International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2020; 4(2): 01-03
Received: 01-01-2020
Accepted: 03-02-2020

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The study of relationship between season of delivery and cord blood TSH

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DOI: https://doi.org/10.33545/gynae.2020.v4.i2a.493

Abstract
Introduction: Newborn suffers hypothermia in the extra-uterine environment, soon after birth, leading to a transient increase in TSH levels. Winters are the most stressful period in terms of cold stress.
Methods: In this observational study, data of cord blood TSH and time of birth 1500 neonates was taken from hospital records which were routinely screened for congenital hypothyroidism at a tertiary care hospital in northern India.
Two groups of neonates were formed on the basis of their birth months. In the first group (i.e. winters), neonates born in December, January and February were taken while those born in April, May and June were included in the second group (i.e. summers).
Results: The cord blood TSH of neonates born in winters (median CBTSH=8.4 mIU/ml) was significantly higher (p=0.001) than that of neonates born in summers (median CBTSH=7.1 mIU/ml). The month wise distribution of CBTSH did also show the same pattern in winters and summers.
The recall rate was also significantly higher (p=0.002) in winters (9.76%) than summers (4.84%).
Discussion: Thyroid hormones play essential role in successful transition to extra uterine life. There is sudden and transient increase in cord blood TSH especially in winters. It leads to increased recall rates (recall of neonates with cord blood TSH >20 mIU/ml for further assessment to rule out congenital hypothyroidism at 3rd postnatal day) for congenital hypothyroidism screening program. Thyroid hormones modulate the other hormones like thymulin in neonates, which are deserved to be studied to enhance immunity and decrease morbidities in them.

Keywords: Seasonal variation, cord blood TSH

Introduction
Adaptation to the environment is essential for survival. Thyroid function suffers the most diverse influences, including the environmental factors (stress, cold and altitude). Newborn suffers hypothermia in the extra-uterine environment, soon after birth, leading to an increase in thyrotropin (Thyroid Stimulating Hormone; TSH) levels peaking at 30 minutes and declining gradually in next 48 hours [1].
Congenital hypothyroidism (CH) is the most common cause of preventable mental retardation among neonates [2]. Cord blood TSH (CBTSH) measurement is a very common method to screen the neonates for congenital hypothyroidism (CH) [3, 4, 5].
The interpretation of such screening test is difficult due to several factors such as physiological changes during the first days of postnatal life, techniques used, the harvest period and adverse conditions present [1].
Cities of north India are well known to have huge temperature difference in different seasons throughout the year, ranging from ~0^0C to ~45^0C in winters and summers respectively. Thus, objective of this study is to observe the differences in cord blood TSH levels in both seasons and its influence on recall rates (recall of neonates with cord blood TSH >20 mIU/ml for further assessment to rule out congenital hypothyroidism at 3rd postnatal day) for congenital hypothyroidism screening program.

Methods
In this observational study, data of 1500 neonates regarding date of birth, gender, gestational age and cord blood TSH was taken from hospital records which were routinely screened for CH at a tertiary care centre in northern India.

For routine screening, 2ml of blood sample was collected in a sterile container from umbilical cord at the time of birth. Samples were allowed to clot for 45 minutes. Serum was separated with centrifugation machine at 3000 rounds/minutes for 5-10 minutes. The TSH in cord blood was analyzed within 3-4 hours of collection in Department of Biochemistry by chemiluminiscence method using sandwich principle on Elecys 2010 with kit from Roche diagnostics.

Two groups of neonates were formed on the basis of their birth months. In the first group (i.e. winters), neonates born in December, January and February were taken while those born in April, May and June were included in the second group (i.e. summers). The other six months were not included in any of these groups to avoid erratic results.

Statistics

The data was analyzed using IBM SPSS 16 software, using standard formula to calculate median CBTSH and interquartile range (IQR). The significance was calculated with Mann Whitney test.

Results

The cord blood TSH of neonates born in winters (i.e. December to February; median CBTSH=8.4 mIU/ml) was significantly higher (p=0.001) than that of neonates born in summers (median CBTSH=7.1 mIU/ml). (Table 1)

The sex distribution and number of preterms were equivalent in both groups. The recall rate was also significantly higher (p=0.002) in winters (9.76%) than summers (4.84%). (Table 1)

The cord blood TSH was higher in winters than in summers and in between both for rest of the year. (Table 2, Diagram1).

Table 1: The distributions, median CBTSH and recall rates in the winter and summer groups of neonates

	Winters (n=420)	Summers (n=330)	p value
Males	241 (57.4%)	180 (54.4%)	> 0.05
Females	179 (42.6%)	150 (45.4%)	> 0.05
Preterms	82 (19.5%)	58(17.6%)	> 0.05
Median CBTSH (IQR)	8.4 mIU/ml (7.10)	7.1 mIU/ml (5.30)	0.001
Recall (CBTSH >20mIU/ml)	41 (9.76%)	16 (4.84%)	0.002

Table 2: Month-wise distribution of neonates and their median CBTSH (in mIU/ml)

	Median CBTSH (mIU/ml)	IQR
Jan (n=161)	8.2	7.6
Feb (n=121)	8.6	6.35
Mar (n=118)	8.3	7.98
Apr (n= 121)	8	7.45
May (n= 116)	7.2	5.2
June (n= 93)	6.4	5.75
Jul (n=132)	6.9	4.38
Aug (n=160)	7.1	5.42
Sep (n= 94)	7.2	6.53
Oct (n=95)	8.2	6.08
Nov (n=151)	8.1	6.4
Dec (n= 138)	8.2	6.48

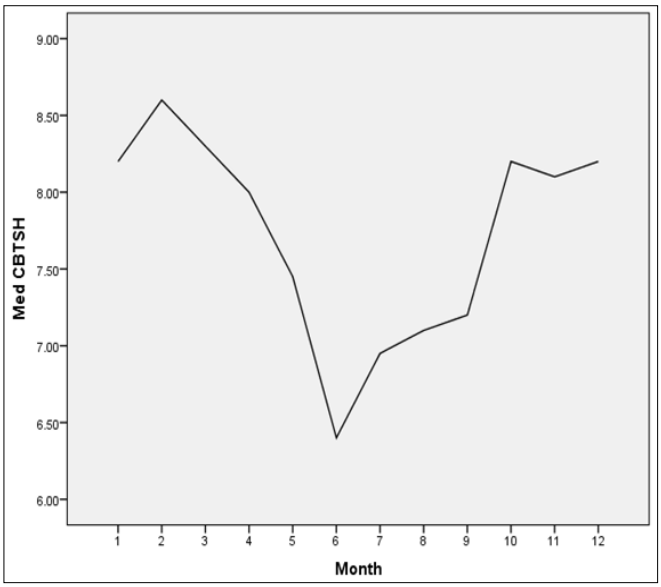

Diagram 1: The line diagram showing month-wise distribution of median CBTSH (months Jan to Dec depicted as 1- 12 on X-axis; median CBTSH in mIU/ml on Y-axis)

Discussion

All newborn babies are prone to heat loss, particularly in the first minutes and hours after birth [6, 7].

The hypothalamic-pituitary-thyroid axis is influenced by the action of various environmental factors, including temperature. Exposure to cold is associated with increased activity of thyroid whose magnitude, nature and duration vary widely, depending on duration of exposure to cold [8]. This response is partly due to the adrenergic stimulation of TSH secretion [1].

In our study, the cord blood TSH of neonates born in winters (median CBTSH=8.4 mIU/ml) was significantly higher than that of neonates born in summers (median CBTSH=7.1mIU/ml)) which signifies that newborns are subjected to higher cold stress in winters. Ordookhani A *et al.* (2010) also reported that neonatal transient hyperthyrotropinemia (THT) occurs significantly more in winters than in other seasons, and this suggests a possible role for time-varying factor(s) contributing to its seasonal preponderance [9].

This is in contrast to that in adults where TSH is higher in summers when signals like melatonin leads to a sustained increase in TSH expression which is actually a part of circadian rhythm [10]. The availability of thyroid hormones in the hypothalamus appears to be an important factor in driving the physiological changes that occur with season [1]. This is mediated by local control of thyroid hormone-metabolising enzymes within specialised ependymal cells lining the third ventricle of the hypothalamus. Within these cells, deiodinase type 2 enzyme is activated in response to summer day lengths, converting metabolically inactive thyroxine (T4) to tri-iodothyronine (T3) [10]. But in neonates, circadian rhythm is not developed.

In laboratory animals, acute exposure to cold rapidly increases serum TSH, leading to an increase in thyroid activity, in order to increase heat production, a form of cold adaptation. These animal studies have suggested that peripheral cold receptors and the pre-optic hypothalamic nuclei stimulate the hypothalamic TRH production center (TSH-releasing hormone) and tonic secretion of TSH. Others report that the increase in thyroid

activity to cold is due to increased peripheral utilization of thyroid hormones, resulting in decreased blood levels of the hormone, which by the feedback mechanism increases the secretion of TSH [1]. Inhibition of thyroid function more chronically prior to birth did interfere with postnatal cardiovascular adaptation and thermogenesis in newborn lambs [11]. Thus, thyroid hormones are essential for successful transition to extra uterine life.

In our study groups, sex distribution was equivalent i.e. statistically indifferent. However, cord blood TSH levels in male and female neonates has been reported similar in various studies. [12, 13].

In month-wise distribution, cord blood TSH was higher in winter months (maximum in February) than in summer months (minimum in June).

The cut -off value for cord blood TSH is >20 mIU/ml, if the value comes higher the neonate is recalled for thyroid function tests (FT3, FT4 and TSH) measurement at 3rd postnatal day (recall). Neonatal transient hyperthyrotropinemia (THT) have been reported significantly more in winter than in other seasons, due to a possible role for time-varying factor (s) contributing to its seasonal preponderance [13]. In our study group, recall rate was almost double in winters (9.76%) than summers (4.84%).

Thus, cord blood TSH should be cautiously interpreted when used for screening of congenital hypothyroidism. Further studies are required to find out whether other hormones are also affected with temperature changes since thyroid hormones modulate other hormones like thymulin [14]. Understanding of such complicated mechanism may bring about better survival and reduced morbidity in neonates.

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