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Research Article

Effect of perinatal asphyxia on thyroid hormones in neonates: A case – control study-Original research article

Ashish Priyadarshi[1], Piush Raj[2], Amit Shekharay[3], Mamta Kumari[4], Shitanshu Anand[5], A K Choudhary[6], Om Prakash Singh[7]

[1]*JR III, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram*
[2]*Senior resident, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram*
[3]*Assistant Professor, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram*
[4]*Assistant Professor, Pediatrics, Narayan Medical College and hospital, Jamuhar, Sasaram*
[5]*JR I, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram*
[6]*Professor, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram*
[7]*Professor, Pediatrics, Narayan Medical College and hospital, Jamuhar, Sasaram V K Mishra, Professor, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasarama.*

Abstract

Background: Perinatal asphyxia is a major contributor to neonatal morbidity and mortality worldwide. It results from impaired gas exchange during the perinatal period, leading to fetal hypoxia, hypercapnia, and metabolic acidosis. Among the various systems affected, the endocrine system—particularly the hypothalamic-pituitary-thyroid (HPT) axis—is notably vulnerable. Thyroid hormones play a critical role in early brain development, and disruption of thyroid function during the neonatal period may lead to adverse neurodevelopmental outcomes. Previous studies have shown that perinatal asphyxia can suppress thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels; however, data specific to this region remains limited. ***Objectives***: To evaluate the effect of perinatal asphyxia on thyroid function in neonates and to determine the prevalence of hypothyroidism and hyperthyroidism in affected newborns. ***Methodology***: This hospital-based case-control study was conducted over a period of 18 months in the neonatal intensive care unit (NICU) of Narayan medical college and hospital, Bihar. A total of 68 neonates were enrolled, including 30 with clinically diagnosed perinatal asphyxia (cases) and 38 without asphyxia (controls). Blood samples for TSH and fT4 were collected between 48– 72 hours of life and analyzed using standard laboratory protocols. Statistical analyses included the Mann–Whitney U test, Welch's t-test, and chi-square test, with a p-value < 0.05 considered statistically significant. ***Results***: Hypothyroidism was observed in 60% of asphyxiated neonates compared to 10.5% of controls. Median TSH levels were significantly lower in the asphyxiated group (1.38 mIU/L, IQR: 0.42–4.5) versus controls (10.4 mIU/L, IQR: 5.82–16.2) ($p < 0.001$ Mean fT4 levels were also significantly reduced in the asphyxiated group (27.2 ± 7.3 nmol/L) compared to controls (44.7 ± 12.3 nmol/L) ($p < 0.001$). Significant associations were found between hypothyroidism and factors such as male gender ($p = 0.006$), preterm and post-term gestation ($p < 0.001$), low birth weight (<2500 gm, $p = 0.047$), caesarean delivery ($p = 0.025$), and multigravida status ($p = 0.046$) among cases. ***Conclusion***: Perinatal asphyxia is significantly associated with suppression of thyroid function, as evidenced by reduced TSH and fT4 levels in the early neonatal period. This central hypothyroid response is particularly marked in neonates with additional risk factors such as prematurity, low birth weight, and operative delivery. Routine screening of thyroid hormones in neonates with perinatal asphyxia may facilitate early identification and timely intervention to prevent long-term neurodevelopmental sequelae.

Keywords: Hand dimension, anthropometry.

Introduction:

Perinatal asphyxia is a serious clinical condition defined by impaired gas exchange before, during, or just after birth, resulting in fetal hypoxemia, hypercarbia, and metabolic acidosis1. According to the World Health Organization, it is characterized by the failure to initiate and sustain breathing at birth2. The American Academy of Pediatrics and the American college of obstetricians and gynecologists further define it based on the presence of profound metabolic or mixed acidemia (umbilical cord pH < 7.0), persistence of apgar scores less than 3 beyond 5 minutes, evidence of neonatal neurological dysfunction (e.g., seizures, hypotonia, or encephalopathy), and involvement of multiple organ systems such as the kidneys, lungs, liver, heart, and gastrointestinal tract3.

Asphyxia remains a major contributor to global neonatal morbidity and mortality, ranking alongside prematurity and infections as one of the three leading causes of neonatal death, especially in low-resource settings4. The cascade of physiological changes following asphyxia includes redistribution of blood flow away from peripheral organs towards vital centres such as the brain, adrenal glands, and heart — a phenomenon known as the "diving reflex"5. While neurological manifestations are often the most apparent and concerning outcomes of perinatal asphyxia, they may overshadow concurrent impairments in other organ systems, including renal, hepatic, gastrointestinal, cardiovascular, and endocrine axes6.

The endocrine system, particularly the hypothalamic-pituitary-thyroid (HPT) axis, is notably susceptible to hypoxic-ischemic injury. Asphyxia has been shown to induce significant alterations in several hormonal axes including thyroid hormones, cortisol, insulin, antidiuretic hormone, aldosterone, and atrial natriuretic peptide7. Among these, thyroid hormone abnormalities are of special concern because of their critical role in early brain development. Thyroxine (T4) and triiodothyronine (T3) are vital for neuronal differentiation, synaptogenesis, myelination, and neuroplasticity, and any deficiency during this sensitive.

Address for Correspondence: Amit Shekharay, Assistant Professor, Pediatrics, Narayan Medical College and hospital Jamuhar, Sasaram. medico_amit4@rediffmail.com

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window can result in long-term neurodevelopmental deficits6. Multiple studies conducted across different populations have demonstrated that perinatal asphyxia is associated with significantly decreased levels of T3, T4, and thyroid-stimulating hormone (TSH), with a severity-dependent suppression of the HPT axis5,7–11. The pathophysiological mechanisms proposed include ischemic injury to the hypothalamus and anterior pituitary gland, leading to reduced secretion of TRH and TSH. Additionally, systemic inflammatory responses and oxidative stress are believed to inhibit peripheral conversion of T4 to T3 and disrupt thyroid hormone metabolism12. These changes often resemble the non-thyroidal illness syndrome (NTIS), which is characterized by transient hormonal suppression in critically ill neonates13.

Fetal thyroid function begins around the 20th week of gestation, although maternal thyroxine remains essential throughout pregnancy for optimal fetal neurodevelopment. The placenta facilitates the transfer of iodine, serving as a reservoir to support fetal thyroid hormone synthesis. Any disruption in this mechanism, particularly under hypoxic stress, can contribute to hormonal insufficiency14. Normally, the neonatal period is marked by a surge in TSH and T4 levels within the first 48 hours of life as part of extrauterine adaptation. However, in neonates affected by asphyxia, this hormonal surge is often absent or blunted, reflecting suppression of the central HPT axis15.

Although central congenital hypothyroidism provides insight into permanent HPT axis defects, most cases of thyroid suppression following perinatal asphyxia are transient. Nevertheless, distinguishing these from true congenital hypothyroidism is crucial, as untreated hypothyroxinemia during the neonatal period is associated with adverse neurodevelopmental outcomes16. Early identification through screening of serum TSH and free T4 levels—ideally within 48–72 hours of life—is therefore recommended for at-risk neonates15.

While several studies from India and other countries have explored thyroid profiles in asphyxiated neonates, findings vary due to differences in methodology, timing of sampling and regional demographics. However, literature specific to this region remains sparse. Hence, the present study is undertaken to evaluate the effect of perinatal asphyxia on thyroid hormone levels in neonates by analyzing serum TSH and free T4 values between 48–72 hours after birth. The aim was to contribute valuable insight into the endocrine implications of neonatal hypoxia and facilitate timely clinical interventions

Aims and objectives
To evaluate the effect of perinatal asphyxia on Thyroid hormones in Neonates.

Objectives

- To study the effect of perinatal asphyxia on thyroid function in newborn babies.
- To find out the prevalence of Hypothyroidism and hyperthyroidism in neonates with perinatal asphyxia.

Material and Methods:
Study Setting
The study was conducted in NICU, Department of Pediatrics, Narayan Medical College & Hospital, Jamuhar, Sasaram.
Study Design
Hospital based case – control study.

Study Duration
18 months (1st June 2023 to 30th December 2024).

Sample Size
The sample size for the study was calculated using G*Power software. A 5% level of significance (α = 0.05) and 95% confidence interval (power = 0.95) were considered, with an anticipated effect size of 0.90 and a case-to-control ratio of 0.8, based on findings from previous literature. Based on these parameters, the estimated sample size was 68 participants. Accordingly, the study included 30 neonates in the case group (with perinatal asphyxia) and 38 neonates in the control group (without perinatal asphyxia). A slightly larger sample was allocated to the control group to enhance the accuracy of comparative analysis, which is a common methodological approach in case-control studies to improve statistical power and account for population variability.
Study Population Selection of Cases Case Definition
WHO defines perinatal asphyxia failure to establish breathing at birth2, whereas as per the American Academy of Paediatrics and the American College of Obstetricians and Gynaecologists, the criteria for diagnosis includes the following14:

- Profound metabolic or mixed acidemia (pH < 7.0) in umbilical cord blood
- Persistence of Apgar score less than 3 for more than 5 minutes
- Signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities)
- Evidence of multiple organ involvement (e.g., kidneys, lungs, liver, heart, intestine)

Inclusion Criteria (Cases)
Neonates who failed to initiate and sustain breathing. Exclusion Criteria (Cases)

1. Maternal history of thyroid dysfunction.
2. Maternal history of antihypertensive and steroid intake.
3. False low APGAR due to maternal sedation.
4. Congenital malformations and metabolic disorders.

Selection of Controls
Source of Controls
Controls were neonates born without any history or clinical evidence of perinatal asphyxia in the Department of Obstetrics and Gynecology, NMCH, Jamuhar.

Sampling Technique
A consecutive sampling technique was used to enroll cases, with parallel recruitment of controls; additional controls were included subsequently to improve the accuracy and reliability of comparisons.

Type of intervention
No intervention was imparted as part of the study; it was purely observational.

Method of follow-up
No follow-up was conducted, as the study was limited to a single point of assessment in the early neonatal period

Study Procedure

This was a hospital-based case-control observational study conducted in the Neonatal Intensive Care Unit (NICU) of Narayan Medical College and Hospital, Jamuhar, Sasaram, Bihar, over a period of 18 months from 1st June 2023 to 30th November 2024. After obtaining ethical clearance, neonates admitted within the first 24 hours of life were screened and recruited based on predefined inclusion and exclusion criteria. Cases included neonates clinically diagnosed with perinatal asphyxia as per the American Academy of Paediatrics and the American College of Obstetricians and Gynaecologists criteria, while controls were neonates without any history or evidence of asphyxia, born in the Department of Obstetrics and Gynaecology, NMCH, Jamuhar.

A consecutive sampling technique was used to recruit eligible cases, with parallel inclusion of controls. Additional controls were subsequently enrolled to enhance the accuracy and reliability of statistical comparisons. The study was non-interventional and observational in nature, and no follow-up was undertaken beyond the initial assessment period.

Detailed maternal and neonatal data were recorded using a structured proforma. All enrolled neonates underwent thyroid function testing between 48 to 72 hours of life. Under aseptic precautions, 3 mL of venous blood was drawn and collected in yellow-top vacutainer tubes. Samples were appropriately labelled and transported to the laboratory within one hour for analysis of serum thyroid-stimulating hormone (TSH) and free thyroxine (free T4). Clinical assessment of the neonates included evaluation for

hypoxic-ischemic encephalopathy (HIE), neurological status, and the presence or absence of seizures

Reference Ranges for Thyroid Hormones in Neonates61

Hormone	Age Group	Reference Range (SI Units)
TSH (Thyroid Stimulating Hormone)	Premature Infants (28–36 weeks), 1st week of life	0.7 – 27.0 mIU/L
	Term Infants (Birth to 4 days)	1.0 – 17.6 mIU/L
Free T4 (Free Thyroxine)	Full Term (Day 3)	26 – 63.1 pmol/L
	Infants (General Range)	12 – 33 pmol/L

Abnormal results on initial screening were confirmed with repeat venous sampling and interpreted accordingly.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using Jamovi Solid Version 2.6.26. Continuous variables were assessed for normality by visual inspection of Q-Q plots. Normally distributed data were expressed as mean ± standard deviation (SD), while non-normally distributed data were summarized using median and interquartile range (IQR). Categorical variables were expressed as frequencies and percentages.

Group comparisons for continuous variables were performed using the Welch's t-test for normally distributed data with unequal variances (e.g., free T4), and the Mann–Whitney U test for non-parametric data (e.g., TSH levels). Comparisons between categorical variables such as gender, mode of delivery, gestational age, gravida status, and birth weight were performed using the Chi-square test of independence. When applicable, degrees of freedom (df) and P-values were reported. A P-value of less than 0.05 was considered statistically significant.

Effect size estimation was conducted during sample size calculation using G*Power software, where an effect size of 0.90, alpha level of 0.05, and power of 95% were assumed for group comparisons. A larger control group was included to increase the accuracy and reliability of estimates in the case-control framework. No imputation was done for missing data, and all analyses were based on complete-case observations.

RESULTS

Descriptive Analysis

Figure 1 Cases and controls distribution (N=68)

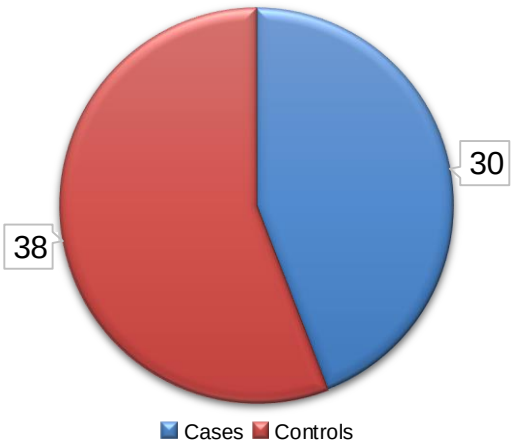

Table 1 Cases and controls distribution (N=68)

Table 1 Cases and controls distribution (N=68)

Group	Count (%)
Cases	30 (44%)
Controls	38 (66%)

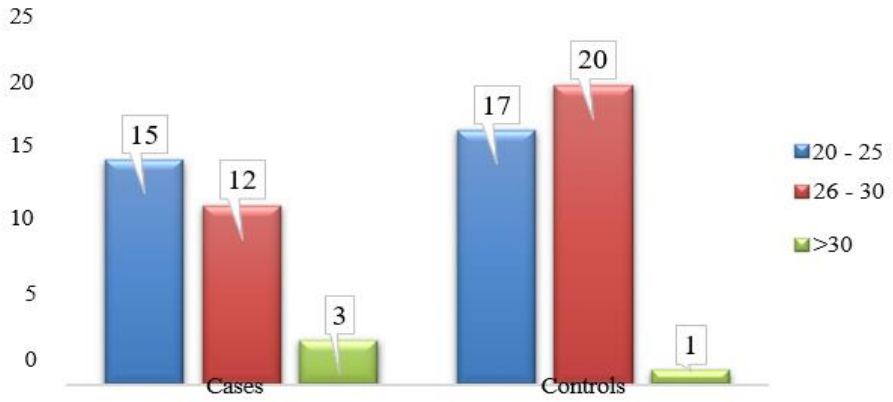

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Table 2 Maternal age categories across the group (N=68)

Maternal Age	Cases	Group	Control
20 - 25	15		17
26 - 30	12		20
>30	3		1

The maternal age distribution showed distinct patterns between cases (N=30) and controls (N=38). Among cases, 15 (50%) mothers were in the 20–25 years category, 12 (40%) in the 26–30 years category, and 3 (10%) in the >30 years category. In contrast, among controls, 17 (44.7%) mothers were in the 20–25 years category, 20 (52.6%) in the 26–30 years category, and 1 (2.6%) in the >30 years category (Figure 2, Table 2).

Figure 3 Period of gestation across the group (N=68)

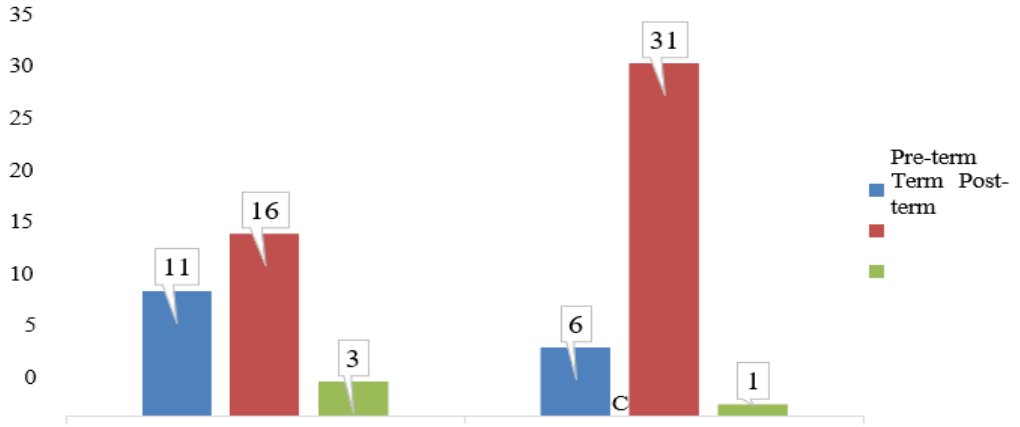


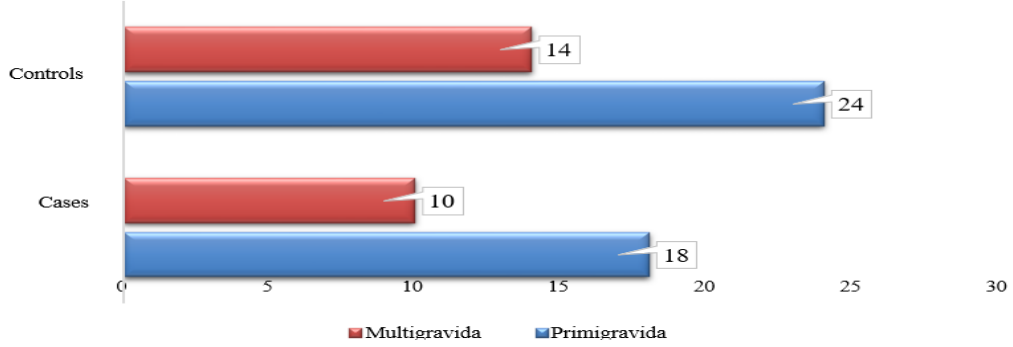
Table 3 Period of gestation across the group (N=68)

	Period of Gestation		
	Pre-term	Term	Post-term
Cases	11	16	3
Controls	6	31	1

Group

Among the cases (N=30), 11 (36.7%) were pre-term, 16 (53.3%) were term, and 3 (10%) were post-term. In the control group (N=38), 6 (15.8%) were pre-term, 31 (81.6%) were term, and 1 (2.6%) was post-term. Term gestation was the predominant category in both groups, with a significantly higher proportion in the control group (Figure 3, Table 3).

Figure 4 Gravida across the group (N=68)



Gravida	Cases	Control
Primigravida	18	24
Multigravida	10	14

Table 4 Gravida across the group (N=68) ***Group***

In the study population, among cases (N=30), 18 (60%) mothers were primigravida, and 10 (40%) were multigravida. In the control group (N=38), 24 (63.2%) mothers were primigravida, and 14 (36.8%) were multigravida. Primigravida mothers constituted the majority in both groups, with a slightly higher proportion observed in the control group (Figure 4, Table 4).

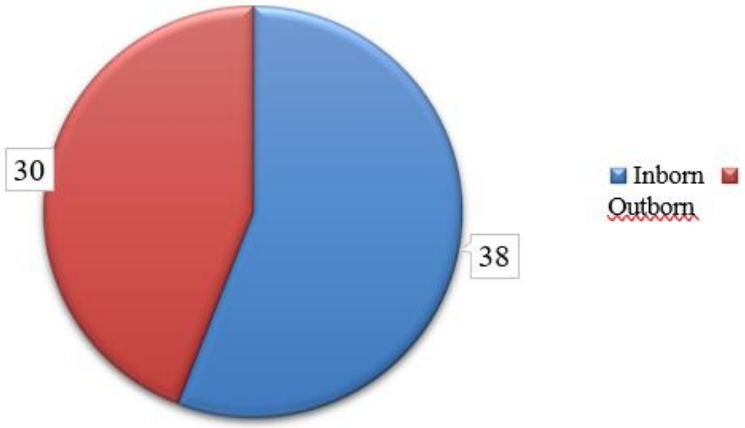
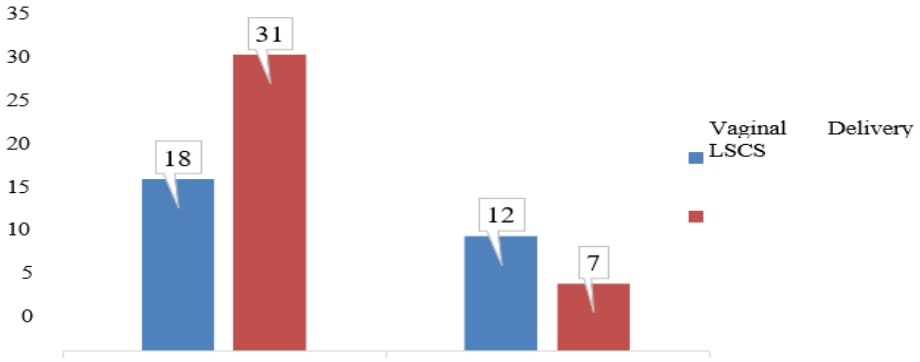


Table 5 Point of delivery (N=68)

Group	Count (%)
Inborn	38 (56%)
Out-born	30 (44%)

Figure 5 and Table 5 shows the point of delivery among the study population (N=68). Of the total neonates, 38 (56%) were inborn, meaning they were delivered at the study hospital, while 30 (44%) were out-born, indicating they were delivered elsewhere and admitted to the NICU at the study hospital.

Figure 6 Mode of delivery across the group (N=68)



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Delivery	Cases	Control
Vaginal Delivery	18	12
LSCS	31	17

Table 6 Mode of delivery across the group (N=68) ***Group***

Figure 6 and Table 6 illustrates the mode of delivery across the study groups (N=68). Among the cases (N=30), 18 (60%) were delivered via vaginal delivery, while 12 (40%) were delivered by lower segment caesarean section (LSCS). In contrast, among the controls (N=38), 31 (81.6%) were delivered by vaginal delivery, and only 7 (18.4%) were delivered by LSCS. The proportion of LSCS deliveries was higher in the case group compared to the control group.

Figure 7 Gender distribution of the newborns across the group (N=68)

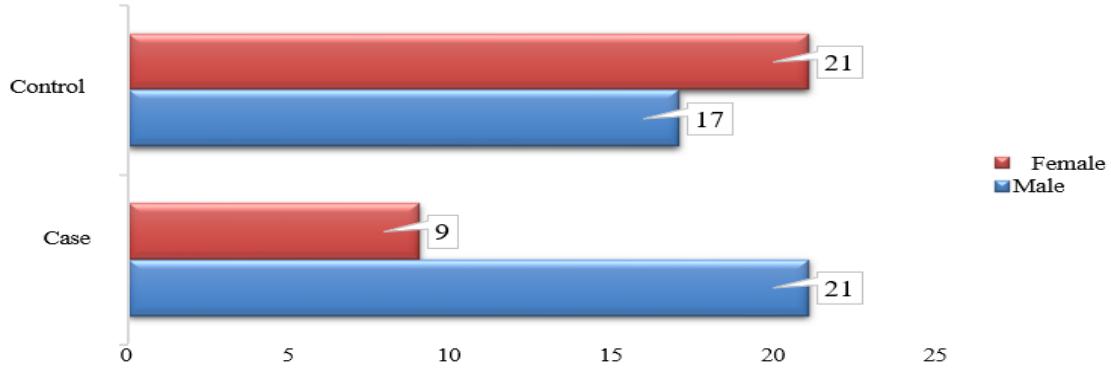

Table 7 Gender distribution of the newborns across the group (N=68)

Group Gender Cases	Control	
Male	21	17
Female	9	21

Figure 8 Birth weight (in gm) categories across the groups (N=68)

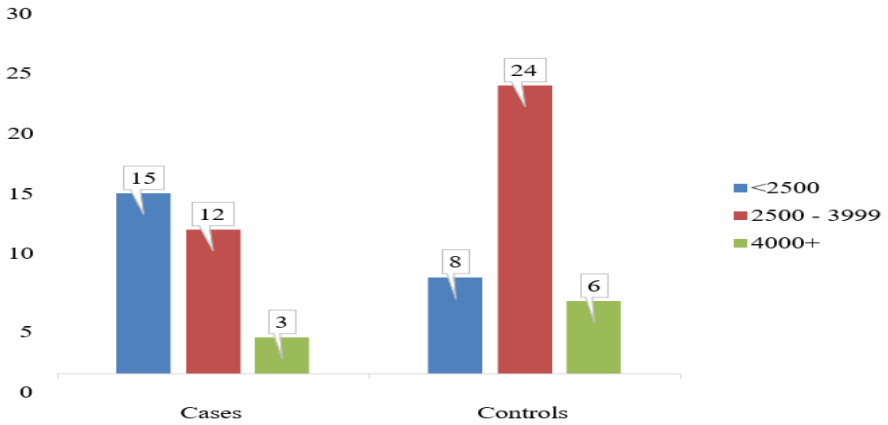

Table 8 Birth weight (in gm) categories across the groups (N=68)

	<2000	2500 - 3999	4000+
Cases	15	12	3
Controls	8	24	6

Birth Weight

Group

Birth weight distribution showed notable differences between the groups. In the case group (N=30), half of the newborns (15, 50%) weighed less than 2500 gm, followed by 12 (40%) in the 2500–3999 gm range, and 3 (10%) weighing 4000 gm or more. In contrast, the control group (N=38) had the majority of newborns, 24 (63.2%), in the 2500–3999 gm range, while 8 (21.1%) weighed less than 2500 gm, and 6 (15.8%) weighed 4000 gm or more. Low birth weight (<2500 gm) was predominantly observed in the case group, whereas most controls fell within the 2500–3999 gm range (Figure 8, Table 8).

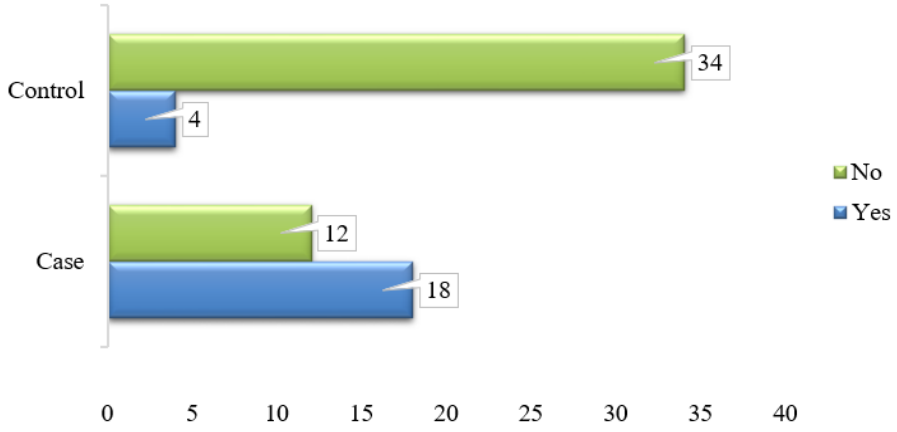

Table 9 Hypothyroidism in newborns across the group (N=68)

	Hypothyroidism Group	
	Yes	No
Cases	18	12
Controls	4	34

Figure 9 and Table 9 present the distribution of hypothyroidism among neonates with and without perinatal asphyxia. In the case group (N = 30), which included neonates with perinatal asphyxia, 18 (60%) were found to have hypothyroidism, while 12 (40%) had normal thyroid function. In contrast, among the control group (N = 38) without asphyxia, only 4 neonates (10.5%) exhibited hypothyroidism, while the remaining 34 (89.5%) were euthyroid. Notably, no cases of hyperthyroidism were observed in either group. These findings highlight a significantly higher incidence of hypothyroidism in neonates with perinatal asphyxia compared to those without, suggesting a strong association between hypoxic insult and central suppression of thyroid function.

Inferential Analysis

Table 10 Association between gender and hypothyroidism across the group (N=68)

Group	Gender	Hypothyroidism		χ2 (df), P-value
		Yes	**No**	
Case	Male	16	7	
	Female	2	5	7.64 (1), 0.006
	Total	18	12	
Control	Male	2	19	
	Female	2	15	0.05 (1), 0.823
	Total	4	34	

In the case group (neonates with perinatal asphyxia), there was a significant association between gender and hypothyroidism ($\chi^2 = 7.64$, df = 1, P = 0.006). Among male neonates, 16 (69.6%) had hypothyroidism, while 7 (30.4%) did not. In contrast, only

2 (28.6%) female neonates had hypothyroidism, and 5 (71.4%) did not.

In the control group (neonates without perinatal asphyxia), no significant association was observed between gender and hypothyroidism ($\chi^2 = 0.05$, df = 1, P = 0.823). Among male neonates, 2 (9.5%) had hypothyroidism, while 19 (90.5%) did not. Similarly, among female

neonates, 2 (11.8%) had hypothyroidism, while 15 (88.2%) did not.

These findings indicate a higher prevalence of hypothyroidism in male neonates within the case group, while no such pattern was observed in the control group.

Table 11 Association between maternal age and hypothyroidism across the group (N=68)

Group	Maternal Age	Hypothyroidism Yes	Hypothyroidism No	χ2 (df), P-value
Case	20 - 25	9	6	
	26 - 30	6	6	
	>30	3	0	
	Total	18	12	
Control	20 - 25	1	16	0.93 (2), 0.628
	26 - 30	3	17	
	>30	0	1	
	Total	4	34	

Maternal age did not show a significant association with hypothyroidism in either group. In the 20–25 years category, hypothyroidism was observed in 60% of newborns in the case group, compared to only 5.9% in the control group. Similarly, in the 26–30 years category, 50% of newborns in the case group had hypothyroidism, while the proportion in the control group was 15%. Notably, all newborns of mothers aged over 30 years in the case group had hypothyroidism, whereas none of the newborns of mothers in this category in the control group were affected.

Although the proportion of hypothyroidism appeared higher in mothers older than 30 years in the case group, the differences across maternal age categories were not statistically significant, with P = 0.287 for cases and P = 0.628 for controls. These findings suggest that maternal age, while showing some trends, did not have a definitive impact on the occurrence of hypothyroidism in either group.

Table 12 Association between period of gestation and hypothyroidism across the group (N=68)

Group	POG	Hypothyroidism Yes	Hypothyroidism No	χ2 (df), P-value
Case	Pre-term	11	0	17.5 (2), <0.001
	Term	4	12	
	Post-term	3	0	
	Total	18	12	
Control	Pre-term	3	3	33 (2), <0.001
	Term	1	30	
	Post-term	0	1	
	Total	4	34	

A significant association was observed between the period of gestation and hypothyroidism in both groups (P < 0.001). In the case group, hypothyroidism was most frequent among pre- term and post-term newborns. All pre-term (11, 100%) and post-term (3, 100%) cases had hypothyroidism. Among term cases, only 4 (25%) were hypothyroid, while 12 (75%) were not.
In the control group, the majority of hypothyroidism cases were also observed among pre- term newborns. Of the 6 pre-term controls, 3 (50%) were hypothyroid, and 3 (50%) were not. For term newborns, hypothyroidism was rare, with only 1 (3.2%) being hypothyroid compared to 30 (96.8%) who were not. Among post-term controls, none were hypothyroid.
The findings indicate that pre-term and post-term gestations are associated with a higher prevalence of hypothyroidism, while term gestation is linked to a lower prevalence in both groups. The association is particularly striking in the case group, where hypothyroidism was universally present in pre-term and post-term newborns.

Table 13 Association between mode of delivery and hypothyroidism across the group (N=68)

	MoD	Hypothyroidism Group		χ2 (df), P-value
		Yes	No	
	Vaginal Delivery	6	9	
Case	LSCS	12	3	5 (1), 0.025
	Total	18	12	
Control	Vaginal Delivery	3	28	
	LSCS	1	6	0.13 (1), 0.720
	Total	4	34	

In the case group, hypothyroidism was significantly associated with the mode of delivery (P = 0.025), with a higher prevalence among newborns delivered via LSCS (80%) compared to Vaginal Delivery (40%). In the control group, there was no significant association between mode of delivery and hypothyroidism (P = 0.720), as hypothyroidism was observed in a

small proportion of both Vaginal Delivery (9.7%) and LSCS (14.3%) deliveries.

Table 14 Association between gravida and hypothyroidism across the group (N=68)

Group	Gravida	Hypothyroidism		χ2 (df), P-value
		Yes	No	
Case	Primi	6	9	
	Multi	12	3	3.9 (1), 0.046
	Total	18	12	
Control	Primi	3	28	
	Multi	1	6	2.8 (1), 0.09
	Total	4	34	

Gravida status showed a significant association with hypothyroidism among newborns with perinatal asphyxia (P = 0.046) but not in those without it (P = 0.09). In the case group, hypothyroidism was more frequent in newborns of multigravida mothers (80%) compared to those of primigravida mothers (40%). In the control group, the prevalence of hypothyroidism was low in both primigravida (9.7%) and multigravida (14.3%) mothers. These findings highlight a potential link between multigravida status and hypothyroidism in the context of perinatal asphyxia.

Table 15 Association between birth weight and hypothyroidism across the group (N=68)

Group	Gravida	Hypothyroidism		χ2 (df), P-value
		Yes	No	
Case	<2500	12	3	
	2500 - 3999	4	8	
	≥4000	2	1	6.1 (2), 0.047
	Total	18	12	
Control	<2500	3	5	
	2500 - 3999	1	23	
	≥4000	0	6	
	Total	4	34	7.9 (2), 0.019

Birth weight showed a significant association with hypothyroidism in both groups. In the case group (P = 0.047), hypothyroidism was most common among newborns weighing less than 2500 gm (80%), while it was less frequent in those weighing 2500–3999 gm (33.3%) and ≥4000 gm (66.7%). In the control group (P = 0.019), hypothyroidism was also more prevalent in newborns with a birth weight of less than 2500 gm (37.5%). However, hypothyroidism was rare in those weighing 2500–3999 gm (4.2%), and no cases of hypothyroidism were observed in newborns weighing ≥4000 gm. These findings suggest that lower birth weight is strongly associated with a higher prevalence of hypothyroidism in both newborns with and without perinatal asphyxia, with the effect being more pronounced in the case group.

Table 16 Descriptive statistics of thyroid stimulating hormone (TSH) across the group (N=68)

Group	TSH Median (IQR)	Mann-Whitney statistic, P - value
Cases	1.38 (0.42 – 4.5)	142, <0.001
Controls	10.4 (5.82 – 16.2)	

Thyroid Stimulating Hormone (TSH) levels showed a significant difference between the two groups (P < 0.001). The case group, consisting of newborns with perinatal asphyxia, had a markedly lower median TSH level of 1.38 mIU/L (IQR: 0.42–4.5). In contrast, the control group exhibited a much higher median TSH level of 10.4 mIU/L (IQR: 5.82–16.2). This stark difference, confirmed by the Mann-Whitney U test, underscores the impact of perinatal asphyxia on thyroid function, suggesting a possible suppression of TSH levels in affected neonates.

Table 17 Distribution of free thyroxine (FT4) across the group (N=68)

Group	T4 Mean ± SD	Welch t statistic, P - value
Cases	27.2 ± 7.3	7.3, <0.001
Controls	44.7 ± 12.3	

Table 17 presents the descriptive statistics of free thyroxine (FT4) levels across the groups. The mean T4 level was significantly lower in the case group (27.2 ± 7.3 nmol/L) compared to the control group (44.7 ± 12.3 nmol/L), with a Welch t-statistic of 7.3 and a P value of <0.001. This significant difference highlights the impact of perinatal asphyxia on thyroid function, as evidenced by reduced T4 levels in affected neonates.

Results

- In this study, a total of 68 neonates were enrolled, comprising 30 cases with clinically diagnosed perinatal asphyxia and 38 controls without asphyxia (Figure 1, Table 1).
- The prevalence of hypothyroidism was markedly higher in the case group (60%) compared to the control group (10.5%), with no cases of hyperthyroidism reported in either group (Figure 9, Table 9).
- Median TSH levels were significantly suppressed in the case group at 1.38 mIU/L (IQR: 0.42–4.5) compared to 10.4 mIU/L (IQR: 5.82–16.2) in controls (P < 0.001, Mann– Whitney U test) (Table 16).
- Mean free thyroxine (fT4) was significantly lower in the asphyxiated neonates (27.2 ± 7.3 nmol/L) than in controls (44.7 ± 12.3 nmol/L), with a Welch t-statistic of 7.3 and P <
- A statistically significant association between gender and hypothyroidism was observed in the case group, where 69.6% of male neonates were hypothyroid compared to 28.6% of females (P = 0.006). No such association was noted in the control group (Figure 7, Table 10).
- Maternal age did not show a statistically significant association with neonatal hypothyroidism in either group (P = 0.287 for cases and P = 0.628 for controls), though all newborns of mothers aged >30 years in the case group were hypothyroid (Figure 2, Table 11).
- A significant association was found between period of gestation and hypothyroidism in both groups (P < 0.001). Among asphyxiated neonates, all preterm and post-term babies (100%) were hypothyroid, while only 25% of term neonates had hypothyroidism (Figure 3, Table 12).
- Mode of delivery showed a significant association with hypothyroidism in the case group (P = 0.025). Among LSCS deliveries, 80% of neonates were hypothyroid compared to 40% in the vaginal delivery subgroup. This pattern was not significant in the control group (Figure 6, Table 13).
- A statistically significant association between gravida and hypothyroidism was found in the case group (P = 0.046), with 80% of neonates born to multigravida mothers affected
- versus 40% from primigravida mothers. The trend was not significant in the control group (Figure 4, Table 14).

- Birth weight was significantly associated with hypothyroidism in both groups. In the case group, 80% of neonates weighing <2500 gm were hypothyroid, compared to 33.3% in the 2500–3999 gm group and 66.7% in ≥4000 gm group (P = 0.047). In the control group, hypothyroidism was seen in 37.5% of those <2500 gm and none in those ≥4000 gm (P = 0.019) (Figure 8, Table 15).
- The study observed no statistically significant association between maternal age and thyroid dysfunction, despite a visible trend of increased hypothyroidism in neonates of mothers aged above 30 years.
- The timing of thyroid hormone sampling within the first 48–72 hours of life allowed early detection of axis suppression, before compensatory recovery phases or delayed transient changes could influence the measurements.

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Discussion

This case-control study was conducted to determine the influence of perinatal asphyxia on neonatal thyroid function through early postnatal measurement of serum thyroid-stimulating hormone (TSH) and free thyroxine (fT4). A total of 68 neonates were evaluated, including 30 asphyxiated neonates and 38 healthy controls. The primary outcome demonstrated a significantly suppressed hormonal profile in the asphyxiated group. The median TSH level in cases was markedly reduced to 1.38 mIU/L (IQR: 0.42–4.5) compared to 10.4 mIU/L (IQR: 5.82–16.2) in controls (P < 0.001), and the mean fT4 level was significantly lower in cases (27.2 ± 7.3 nmol/L) compared to controls (44.7 ± 12.3 nmol/L) (P < 0.001). Hypothyroidism was identified in 60% of the asphyxiated neonates and only 10.5% of controls, with no incidence of hyperthyroidism in either group. Among asphyxiated neonates, hypothyroidism was significantly more prevalent in preterm (100%), post-term (100%), low birth weight (<2500 gm, 80%), male neonates (76.2%), those delivered via caesarean section (80%), and those born to multigravida mothers (80%), all with statistically significant associations. These findings substantiate that perinatal asphyxia independently contributes to a suppression of thyroid hormones, most likely through central hypothalamic-pituitary axis disruption.

The observed reduction in TSH and fT4 levels aligns strongly with multiple recent investigations. Brid and Pawar (2024)10 reported FT3 and FT4 levels significantly lower in asphyxiated neonates (1.2 pg/mL and 0.7 ng/dL, respectively) versus controls (2.5 pg/mL and 1.5 ng/dL), supporting a suppressed thyroidal axis in line with the present findings10. Similarly, Pradhan et al. (2023)17 noted a progressive decline in TSH from 8.7 ± 2.4 mIU/L in controls to <1.0 mIU/L in severe HIE neonates, suggesting a dose-dependent hormonal suppression which mirrors the inverse correlation between severity of asphyxia and TSH observed in this study17. The present work further confirmed that all neonates with both preterm and post-term gestation exhibited hypothyroidism (100%), a finding that reflects the broader trend of increasing thyroid suppression with worsening neonatal compromise seen in other studies such as Umesh et al. (2016)7 and Prabhakar et al. (2016)6, where a drop in fT4 and TSH was observed with increasing HIE grades; however, since HIE staging was not an objective of the current study, direct stage-based comparisons were not undertaken.

Kumar et al. (2023)11 demonstrated significant inverse correlations between 1-minute APGAR scores and both T4 and TSH in cord blood, which adds strong external validity to the findings here where asphyxiated neonates—identified primarily through low Apgar scores—showed depressed hormone levels11. Although cord-based assessments may be confounded by perinatal stress surges, the current study utilized postnatal serum at 48–72 hours, thereby avoiding the well-documented transient TSH spikes described by Joshi and Menon (2014)26 and Lee (2016)24. This ensured more accurate reflection of central suppression rather than stress-induced stimulation. Importantly, this timing aligns well with the interval suggested by Tikkas et al. (2015)25, who demonstrated that thyroid hormone suppression is most detectable between 18- and 24-hours post-birth and accentuates further into the second day25.

Pawar et al. (2023)9 monitored longitudinal hormone trends and revealed that while TSH and T4 may recover partially within 24 hours, FT3 remains persistently low in moderate-to-severe HIE, suggesting prolonged pituitary suppression. Although FT3 was not measured in the present study, the persistently depressed fT4 values and markedly reduced TSH levels reflect the likelihood of ongoing hypothalamic-pituitary dysfunction9. Yazici et al. (2023)18, evaluating 111 neonates under therapeutic hypothermia, reported lower fT4 and more variable early TSH levels in HIE patients, findings that though not always statistically significant, paralleled the suppression profile seen here. These results reinforce the vulnerability of the HPT axis to both hypoxia and intervention stress. The absence of therapeutic interventions in the current cohort offers a purer physiological insight into the endocrine impact of asphyxia without iatrogenic confounders18.

The prognostic role of fT4 was examined by Tunç et al. (2022)19, who found that levels below
1.52 ng/dL were significantly associated with prolonged mechanical ventilation and seizure incidence. These values align closely with the present cohort's mean fT4 of 27.2 nmol/L (~2.1 ng/dL), suggesting that the degree of suppression observed may hold important clinical implications beyond biochemical diagnosis19. Kim et al. (2022)20 also reported that reduced postnatal TSH was independently predictive of respiratory distress syndrome in neonates, a condition often co-existing with perinatal hypoxia. The endocrine alterations described by both studies resonate with the fT4-TSH depression pattern observed in the current asphyxiated group20.

Older studies also reinforce these findings. Kumar and Krishna (2018)21 reported FT3 and FT4 values of 1.1 pg/mL and 0.6 ng/dL in asphyxiated neonates versus 2.4 pg/mL and 1.4 ng/dL in controls (P < 0.001), which reflects a hormonal shift comparable to the 27.2 vs. 44.7 nmol/L fT4 drop recorded here21. Hemasundar et al. (2018)22 observed significant suppression of TSH, T3, and T4 across both term and late preterm neonates with asphyxia, a finding consistent with our observation that central hypothyroidism occurred regardless of gestational maturity once hypoxia was present22. The study by Kumar (2017)5 also recorded a T4 reduction from 48.3 ± 6.4 to 31.8 ± 5.2 nmol/L in asphyxiated neonates, matching the magnitude and direction of T4 decline observed here5.

In the present study, hypothyroidism was more frequent among neonates with birth weight
<2500 gm (80%), mirroring reports by Gupta et al. (2013)27, who found elevated TSH levels in neonates with low birth weight and higher resuscitative needs27. This association was also noted by Lakshminarayana et al. (2016)23, who identified strong correlations between low birth weight, adverse Apgar scores, and suppressed thyroid function. Notably, the control group here demonstrated only 21.1% hypothyroidism in low-birth-weight neonates, strengthening the argument that hypoxia—not weight alone—may be the precipitating factor23.

Another key association emerged with gender. Male neonates in this study exhibited hypothyroidism in 76.2% of cases, significantly higher than the 28.6% in females (P = 0.006). While most prior studies did not report gender-stratified hormonal outcomes, Hemasundar et al. (2018)22 documented significantly lower FT3 levels in male neonates, particularly among preterms, suggesting sex-specific vulnerability that deserves further exploration22.

The present findings regarding mode of delivery offer a unique perspective. Contrary to Armanian et al. (2013)29, who observed elevated cord TSH in neonates delivered vaginally our study found higher hypothyroidism in caesarean-delivered neonates (80%) versus vaginal deliveries (40%, P = 0.025). This likely reflects selection bias in the clinical decision to proceed with emergency caesarean in compromised fetuses, highlighting that LSCS may act more as a surrogate for underlying fetal hypoxia than a direct cause of endocrine disturbance29. A similar inference was drawn by Kumar and Krishna (2018)21, who noted lower thyroid values in emergency LSCS deliveries than in elective procedures21.

Multigravida status was another independent risk factor, with 80% hypothyroidism among neonates of multigravida mothers compared to 40% in primigravida (P = 0.046). While this relationship has been largely underreported, Gupta et al. (2013)27 and Rashmi et al. (2007)8 both hinted at similar trends, possibly attributable to progressive placental insufficiency or higher cumulative fetal risk across pregnancies.

The use of TSH and fT4, though less comprehensive than a full FT3-FT4-TSH panel, remains clinically relevant and in alignment with routine newborn screening practices, especially in resource-limited contexts. As emphasized by Williams and Hume (2008)32, interpreting fT4 levels relative to gestational norms is essential, particularly in preterm populations where transient hypothyroxinaemia is common32. Although total T4 was used in this study due to laboratory limitations, the observed hormonal

differences maintained statistical and clinical significance.

Additionally, this study's rigorous methodology enhances interpretative robustness. The case definition of perinatal asphyxia was based on internationally accepted criteria, and confounders such as maternal thyroid illness or glucocorticoid exposure were excluded. Sampling within 48–72 hours ensured that results were not skewed by perinatal TSH surge or delayed recovery. The statistically significant associations across multiple variables— gestation ($P < 0.001$), birth weight ($P = 0.047$), sex ($P = 0.006$), gravida ($P = 0.046$), and delivery mode ($P = 0.025$)— add further granularity to the biochemical findings and reinforce the assertion that perinatal asphyxia exerts a profound and multi-factorial suppression of the neonatal HPT axis.

This work builds upon foundational research such as that by Pirrone et al. (2013)30, who identified hypoxia-induced ischemic injury to the hypothalamus and pituitary as central mechanisms of endocrine suppression30. Dilli et al. (2010)31 observed transient hypothyroxinaemia in preterm neonates requiring intensive respiratory support, a condition that overlaps with the preterm cases in this study, all of whom demonstrated thyroid dysfunction. Bagnoli et al. (2013)28 observed thyroid suppression in small-for-gestational- age infants exposed to intrauterine hypoxia, reinforcing the stress-sensitivity of fetal endocrine systems. Kim et al. (2005)33 offered early empirical evidence that FT4 suppression in asphyxiated neonates may coexist with elevated early TSH, potentially reflecting biphasic pituitary response transitioning to fatigue—a mechanism avoided in the current study by sampling during the suppression phase33.
In synthesizing these findings, this study reaffirms the importance of early thyroid screening in neonates exposed to perinatal asphyxia. The high incidence of hypothyroidism among affected neonates (60%), alongside significant statistical correlations with prematurity, birth weight, sex, and maternal gravida status, highlights the multi-layered vulnerability of this group. Central suppression, as evidenced by concordant reductions in fT4 and TSH, rather than isolated glandular failure, appears to be the predominant mechanism, consistent with the majority of referenced studies.

Strengths
One of the major strengths of this case-control study lies in the precise timing of hormone assessment, with TSH and free T4 levels measured between 48 to 72 hours of life—a window that effectively captures early hormonal suppression while minimizing the confounding influence of the immediate postnatal TSH surge. The clear definition of cases and controls, with healthy neonates serving as parallel controls, enhanced the internal validity and allowed for direct comparison of thyroid profiles. The use of free T4, rather than total T4, improved the specificity of the hormonal evaluation by reflecting the biologically active fraction relevant to tissue function. Stratification based on multiple perinatal variables—such as gestational age, birth weight, sex, mode of delivery, and maternal parity—enabled comprehensive analysis of risk modifiers influencing thyroid suppression in the context of perinatal asphyxia. The statistically significant associations observed across these subgroups further reinforce the robustness of the findings. Additionally

the use of commonly available tests like TSH and free T4 ensures practical applicability, particularly in resource-constrained settings, thereby enhancing the translational relevance of the study outcomes.
Limitations

This case-control study has several limitations. While both TSH and free T4 were assessed— enhancing the reliability of thyroid function evaluation—the absence of FT3 limited the ability to assess peripheral conversion and complete thyroid axis dynamics. HIE severity staging was not included as part of the study objectives, which precluded correlating hormonal alterations with the gradation of hypoxic injury. The use of a single time-point measurement between 48 to 72 hours postpartum prevented assessment of the persistence or resolution of hormonal suppression over time. Though the sample size was sufficient for detecting significant group differences, it may have limited the power to uncover subtler associations across subgroups such as gestational age or delivery mode. As a single-center study, external generalizability is constrained, and findings may not extrapolate to different neonatal populations. Finally, by the inherent nature of the case-control design, this study can establish association but not causation; while strong links between perinatal asphyxia and thyroid suppression were demonstrated, temporal or mechanistic conclusions cannot be drawn. Nonetheless, the study provides important evidence supporting early thyroid screening in neonates with perinatal asphyxia

Conclusion
This study demonstrated that perinatal asphyxia has a significant suppressive effect on thyroid function in neonates, resulting in a high prevalence of central hypothyroidism among affected infants. The disruption of the hypothalamic-pituitary-thyroid axis was evident through reduced thyroid hormone levels in the early postnatal period. Several perinatal factors, including gestational age, birth weight, mode of delivery, gender, and maternal parity, were found to influence the occurrence of hypothyroidism in asphyxiated neonates. These findings affirm that perinatal asphyxia independently contributes to endocrine dysfunction, particularly through central mechanisms, and highlight the physiological vulnerability of neonates to hypoxic insult.

The implications of this study are both clinical and public health-oriented. Early screening for thyroid dysfunction in neonates with perinatal asphyxia should be considered a critical component of neonatal care, especially in high-risk settings. Assessing thyroid hormones in the first few days of life allows for timely identification of hormone suppression and enables appropriate follow-up and intervention. Incorporating such evaluations into standard neonatal protocols can aid in preventing long-term neurodevelopmental consequences. Furthermore, the findings support the use of basic thyroid parameters, such as TSH and fT4, which are accessible and cost-effective, making them suitable for widespread implementation, particularly in resource-constrained environments.

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