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Delayed Thyroid Function in Preterm Infants Especially in Low Weight Birth Infants

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Abstract: **Hypothyroidism is more typical in preterm infants than in term infants, particularly in sick preterm infants. Preterm infants have lower levels of tri-iodothyronine (T3) and free thyroxine (T4) than term infants during the very first several weeks, which is more extreme in the tiniest and least fully grown preterm infants. Therefore, this systematic review study aimed to evaluate the delayed thyroid function in newborns especially in low birth weight (LBW), from different aspects, also we aimed to discuss the complications that occur in consequence to this condition. We conducted our electronic search for relevant articles through several databases such; PubMed (MIDLINE), EMBASE, and GOOGLE scholar, up to December 2016, this searching for articles was done by combining the search terms premature*, preterm, low birth weight, thyroid function. Then lists of published articles were hand-searched to identify additional relevant studies. Thyroid dysfunction is frequently observed among the comorbidities related to prematurity. An immature hypothalamic-pituitary-thyroid axis, postnatal exhaustion of thyroid stores, non-thyroidal health problem, and administration of drugs (such as dopamine and steroids) can all lead to derangement in thyroid function in preterm newborns. Many aspects, taken together, might represent high danger conditions for thyroid problems that can impact these children in the neonatal duration as well as later on in life.**

Keywords: **Hypothyroidism, tri-iodothyronine.**

1. INTRODUCTION

Congenital hypothyroidism takes place in roughly 1 in 2000 to 1 in 4000 newborn babies worldwide, with substantial local and racial/ethnic variation. It is among the most common treatable reasons for intellectual special needs (mental retardation). Nevertheless, most newborn babies with this disorder have couple of or no scientific manifestations of thyroid shortage, and most of cases are sporadic [(1)]. Hypothyroidism is more typical in preterm infants than in term infants, particularly in sick preterm infants [(2)]. Preterm infants have lower levels of tri-iodothyronine (T3) and free thyroxine (T4) than term infants during the very first several weeks, which is more extreme in the tiniest and least fully grown preterm infants [(3)]. Several physiologic and nonphysiologic elements are understood to add to hypothyroidism in preterm infants, consisting of an immaturity of the hypothalamic-pituitary-thyroid axis, an immaturity of thyroidal capacity to manufacture and concentrate iodine, an immaturity of thyroid hormonal metabolism, a boost of thyroid hormonal agent requirement needs for thermogenesis and disease of preterm infants, iodine insufficiency and iodine excess [(3,4)].

Throughout fetal life, the thyroid gland establishes with production of thyroxine (T4) and triiodothyronine (T3) and secretion into the serum from about 12 weeks' pregnancy, the levels of which increase to term. In locations of endemic iodine deficiency, iodine supplements to women before pregnancy or up to the end of the second trimester protects the fetal brain from the effects of iodine shortage whereas 3rd trimester or neonatal supplementation does not improve neurological outcome [(6)].

In the preterm child, and fetus of similar pregnancy, the thyroid axis is immature, with reduced hypothalamic TRH production and secretion, an immature reaction of the thyroid gland to TSH, an ineffective capability of the follicular cell of the thyroid to originally iodine, and a low capacity to transform T4 into active T3. Hence, when a child is born preterm, the level of T4 is lower than that of term children and correlates with gestational age and birth weight [7].

The primary factors that influence delayed thyroid function in low weight infants are immaturity of the hypothalamic-pituitary-thyroid axis, immature thyroid hormone synthesis, immature thyroid hormone metabolism, and systemic diseases. Excessive or inadequate iodine consumption also influence preterm thyroid function [3]. Improvements in neonatal and perinatal care have actually increased the survival rate of an increasing variety of extremely low birth weight (LBW) infants. Newborn screening programs need to account for such infants. Most hereditary hypothyroidism screening programs in the United States determine thyroxine (T4) levels as the preliminary screening test, with thyrotropin (TSH) determined on samples [8,9].

Therefore, this systematic review study aimed to evaluate the delayed thyroid function in newborns especially in low birth weight (LBW), from different aspects, also we aimed to discuss the complications that occur in consequence to this condition.

2. METHODS

Systematic review study was designed to evaluate the delayed thyroid function in newborns especially in low birth weight (LBW) and that was based on guideline for systematic reviews.

Search methods:

We conducted our electronic search for relevant articles through several databases such; PubMed (MIDLINE), EMBASE, and GOOGLE scholar, up to December 2016, this searching for articles was done by combining the search terms premature*, preterm, low birth weight, thyroid function. Then lists of published articles were hand-searched to identify additional relevant studies. Our included articles were according to specific inclusion criteria, and one of the most important criteria, that trails must be discussing the thyroid function among premature infants, and only human studies were included, also we restricted our search to English language articles only.

3. RESULTS & DISCUSSION

The most typical pattern is transient hypothyroxinemia of prematurity (THOP; low T4 with regular TSH), which is observed in up to 50% of infants born before 28 weeks [10]. The only interventional trial to examine the effect of L-thyroxine treatment of THOP on developmental result revealed an initial benefit at 2 years of age in infants born < 27 weeks' pregnancy, but a lower IQ in more fully grown infants, with no considerable difference in either group by the age of 10 years [11,12,13]. In a nationwide case control study, the risk of circulatory collapse was greater in VLBW infants treated with L-thyroxine than in without treatment controls (4.2% vs. 1.8%) [14].

In addition to Transient hypothyroxinemia of prematurity (THOP), very LBW infants have a threat of primary hypothyroidism (low T4 with elevated TSH) about 14 times higher than that of normal birth weight children (1:250) [16]. Of very LBW infants with hereditary hypothyroidism (CH) discovered on newborn screening, nearly two-thirds exhibit a pattern of "delayed TSH increase," in which the TSH is later however initially normal ends up being elevated [16,17]. Woo et al. retrospectively studied 22 patients with congenital hypothyroidism and postponed TSH rise determined by screening 92,800 infants over 7 years in Rhode Island, USA. The incidence of CH with delayed TSH increase increased strikingly with lower birth weight: 1:58 in extremely low birth weight (ELBW, <1000 g) infants, 1:95 in VLBW infants, and 1:30, 329 in infants with birth weight ≥1500 g [18]. In 19 ELBW/VLBW infants, delayed rise in TSH was detected at a mean age of 22 days, the mean initial T4 concentration was low (4.7 µg/dL), and the mean peak TSH concentration was 62.3 mµIU/L (**TABLE 1**). 3 of 19 infants (15.8%)had a peak TSH concentration > 100 mIU/L and were treated with L-thyroxine, while the remaining patients were unattended. All cases of CH with delayed TSH rise were short-term and resolved at a typical age of 51 days, in contrast to another series where 30% of cases were long-term [19]. Subsequent data, consisting of developmental assessments, were gotten at 18 months of age in 9/16 surviving patients (55%). Compared to matched controls, patients with postponed TSH rise revealed no difference in neurological exam, or psychological, or psychomotor advancement but had an increased occurrence of small head circumference <10th percentile (33% vs. 0%), a finding of unclear scientific significance [18].

TABLE1: Clinical characteristics of infants with delayed TSH rise detected on newborn screening Data were extracted from Ref# [18].

	VLBW and ELBW	≥1500 grams
Number of cases	19	3
Gestational age, mean (weeks)	25.9	—
Birth weight, mean (grams)	790	—
Age at initial TSH elevation, mean (days)	22	25
Initial T4, mean (µg/dL)	4.7	8.1
Initial T4 < 5 µg/dL, *n* (%)	10 (52.6)	1 (33.3)
Peak TSH, mean (mIU/L)	62.28	26.05
Peak TSH > 40 mIU/L, *n* (%)	4 (21.1)	0 (0)
Peak TSH > 100 mIU/L, *n* (%)	3 (15.8)	0 (0)
Age at resolution, mean (days)	51.1	—

The high incidence of thyroid dysfunction in preterm infants has several causes. These infants are frequently seriously ill and for that reason may have low serum T4 and T3 concentrations due to non-thyroidal illness (NTI). Due to the fact that inflammatory cytokines have been linked in the pathophysiology of NTI, Dilli et al. [20] examined the relationship of markers of systemic inflammation with thyroid function in 148 infants born at <33 weeks' gestational age [20]. The authors verified a negative correlation between serum T3 concentration and levels of inflammatory markers (IL-6 and CRP), along with a significantly higher rate of sepsis in patients with a low T3 concentration (<65 ng/dL) [20].

Overview of different studies results determine the low birthweight correlation with thyroid function:

Hunter et al [21] reviewed the type and frequency of thyroid conditions discovered by the Northwest Regional Newborn Screening Program throughout a 20-year duration. Twenty-five infants had a delayed increase in TSH discovered only on a 2nd screen in between 2 and 6 weeks of age. Clinical information was readily available for 15 of 25 infants: 7 were preterm infants and 5 of the 7 had birth weights less than 1.35 kg. Continued follow-up for infants with low T4 and nonelevated TSH on initial screening test outcomes was advised [21]. In a retrospective analysis of more than 300,00 thyroid screening tests, Mandel et al [22] spotted 18 infants with "atypical hypothyroidism," specified as low T4 and normal TSH on initial screening specimen followed by an elevated TSH on a repeat blood specimen. 10 of the infants were VLBW infants. The reasons for the late rise in TSH in VLBW or extremely premature infants include developmental hold-up in hypothalamic-pituitary-thyroid axis maturation, impaired iodine and thyroglobulin storage in the thyroid gland, [23] and extreme illnesses, some requiring treatment with agents such as dopamine, which is known to suppress TSH secretion [24].

One consisted of research study [25] have actually observed that low serum T4 concentrations can happen transiently after birth in low birthweight infants have actually now been reached reveal that a serum T4 concentration of less 3.0, ug/100 ml is a remarkably typical occurrence. These low levels took place at some time in the first 3 weeks of life in 24% of AGA babies, in 35% of infants with HMD, and in 50% of those who were SGA. The cases of short-term hypothyroxinaemia reported earlier [26,27].

4. COMPLICATIONS AND TREATMENT

If dealt with early and with appropriate doses of T4 [28,29], infants with even serious permanent genetic hypothyroidism have outstanding developmental results. Depending upon the specific state reporting mechanisms, transient hypothyroxinemia and transient hypothyroidism might or might not be sufficiently detected. The long-lasting results of moderate hypothyroidism, along with short-term hypothyroidism especially in VLBW infants, are not yet fully known. Short-term hypothyroidism may not be a benign condition. Infants with transient hypothyroidism have an increased danger of associated extra thyroid congenital anomalies [30,31], as well as impaired developmental outcomes [32,33]. Potential research studies that consist of cautious evaluation combined with consistent long-lasting follow-up will assist

clarify the effect of transient hypothyroidism. Missing proof of absence of negative results of short-term or moderate hypothyroidism treatment with T4 is suggested [34,35]. Short-term low T4 values, a typical finding in VLBW infants, may be related to adverse long-term outcomes [36,37,38]. These concerns have actually led to trials of treatment of infants with VLBW and hypothyroxinemia. The biggest research study to date addressing this problem was performed by VanWassenaer et al [12] who enrolled 200 infants Less than 30 weeks' pregnancy into a randomized, placebo-controlled scientific trial of T4 administration (8 µg/ kg/day) for 6 weeks [12].

5. CONCLUSION

Thyroid dysfunction is frequently observed among the comorbidities related to prematurity. An immature hypothalamic-pituitary-thyroid axis, postnatal exhaustion of thyroid stores, non-thyroidal health problem, and administration of drugs (such as dopamine and steroids) can all lead to derangement in thyroid function in preterm newborns. Many aspects, taken together, might represent high danger conditions for thyroid problems that can impact these children in the neonatal duration as well as later on in life. Preterm infants with these features ought to be considered an unique danger category for relentless thyroid dysfunction and need to be closely followed up with periodical thyroid function screening and endocrinologic examinations.

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