that did not find any difference [17]. Even, some studies have reported higher TSH levels in newborns delivered with an elective cesarean section [18]. Moreover, there are studies reporting differences between elective-emergency cesarean section and spontaneous-instrumental vaginal deliveries [10]. These differences depending on the type of delivery are explained by the interaction between stress-cortisol and THs associated with vaginal delivery. Study designs investigating the relationship between delivery mode and neonatal TSH are always faced with some challenges, as they may coincide with other perinatal risk factors [19]. However, it seems that the mode of delivery alone, without other perinatal factors, does not significantly affect neonatal TSH levels, at least no requiring changes in TSH cutoff levels in screening programs [15, 17]. To clearly examine the relationship between neonatal TSH and placental iodine in the present study, all women were chosen from participants who underwent elective unlabored caesarean section following uncomplicated pregnancies at term.

This study found no significant correlation between iodine levels in AF and neonatal TSH1 peaks. Iodine levels in AF are reported as not being dependent on iodine intake

in the maternal diet [20]. In a previous study, it was reported that there was a positive correlation between amniotic and maternal urine iodine levels and neonatal TSH peaks [21]. However, the correlations in this study are not significant and weak ($r=0.170$, $p=0.01$, and $r=0.210$, $p=0.015$). The results show that the placental iodine level is the main determinant in iodine-thyroid regulation between the mother and the fetus rather than the amniotic fluid or urine. The present study showed that there was a moderate positive correlation between *ucTSH* and postpartum TSH1 levels ($r=0.548$, $p<0.001$). Although studies report that there is a relationship between urine iodine and AF iodine levels and *ucTSH*, those correlations were weak [21, 22]. Our findings show that umbilical cord TSH and neonatal TSH1 act in the same direction.

There is a well-known relationship between maternal iodine status and neonatal thyroid functions or congenital hypothyroidism. While congenital hypothyroidism is common in iodine-deficient countries, it has decreased in countries, where iodine replacement is applied to pregnant women [6]. However, the relationship between maternal dietary iodine intake and neonatal thyroid functions is not fully explained. While maternal excessively low iodine intake is expected to cause low TH biosynthesis in their newborns, it is reported that most of the newborns of these pregnant women do not present with a clear thyroid dysfunction symptoms [23]. On the other hand, a linear relationship could not be established between urinary iodine analyzes used to determine maternal iodine status and neonatal THs

Table 5 Correlation between logiodine, logTSH, logHCG, and logPRL each other

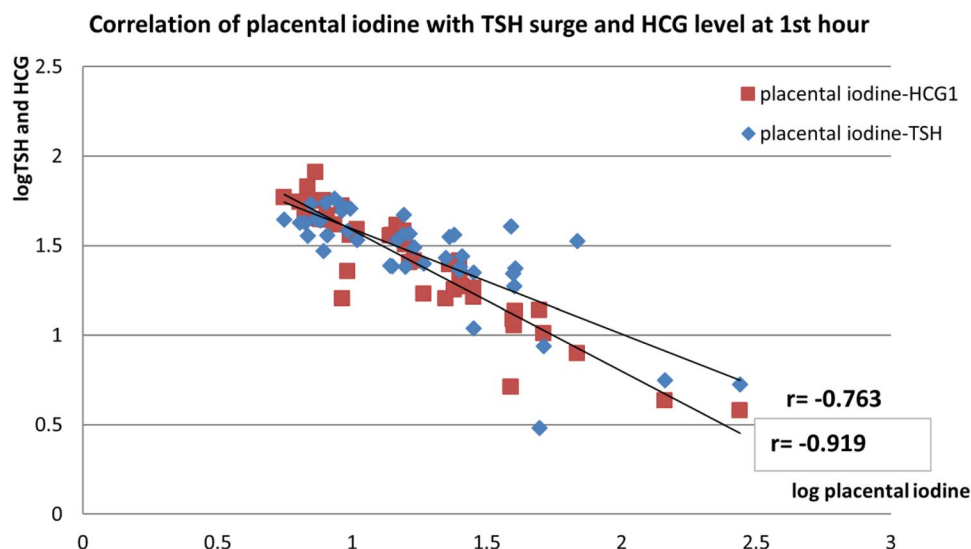
Variable	Iodine				HCG 1st hour			PRL 1st hour			
	Sample site	Correlations	Placental	Amnion fluid	Urine	Blood at 1st hour	Umbilical cord	Maternal	Blood at 1st hour	Umbilical cord	Maternal
TSH 1st hour		Correlation coefficient	-0.763	-0.133	-0.036	0.675	0.151	0.022	0.282	0.455	0.492
		Sig.(2-tailed)	<0.001*	0.696	0.816	<0.001*	0.339	0.890	0.092	0.011	<0.001*
TSH umbilical		Correlation coefficient	-0.510	0.037	0.046	0.538	-0.068	0.045	0.134	0.089	-0.281
		Sig.(2-tailed)	<0.001*	0.675	0.745	<0.001*	0.453	0.629	0.098	0.677	0.044
Iodine		Correlation coefficient	1	0.111	-0.07	-0.919	-0.08	-0.05	-0.312	-0.533	0.597
		Sig.(2-tailed)	<0.001*	0.428	0.659	<0.001*	0.618	0.753	0.044	<0.001*	<0.001*
HCG 1st hour		Correlation coefficient	-0.919	-0.006	-0.002	1	0.105	-0.019	0.340	0.557	-0.476
		Sig.(2-tailed)	<0.001*	0.705	0.989	<0.001*	0.508	0.904	0.027	<0.001*	<0.001*
PRL 1st hour		Correlation coefficient	-0.312	-0.196	-0.283	0.340	-0.93	0.079	1	0.548	-0.016
		Sig.(2-tailed)	0.044	0.213	0.069	0.027	0.558	0.618	<0.001*	<0.001*	0.919

Correlation is significance at the 0.05 level (2-tailed). *Correlation is significance at the 0.01 level (2-tailed)
TSH thyrois stimulating hormone, HCG human chorionic gonadotropin, PRL prolactin

levels [24–26]. Most of the studies did not found any relationship between maternal urinary iodine levels and neonatal TSH levels. Similar to these studies, the present study did not find a correlation between maternal urinary iodine and neonatal TSH levels at the 1st and 24th hours. Previous researches reveal that the placenta does not only provide the delivery of maternal iodine resources to the fetus, but also acts as a compensatory iodine storage organ that protects the fetus susceptible to iodine fluctuations in case of insufficient maternal iodine supplies [6]. The present study found a significant correlation between placental iodine content and neonatal TSH peak. The results of the present study confirm the role of placental iodine on TSH regulation.

One of the most important findings of the study is that there was a strong negative correlation between the postpartum TSH1 peaks and placental iodine levels ($r = -0.763$, $p < 0.001$). This finding suggests that the placental iodine content is the main driving force in determining perinatal TSH fluctuations. Although it is well known that the placenta plays an important role in iodine regulation throughout pregnancies, there are limited numbers of studies on iodine content within placental tissue [5, 12]. It is reported that the placenta is the largest organ following the thyroid gland to serve as an iodine reservoir. The placenta plays an important role in the uptake, storage, and fetal transport of the iodine that is required for thyroid hormone synthesis from the beginning of fetal implantation [27]. The placenta supplies the iodine and thyroid hormones that the fetus needs in the first half of pregnancy. It is known that sodium/iodide (Na/I) symporter pumps in the thyroid have also been found in the placenta [28]. Not only is iodine taken in by mothers who have sufficient diets, but it must also be transported to fetuses. Our study not only found that the placental iodine content did not correlate with the AF and maternal urine iodine levels but also showed a strong correlation with neonatal TSH levels. Developing fetuses are very sensitive to iodine fluctuations throughout the intrauterine period and have placenta iodine reservoirs as compensatory mechanisms that supply the fetal requirements. The placenta can be considered as "an iodine islet in the ocean within us," providing iodine-rich oceanic living circumstances throughout the intrauterine period. The results of our study reveal the clinical importance of placental iodine content. The higher the placental iodine content, the lower the neonatal TSH peak, and vice versa. Placental iodine storage determines the pattern of the TSH surge, contributing to adaptation in the transition from intrauterine to extrauterine life. The iodine content in the placenta may also play a role in determining the levels of TSH peak in newborns with varying perinatal risk factors. That is, the levels of the TSH peak are designed by the placental iodine levels. As a result, the TSH surge reflecting efforts to adapt to the transition from iodine-rich aquatics to iodine-deficient terrestrial life.

Fig. 5 Correlation of placental iodine with TSH and HCG levels at first hour. TSH1, HCG1: at 1st hour



Another important finding is that there is a very strong negative correlation between levels of placental iodine and neonatal HCG1 ($r = -0.919$, $p < 0.001$). Based on this, it seems that HCG acts in a similar direction to TSH1. HCG begins to be synthesized by the syncytiotrophoblasts immediately after the placental invasion [29]. HCG plays a critical role in fetoplacental iodine regulation and thyroid hormone support, especially during the first half of pregnancy. It is known that HCG increases iodine uptake over Na/I symporter expression. HCG levels are regulated by negative feedback with the iodine levels [30]. Postpartum neonatal HCG peak has a pattern similar to the TSH peak. In vitro studies have shown that the HCG response to iodine occurs within 3 days [31]. If the dramatic TSH peak postpartum reflects an effort to treat iodine deficiency, it may be asked, then, why it declines rapidly within days. The reason for this rapid decline may be the cessation of the placental support of HCG, a TSH stimulator after the umbilical cord is cut and the placenta is separated.

Another remarkable result of the study is that neonatal PRL1 also shows correlations similar to TSH1 and HCG1. Although the interaction of PRL1 in placental iodine regulation is unknown, it has been reported to increase Na/I symporter expression in the mammary glands and increase iodine uptake [32]. Given the correlation of PRL with HCG in the same direction, the same effect is likely to be on the placental iodine. The role of PRL in neonatal TSH regulation is not known enough.

There was a moderate positive correlation between *uc*TSH and TSH1 ($r = 0.548$, $p < 0.001$). In addition, *uc*TSH can provide predictions with the neonatal TSH1 peak. Investigations are reporting that umbilical TSH measurement is predictive in predicting perinatal risk factors [33, 34].

Conclusion

This study shows that although placental iodine levels demonstrate a strong inverse correlation with neonatal TSHs and HCGs, these levels have a weak but inverse correlation with PRL levels, and there are moderate-weak but positive correlations between the levels of HCG and PRL and the TSH levels. This indicates that HCG and PRL act in the same direction as TSH, which plays a primary role in adaptation to the transition from intrauterine to extrauterine life, and that placental iodine content is a pivotal player that drives the hormonal regulation that determines the course of neonatal TSHs.

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Author contributions Dr. Karaoglan conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. İsbilen analyzed placental iodine, studied hormone assays, collected and analyzed data.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

Ethical approval This research was approved by Gaziantep University Clinical Research Ethics Committee with decision no 2018/353;19.12.2018.

Research involving human participants and/or animals Authors declared that all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Authors declare that informed consent was obtained from all mothers for the study.

Consent for publication Mothers have signed an consent publication form to use their data and placental photos. We also declare that these forms were held by the treating institution.

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