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Newborn Screening-A Bolstering Step towards Quality Health in Neonates

Paediatrics Section

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ABSTRACT

Introduction: Newborn Screening (NBS) is considered the need of the hour for quality health in neonates. It is also important to understand that the rising trend of prevalence of inherited metabolic disorders and the various maternal factors that might influence genetic changes in the foetus in-utero affecting the neonatal outcome.

Aim: The primary objective of the study was to determine frequency of Congenital Hypothyroidism (CH) and Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency in a most approachable tertiary care hospital. The secondary objectives were to find out impact of maternal factors on the frequency of the disease and the impact of the disorder on the neonate's health.

Materials and Methods: The cross-sectional study was conducted on 1282 neonates of 48 hours upto eight weeks of age. The Dried Blood Spot (DBS) specimens collected were analysed for Thyroid Stimulating Hormone (TSH) level and G6PD enzyme activity. Details of neonatal characteristics and antenatal history were documented. Prevalence of CH and G6PD deficiency was calculated and maternal and neonatal variables were analysed for association using Statistical Package for the Social Sciences (SPSS) version 20.

Results: The prevalence of CH and G6PD were respectively 3.3/1000 and 6.6/1000 making the overall prevalence of metabolic disorders as 9.8/1000. A 27.3% had Low Birth Weight (LBW) and 62% had low Ponderal Index (PI). The odds for raised TSH was 6.62 times in sick neonates. The probability for high TSH in LBW babies was more by 94% and in female neonates by 18%. The neonates with higher TSH values depicted significant association with maternal age (p=0.016), gestational age (p=0.019) and maternal anaemia (p<0.001). Babies born by caesarean section showed twice the chances for screening positive for TSH.

Conclusion: The high prevalence estimated in this study and association with maternal factors urges new queries and recommends an obligatory need for NBS program in this region.

Keywords: Congenital hypothyroidism, Dried blood spot, Glucose-6-phosphate dehydrogenase, Maternal factors

INTRODUCTION

The prognostic implication of NBS is still trivialised in many developing countries inspite of the rising trend of prevalence of disorders of Inborn Errors of Metabolism (IEM), evidenced since a decade [1]. Delayed diagnosis is often associated with permanent neurological sequelae ending up in retarded growth, mental retardation, cerebral palsy and many other signs associated with damage to central nervous system. The ultimate burden on family is reflected few months after when the child is diagnosed to have the disorder which become untreatable at that stage. These facts actually call an attention towards the significance of early diagnosis of the treatable disorders by screening for the same at the neonatal age [2].

Indian registry yet lacks a national data on the burden of the various disorders of IEM. These disorders do not get enough attention because of its relatively rare prevalence and slow progressing nature. More so, the diagnostic facilities are also a major limiting factor for not being available within approachable areas at an affordable cost. CH being the most common and most cost-effective is being screened in most countries [2]. Except for few institutes, screening for CH is under regular practice in India. Again, the haemoglobinopathies like Sickle Cell Disease (SCD) and G6PD deficiency are quite prevalent in some parts of India, mostly in the tribal population where consanguinity is very high [3]. Since, these population usually live-in interiors and very much far away from adequate health care services. Irrational use of anti-malarial drugs and remote access to health care services make them highly vulnerable for haemolytic anaemia and associated mortality. Diagnosing G6PD deficiency in the individuals becomes highly essential in these areas so, that caution must be taken for drug treatments [3].

Hence, setting up off a diagnostic facility at a very much approachable tertiary care hospital is of utmost importance. Government efforts are not enough to estimate the national

burden and accordingly meet the demand for infrastructure and diagnostic facilities. Large scale studies are not feasible because of either unavailability of infrastructure or due cost constrain. Rather, small pilot projects are encouraged in different regions which can be summed up to provide an idea for the prevalence and establish a diagnostic set up in the state [1]. It is also important to understand that the rising trend of prevalence might be the impact of other factors that influence genetic changes in the foetus in-utero including the maternal factors. Maternal variables like age, gestational age, parity, mode of delivery, maternal thyroid status, associated medical illness in mothers, maternal anaemia and many others have been proposed by researchers for having an influence on neonatal thyroid hormone levels [4-6]. The primary objective of the study was to determine frequency of CH and G6PD deficiency in a most approachable tertiary care hospital. The secondary objectives were to find out impact of maternal factors on the frequency of the disease and the impact of the disorder on the neonate's health.

MATERIALS AND METHODS

The cross-sectional study was conducted on 1282 neonates of 48 hours upto eight weeks of age who were delivered or admitted in the institute, irrespective of their gender. The study was conducted in Department of Biochemistry in collaboration with Department of Neonatology of the institute. The study was initiated only after ethical clearance by the Institutional Ethics Committee (105/IEC/AIIMSRPR/2016). Written informed consent from their parents/legal guardians were obtained prior to enrolment and none of them were financially charged for the screening test reagents and consumables.

Inclusion criteria: All neonates, after 48 hours who were brought to the out-patient or in-patient department in the institute, were included for the study and samples were collected for analysis.

Exclusion criteria: Neonates of those parents/legal guardians who did not give consent, those with any history of blood transfusion and those who did not respond for repeat testing or confirmatory testing, were excluded.

The neonates who were clinically found sick, samples were collected on the day of discharge. The neonates were clinically evaluated by the neonatologist for respiratory count, heart rate, skin colour and appearance, Apgar Score and other vital parameters required to diagnose for neonates' health status. Details of the neonate's anthropometric measures and clinical evaluation were entered in pre-approved case record form. Maternal variables in terms of age, rural or urban area they belong to, parity, number of antenatal visits, gestational age at delivery, associated medical illness, anaemia status and mode of delivery were also documented.

Taking all aseptic measures, two spots of capillary blood were collected from the heel on an adsorbent filter paper (Whatman 903). The sample was dried at room temperature for three to four hours and then zip locked for transportation in zipper plastic bag.

The collected DBS samples were quantified for TSH level and G6PD enzyme activity by immunofluorescence method as per the kit based protocol provided by Labsystems Diagnostics Oy, VANTAA, Finland. The cut-off values for TSH screening was considered as 10 mIU/L and that for G6PD activity was 3 U/Gm of Hb. TSH values higher than 10 mIU/L and G6PD values less than 3 U/GmHb were considered screening positive and were called immediately for confirmatory testing. For confirmation, serum TSH and total T4 levels were quantified by Chemiluminescence method in Advia Centaur XP automated immunoanalyser. G-Six kit from Tulip Diagnostics was used for quantitative G6PD activity through enzyme kinetic method in the whole blood collected in Ethylenediaminetetraacetic Acid (EDTA). The biological reference ranges for these parameters and the reference variables considered for the study are tabulated in [Table/Fig-1] [7-9].

Parameters	Remarks
Serum TSH (Chemiluminescence method)	0.51-4.3 mIU/L (Biological reference level as per kit insert)
Serum T4 (Chemiluminescence method)	0.76-1.7 ng/dL (Biological reference level as per kit insert)
Blood G6PD (Kinetic) activity	3 U/Gm of Hb (Biological reference level as per kit insert)
Normal birth weight [8]	≥2500 Gm
Ponderal index [7]	>2
Premature delivery	Gestational age <37 weeks
Normal haemoglobin (Hb) [9]	Hb ≥11 gm/dL
Mild grade anaemia	Hb 10-10.9 gm/dL
Moderate grade anaemia	Hb 7-9.9 gm/dL
Severe grade anaemia	Hb <7 gm/dL

[Table/Fig-1]: The remarks for the variables [7-9].
G6PD: Glucose-6-Phosphate Dehydrogenase; TSH: Thyroid stimulating Hormone; T4: Thyroxine

STATISTICAL ANALYSIS

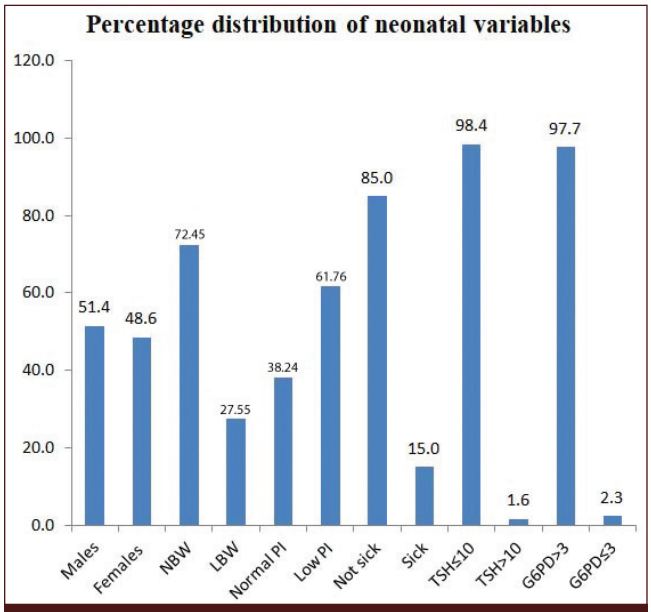
The continuous variables were checked for normal distribution and the frequencies were presented as percentages. The mean with the Standard Deviation (SD) were compared using Student's t-test. The neonates with high and normal TSH levels were analysed for association with the maternal and neonatal factors using Chi-square with degree of freedom (χ^2df) and odds ratio (OR) with 95% confidence interval (95% CI). Multinomial regression was performed for the association of categorical variables of more than three categories. The p-value less than 0.05 ($p<0.05$) were considered significant for all statistical analysis. All the analysis were performed in IBM@SPSS version 20.

RESULTS

A total number of 1282 neonates were enrolled for the study. Although, total recruitment call was 1362 neonates attending the institute, 80 of them did not agree for consent to participate and hence, the number of babies enrolled for the study was 1282. Out of the total 1282 neonates, 66 (4.9%) parents were non responsive for recall for re-sampling of DBS samples as those were found unacceptable for analysis. Rest 1216 neonates were analysed and ultimately included for the study. It comprised of 625 male babies and 591 female babies.

Characteristics of the Neonates Under Study

The frequency percentages of the neonatal variables are shown in [Table/Fig-2]. The gender frequency was almost equivalent with 51.4% male and 48.6% female neonates. The mean (SD) of the birth weight of the enrolled neonates was 2716 (16.3) grams. 27.5% (n=335) were of LBW and 61.76% (n=751) of them had low Ponderal Index (PI). A total of 182 children (15%) were admitted with neonatal complications like neonatal hyperbilirubinemia, sepsis, acute respiratory distress, fever, irritability and many others [Table/Fig-2].

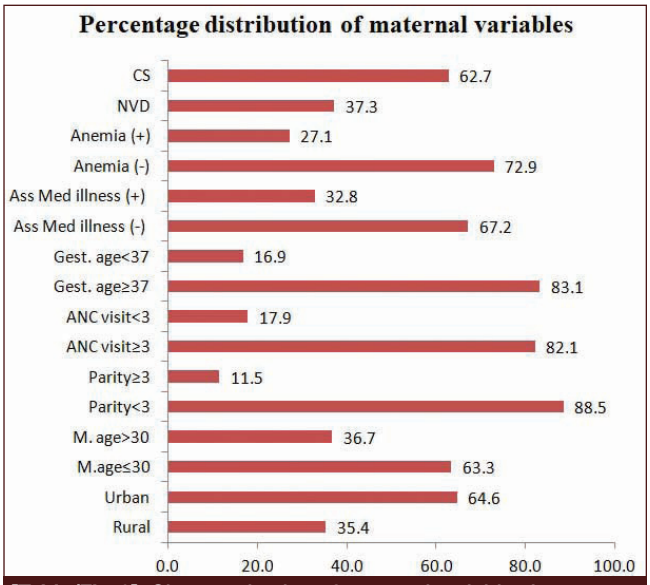


[Table/Fig-2]: The frequency percentages of the neonatal variables of the study population (N=1216).
NBW: Normal birth weight; LBW: Low birth weight; PI: Ponderal index; G6PD: Glucose-6-Phosphate Dehydrogenase; TSH: Thyroid stimulating hormone

Screening for TSH was positive for 19 (1.6%) neonates and that for G6PD in 28 (2.3%) babies. Almost 70% parents responded for confirmatory testing, out of which four neonates confirmed for CH (3.3/1000) and eight for G6PD deficiency (6.6/1000) in the evaluated study population of 1216. The overall prevalence of metabolic disorders rated was 9.8/1000 in the present study.

Characteristics of the Mothers of Neonates under Study

The frequency percentages of the maternal variables are reflected in [Table/Fig-3]. Majority of the mothers of the neonates of under study belonged from urban areas (64.6%). A 446 (63.3%) of the mothers were under 30 years of age and more than 80% of them had parity <3. Most of the mothers gave history for undergoing ≥3 ANC visits (82.1%). A 16.9% delivered prematurely before 37 completed weeks of gestation. Of them all, 32.8% of the mothers had some or other associated medical illness like hypothyroidism, gestational hypertension, gestational diabetes and many others along with anaemia of mild to severe grade is 27.1%. The major mode for delivery conducted was Lower Segment Cesarean Section (LSCS) (62.7%).



[Table/Fig-3]: Characterisation of maternal variables in frequency percentages (N=1216).
M: Maternal; ANC: Antenatal care; Gest: Gestational; Ass: Associated; NVD: Normal vaginal delivery; CS: Cesarean section

Association of neonatal TSH status with other variables: The association of the neonatal TSH status with other variables of neonates is depicted in [Table/Fig-4]. In neonates with high TSH values, one of them had hydronephrosis, six presented with respiratory distress, four neonates had jaundice, two presented with sepsis and one death. Few of them had overlap of clinical manifestations. The TSH values exhibited a significant association with the neonatal health ($p<0.001$) showing higher odds (6.62) of having higher TSH values in sick babies as compared to healthy babies. TSH status did not reveal any gender discrimination ($p=0.7$). The birth weight and PI were comparable between the groups ($p=0.15$ and $p=0.19$). However, odds for elevated TSH values were 94% increase in LBW babies than the Normal Birth Weight (NBW) babies. The female neonates recorded higher odds (18%) for raised TSH values.

Parameters	TSH >10 (n=19) (%)	TSH ≤10[R] (n=1197) (%)	χ^2df	p-value	OR (95% CI)
Gender					
Females	10 (52.6)	581 (48.5)	0.131	0.7	1.18 (0.47 to 2.92)
Males[R]	9 (47.4)	616 (51.5)			
Birth weight					
Low	8 (42.1)	327 (27.3)	2.051	0.15	1.94 (0.77 to 4.85)
Normal[R]	11 (57.9)	870 (72.7)			
Neonatal health					
Sick	10 (52.6)	172 (14.4)	21.521	<0.001*	6.62 (2.65 to 16.53)
Normal[R]	9 (47.4)	1025 (85.6)			
Ponderal index					
Low	9 (47.4)	742 (62)	1.691	0.19	0.55 (0.22 to 1.37)
Normal[R]	10 (52.6)	455 (38)			

[Table/Fig-4]: Association of neonatal variables with the TSH status of the neonates.
[R]denotes the reference category as per table-1; n% denotes the column percentages; χ^2df denotes the Chi-square test with degree of freedom; OR(95%CI) denotes odds ratio with 95% confidence interval; *significant at p<0.05; TSH: Thyroid stimulating hormone

[Table/Fig-5] reflected the association of maternal variables with neonates TSH levels. The present study observed a significant association of maternal factors like maternal age (p=0.016), gestational age (p=0.019) and maternal anaemia (p<0.001) with the neonatal TSH status. The odds for higher TSH values were 6.02 times in babies born to anaemic mothers than the non anaemic mothers. Similarly, the chances for having the baby raised TSH was nearly three times, if delivered prematurely and in those born to mothers of more than 30 years of age. Similarly, mothers who had less Antenatal Care (ANC) visits showed 64.9% (OR:1.649; 95% CI: 0.59 to 4.63) more probability for higher TSH values. The chances for an increase in neonatal TSH level was also found to be 2.3 times in those who were delivered by LSCS than Normal Vaginal Delivery (NVD).

Parameters	TSH >10 (n=19) (%)	TSH ≤10[R] (n=1197) (%)	χ^2df	p-value	OR (95% CI)
Locality					
Rural	6 (31.6)	424 (35.4)	0.121	0.73	0.84 (0.32 to 2.23)
Urban[R]	13 (68.4)	773 (64.6)			
Parity					
≥3	2 (10.5)	138 (11.5)	0.021	0.89	0.9 (0.21 to 3.95)
<3[R]	17 (89.5)	1059 (88.5)			
Antenatal care					
<3 visits	5 (26.3)	213 (17.8)	0.921	0.34	1.65 (0.59 to 4.63)
≥3 visits[R]	14 (73.7)	984 (82.2)			
Maternal age (years)					
>30	12 (63.2)	434 (36.3)	5.831	0.016*	3.01 (1.18 to 7.71)
≤30[R]	7 (36.8)	763 (63.7)			
Gestational age (weeks)					
<37	7 (36.8)	198 (16.5)	5.491	0.019*	2.94 (1.14 to 7.57)
≥37[R]	12 (63.2)	999 (83.5)			
Maternal anaemia					
Present	13 (68.4)	317 (26.5)	16.341	<0.001*	6.02 (2.23 to 15.96)
Absent[R]	6 (31.6)	880 (73.5)			
Associated medical illness					
Present	6 (31.6)	393 (32.8)	0.011	0.91	0.94 (0.36 to 2.50)
Absent[R]	13 (68.4)	804 (67.2)			
Mode of delivery					
LSCS	15 (78.9)	739 (61.7)	2.351	0.13	2.3 (0.77 to 7.05)
NVD[R]	4 (21.1)	458 (38.3)			

[Table/Fig-5]: Association of maternal variables with the TSH status of the neonates.
[R]denotes the reference category as per table-1; n% denotes the column percentages; χ^2df denotes the Chi-square test with degree of freedom; OR (95%CI) denotes odds ratio with 95% confidence interval; *significant at p<0.05; TSH: Thyroid stimulating hormone; LSCS: Lower segment cesarean section; NVD: Normal vaginal delivery

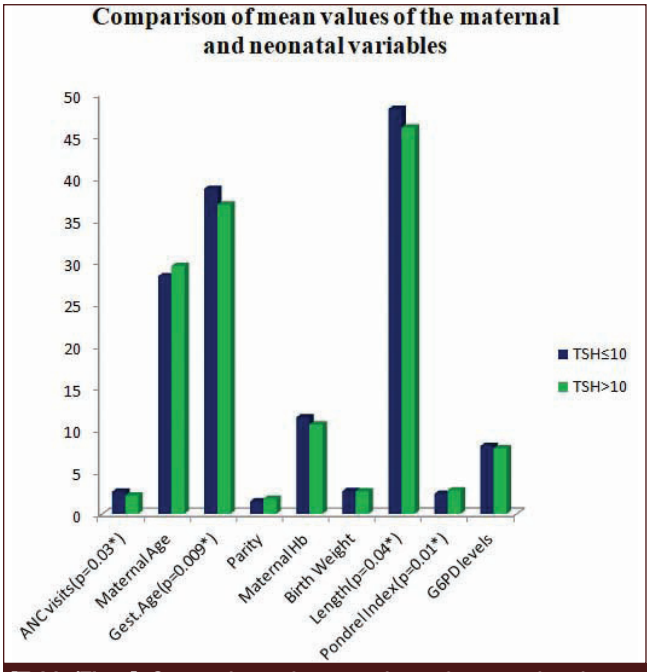
[Table/Fig-6] demonstrate the neonate's anthropometric measures and clinical evaluation in the study population. Comparison of neonatal and maternal variables between the high and low TSH levels is graphed in [Table/Fig-7]. The number of ANC visits of mothers (p=0.03) and gestational age for delivery (0.009) were significantly lower in neonates showing TSH >10 mIU/L. The mean length of the neonates were also significantly lowered in them (p=0.04), but, the PI was also significantly higher in this group (p=0.01). Out of the eight babies with G6PD deficiency, three of them presented with hyperbilirubinemia and got discharged after two weeks after getting treated successfully.

DISCUSSION

The main purpose of the study was to implement NBS in a tertiary care hospital to bring forth diagnostic services for early diagnosis of serious yet treatable disorders. This foremost step would not only meet the demand for diagnosing wide range of metabolic disorders at an affordable cost but also assess the burden in this region. To start with, the work was focused on the most common disorders, CH and G6PD. The work was quite challenging since the parents were completely unaware of NBS and it was hard to counsel them to participate with two drops of their neonates. The success for counselling was however, 94.1% as 1282 parents gave consent to participate out of the 1362 approached (data not shown). Regular distribution of educative materials through printing materials and one-to-one communications aided in improvising the enrolment through the study period. Even the associated nursing and technical staffs were also trained regularly in order to achieve a reduction in sampling errors by more than 25% towards the end of the study. The present findings are in agreement to previous studies that suggested for educating the health care

Neonatal variables	Mean	SD
Weight (gm)	2716.12	16.3
Length (cm)	48.13	4.38
Head Circumference (cm)	32.19	4.06
Ponderal Index	2.46	0.67
Respiratory rate/min	47.72	8.94
Heart rate/min	142.80	13.09
Apgar Score (in first min)	8.13	1.33
TSH (mIU/L)	3.37	4.05
G6PD (U/Gm of Hb)	8.1	2.97
94 neonates presented with Acrocyanosis		
33 had with physiological jaundice		
1 neonate presented with occulocutaneous hypopigmentation		
1 neonate presented with generalized rashes all over		
1 diagnosed with hydrocephalous (Downs syndrome)		
45 neonates had respiratory distress		
1 newborn had dextrocardia		

[Table/Fig-6]: Neonate's anthropometric measures and clinical evaluation in the study population.
SD: Standard deviation



[Table/Fig-7]: Comparison of mean values of maternal and neonatal variables between high and low neonatal TSH values.
ANC: Antenatal care; Gest: Gestational; Hb: Hemoglobin; G6PD: Glucose-6-Phosphate Dehydrogenase; TSH: Thyroid stimulating hormone; Student's t-test

professionals regarding NBS and training them for efficient handling of samples for the success of NBS [10,11]. The local physicians and midwiferies would be the best target to achieve higher awareness and consent rate in the parents [12,13].

The overall prevalence of metabolic disorders was 9.8/1000 neonates. The estimated prevalence of CH was found to be 3.3/1000 population in this hospital based study. Half of them diagnosed for dyshormonogenesis after thyroid uptake procedure. The prevalence reported in other areas varied from one in 727 to 2.1 in 1000. The multi-centric study conducted by Indian Council of Medical Research (ICMR) reported prevalence of one in 1172 [14-17]. Prior studies have observed maternal hypothyroidism in 4% to 13% antenatal cases. The studies have proposed that altered thyroid status like iodine deficiency, intake of anti-thyroid medications, presence of antibodies in mother might have an influence on baby's thyroid dyshormonogenesis [18,19]. Frequency of hypothyroidism in mothers of the neonates under present study was high with a percentage of 16.8% out of which nearly 3% babies depicted high TSH levels and only one was diagnosed for CH. Genetic factors related to mutations in the genes of the enzymes involved in thyroid hormone synthesis and metabolism are currently under much research. The enzyme cascades like thyroid oxidase, dualoxidase, thyroglobulin, iodotyrosine deiodinase and many others are under extensive research for their impact on fetal thyroid development. Studies have also suggested for higher recall rate for screening in infants of mothers diagnosed for thyroid related issues [5,19,20].

A significant association of TSH derangement with maternal age, gestational age and anaemia in mothers was observed in the present study. The chances for higher TSH in babies were two to three times more in mothers above 30 years and those who delivered prematurely. Preterm babies depicted higher incidence of impaired thyroid hormones. This could be attributed to immature hypothylamic-pituitary-thyroid axis to maintain the optimal level [21]. Various maternal factors have been postulated to influence the same that included stress factors in-utero, due to other medical or surgical illness. Present findings were in agreement to a case-control study for risk factors of CH revealed significant association for female gender and gestational age >40 weeks. The probability for CH was also found to be more among neonates born to mothers with associated thyroid disorders and gestational diabetes [22]. Transient form of TSH elevation was also seen in premature deliveries and those with intrauterine growth retardation. Though the neonates depict transient rise in TSH but some cohort studies also have reported cognitive sequelae due to high TSH during neonatal period [19,22,23]. This is suggestive of distinctive role of TSH and thyroid hormones in development starting very much from the neonatal period. A time based serial monitoring of TSH in such children would be beneficial to explore the physiology of hormone metabolism during the developmental process.

The results of the present study also accorded to other studies that observed an association of maternal age with lower fetal

thyroid FT3 in cord blood. Advanced age of mother had shown to increase risk for subclinical hypothyroidism and neonatal CH [5,24]. Though mode of delivery did not have significant impact on TSH profile, yet the probability to screen positive for TSH is two times higher than NVD. Few other studies also observed higher level of TSH in LSCS cases, though it was transient only [5,23]. Maternal anaemia predicts altered thryoid hormone profile in gestational period and might directly or indirectly influence on the neonate. Although not yet proved, few studies have shown that iron deficiency anaemia might alter the efficacy of iodised salt and thyroid peroxidase activity and thus, impairs the thyroid hormone peripheral conversion [6,25,26]. Present study results also revealed a significant association with maternal anaemia ($p<0.001$). More than 65% of neonates with higher TSH values were born to anaemic mothers. Even the mothers with mild anaemia depicted greater chances by 9.54 times (95% CI:3.42 to 26.58); ($p<0.001$) to give birth of baby with elevated TSH.

The mean PI (2.85±1.19) was significantly ($p=0.01$) higher in the neonates with raised TSH levels when compared to PI (2.45±0.65) in neonates with normal TSH levels. Birth weight was comparable but the length of the baby was significantly ($p=0.04$) smaller (46.12±4.68) than the normal TSH group (48.17±4.33). This asymmetric condition might be a measure for future obesity [7]. Prevalence of G6PD deficiency observed in present study was 6.6/1000. Few studies in this area reported frequency of 7.7% in the tribal area [3]. Another study revealed prevalence of 11.18% in tribal people and 1.2% in urban population [27]. The low prevalence recorded in this study could be due to the inflow of the patients to the institute. Being a tertiary care centre in the capital of the state, much of the patients' inflow is from the urban and close by rural areas.

Limitation(s)

The major limitation of the study was that it was a hospital based study with limited sample size and few metabolic disorders were studies. Large scale studies with regular follow-up of mothers from their antenatal period till six months of age of the baby, including a range of metabolic disorders would provide more accurate information regarding the factors associated with these disorders.

CONCLUSION(S)

The overall prevalence of metabolic disorders was 9.8/1000 in present study. The prevalence for CH being 3.3/1000 was quite high as compared to other frequencies reported in various studies. Being a hospital based study, the prevalence of G6PD was low (6.6/1000) as compared to other parts of this region. Various maternal factors like maternal age, gestational age and maternal anaemia could be considered as predictive indicators for neonatal outcome and a need a comprehensive approach towards dealing with these factors during ANC. It is recommended for development of strategy in order to improvise and up-grade the regional tertiary and secondary level health care centres with diagnostic facilities to cater these testings.

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