Newborns with Hypoxic Ischemic Encephalopathy Treated with Therapeutic Hypothermia have Elevated TSH Levels on Newborn Screening

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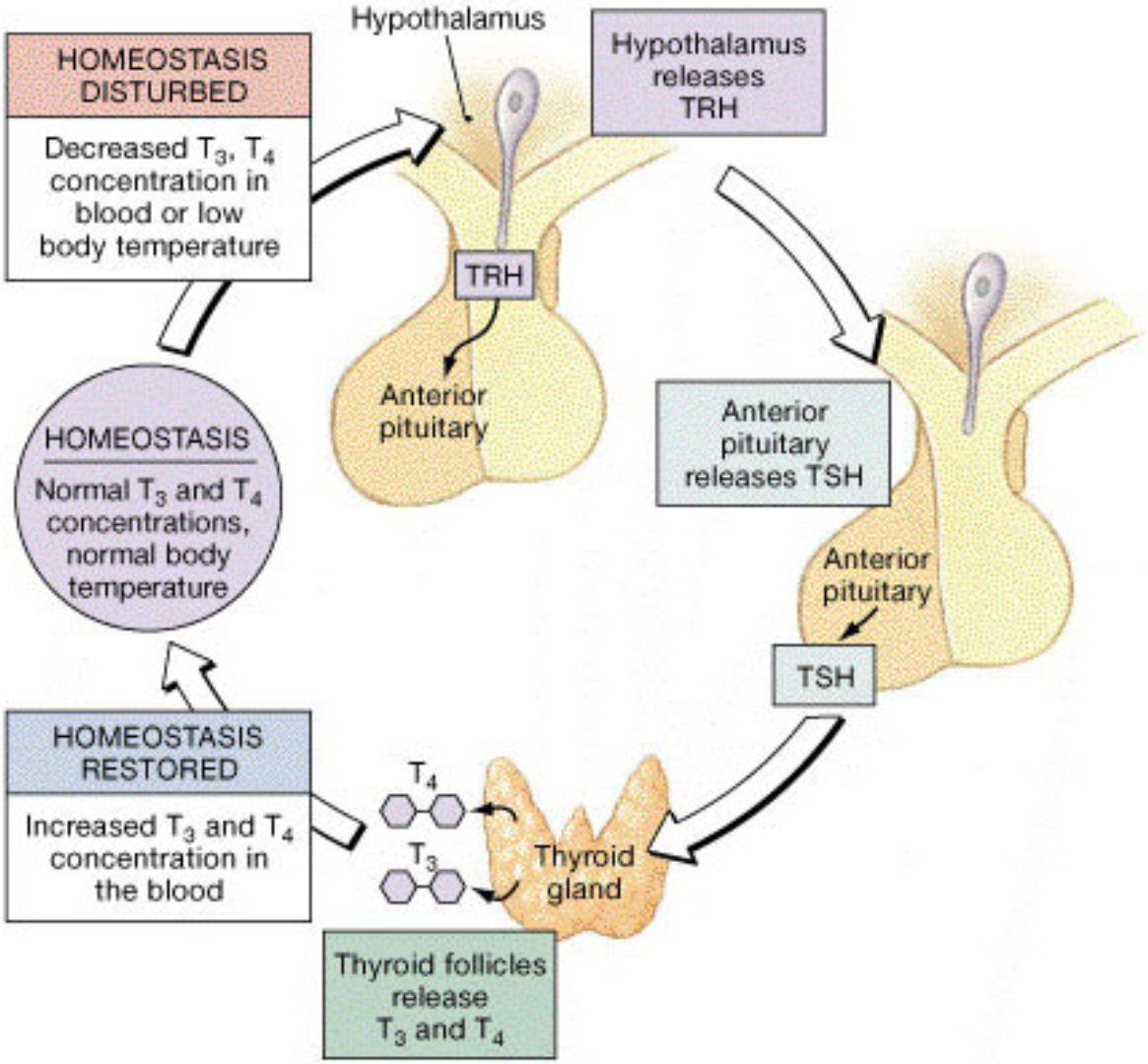
Background

- Therapeutic hypothermia (TH) has become standard care for the newborn with Hypoxic Ischemic Encephalopathy (HIE) at birth.
- It is biologically plausible that cold stress in newborns may cause Thyroid Stimulating Hormone (TSH) elevation.

Pathophysiology



Hypoxic Ischemic Encephalopathy (HIE) Definition

- HIE occurs in the setting of the fetus receiving a diminished oxygen supply (e.g. cord accident, placental abruption), often clinically evident as fetal distress or hypotonia and apnea after a difficult delivery.
- Mild, Moderate and severe HIE categories:
  - metabolic acidosis
    - Umbilical arterial pH <7.0 or base deficit ≥ 12 mmol/L
  - early onset of encephalopathy
- Moderate and severe associated with multisystem organ dysfunction

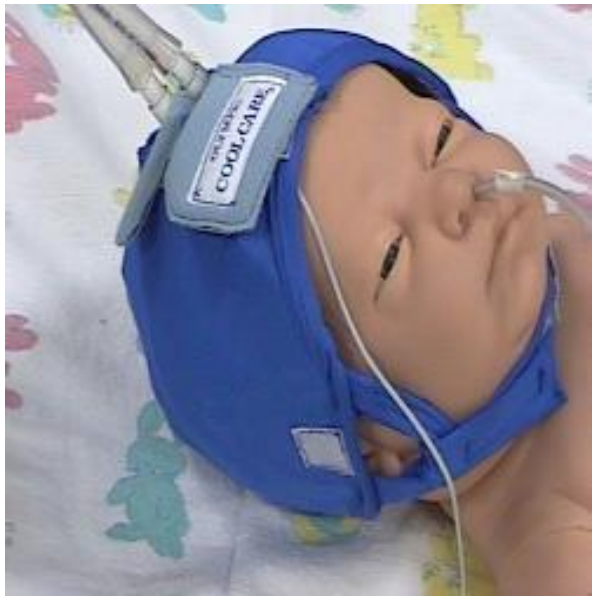
HIE Epidemiology

- Incidence: 1.5/1000 term births
- Mortality: 15 – 20%
- Morbidity: 25% long-term disabilities
  - *Mild* HIE: Low risk of motor or cognitive defects
  - *Moderate* HIE: significant motor deficits, fine motor disability, memory impairment, visual or visuomotor dysfunction, increased hyperactivity and delayed school readiness
  - *Severe* HIE: 85% die, high risk of CP, MR in survivors

HIE Pathophysiology
Damage Mechanisms: 2 Phases

- Primary Energy Failure
  - $\downarrow$ CBF, O_2 substrates, high-energy PO_4 compounds (ATP), low tissue pH
  - Excitotoxic-oxidative cascade (excess neurotransmitter stimulation)
  - Loss of ionic homeostasis across membranes (depolarization), entry of intracellular $Ca^{2+} \rightarrow \uparrow$NOS $\rightarrow \uparrow$ RO/NS $\rightarrow$ mitochondrial disruption $\rightarrow$ apoptosis $\rightarrow$ necrosis
- Reperfusion - Therapeutic window = by 6 hours after insult
- Secondary energy failure (DIMINISHED BY HYPOTHERMIA)
  - Continuation of excitotoxic-oxidative cascade
  - Activation of microglia—inflammatory response
  - Activation of caspases
  - $\downarrow$ growth factors, protein synthesis
  - Apoptosis–necrosis continuum

Therapeutic Hypothermia
Body vs. Head



- Treatment started by 6 HOL
- Body cooled to 33.5 C for 72h
- Rewarmed over a 12 hour period
- Back to normal temperature by 90 HOL
- All on parenteral nutrition

Hypothesis

There is an association between treatment of HIE newborns with TH and (or HIE itself) elevated TSH levels on NBS reports

Approach

Compare NBS TSH levels in two NICU cohorts:

- Term newborns with HIE treated with TH
- Term newborns with disorders other than HIE who did not undergo TH

Methods

- NICU: Brigham and Women's Hospital Boston, MA
  - admitted between 6/15 - 11/16
- NENSP algorithm: TSH and T4 on all NICU patients
- NBS TSH results were collected on 2 cohorts:
  - 82 newborns with HIE who had undergone TH for HIE
  - 80 controls matched by age, sex, and weight
- TSH levels were categorized as normal or abnormal, based on NENSP cutoffs:

NORMAL TSH REFERENCE RANGES:

Hours after birth		TSH μU/mL
< 24	(<1 day)	< 25
24 - 96	(1-4 days)	< 20
> 96	(>4 days)	< 15

Demographics

	Control (n=80)	Cooled (n=82)
Male (%)	60	61
GA (wks)	39.1	39.1
Weight (gms)	3256	3195
Apgar 1min	7.2	2.9*
Apgar 5min	8.2	5.8*
Race (%)		
- White / Caucasian	57.5	58.5
- Black / African American	10	20.7
- Asian	6.3	4.8
- Hispanic / Latino	12.5	4.8
- Other	10	7.3
- Declined	2.5	0.0
- Unknown	1.25	3.7

* $p < 0.05$

Results

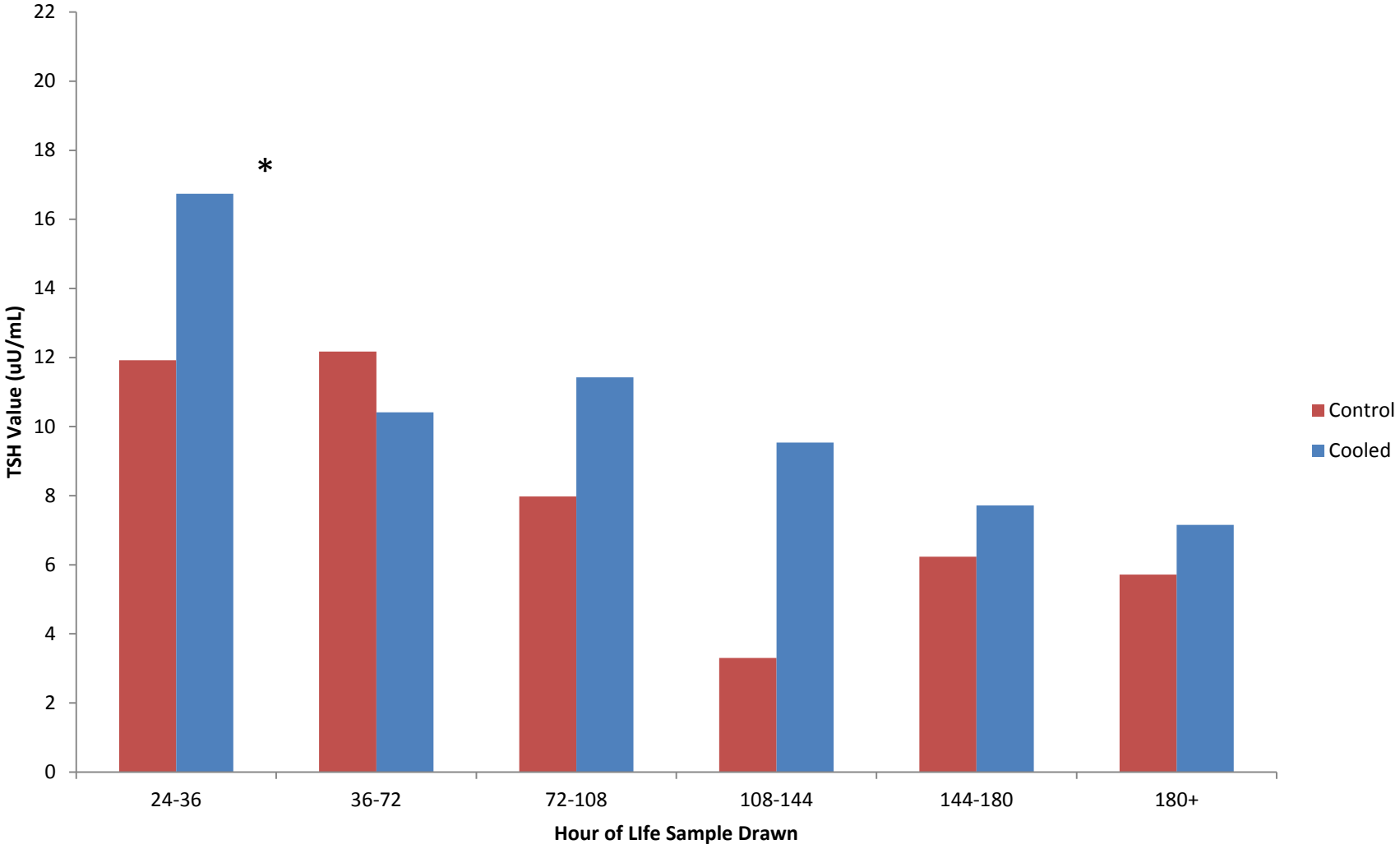
- **19/82 (23.2%)** TH newborns had an elevated NBS TSH while in-hospital, as compared to **7/80 (8.8%)** of matched NICU controls (p=0.018).
  - **Of note, 58% of HIE?TH newborns had some NBS abnormality and 70% of abnormal NBS had an abnormal MS/MS amino acid pattern c/w TPN**
- TH newborns had **2.3** NBS TSH levels vs. **1.7** for controls (longer hospitalization and higher rate of abnormal first screen).
- In almost all TH cases with an abnormal TSH, the elevation was **identified on the first valid sample**.
- **Most** TSH elevations **resolved** by discharge in both groups.
- Two TH newborns had an **initial low T4 without TSH elevation**, and elevated TSH were associated with low T4.
- There was **no difference** between the two groups in the likelihood of having an elevated TSH level **on discharge** (4 TH vs. 3 controls, p=1.0).

Abnormal TSH Levels (mean)

	Control	Cooled
1st Sample	21.7 (20.2-25.3)	28.7* (20.1-54.4)
2nd Sample	17.8	28.3 (15.9-53.9)
3rd Sample	19.6	22.0

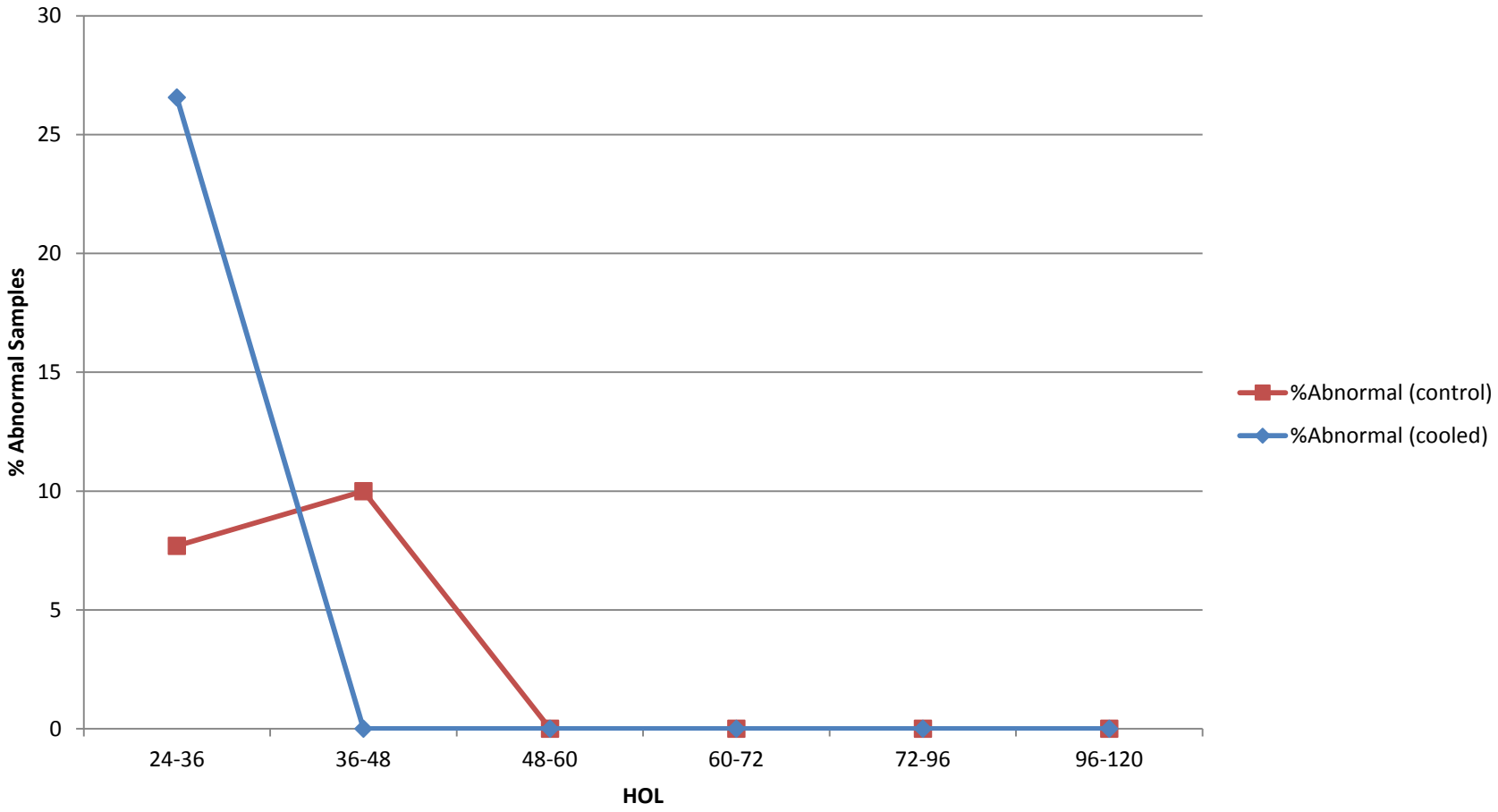
* $p < 0.05$

Average TSH Values by Age Sample Drawn

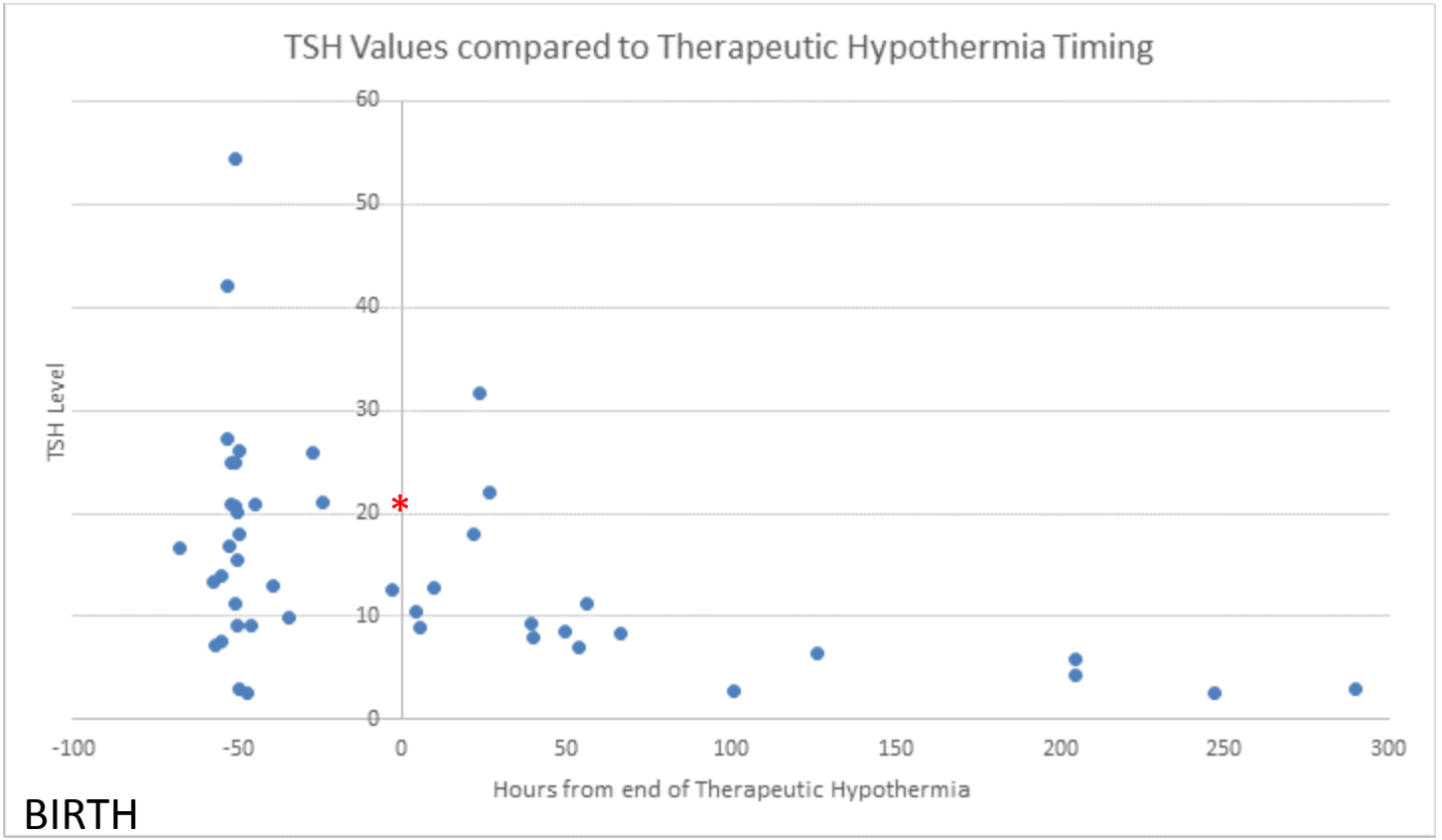


*p < 0.05

% Abnormal TSH on first sample by hour of life first sample drawn



TSH values obtained During vs. After Cooling



BIRTH

COOLING STARTS

COOLING ENDS (~78 hours of life)

Limitations

- Although it is likely that higher TSH is related to TH therapy, it is possible that it could be related to the injury that caused the HIE.
- Because TH is now standard care for HIE, we did not have a control group of newborns with HIE not treated with TH for comparison.

Conclusions

- To our knowledge, this is the first report of increased risk of elevated NBS TSH levels in newborns with HIE treated with TH.
- The elevation is generally transient and not a marker of intrinsic hypothyroidism.

Conclusions

- Given the observed spontaneous resolution of elevated TSH levels in cooled infants, **TH** may be considered a **source of false positive** result for congenital hypothyroidism.
- Awareness of this increased false positive risk will aid the clinician in assessment and counseling of parents.
- A slight delay in sending the initial NBS sample (48–72 hours) on newborns with HIE treated with TH could minimize the likelihood of such false positive results.