e-ISSN: 0976-822X, p-ISSN:2861-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(5); 213-220

Original Research Article

A Retrospective Observational Assessment of Congenital Anomalies and Neonatal Outcomes in Pregnancies Affected by Hypothyroidism

Renu Prabha[1], Randhir Kumar Mishra[2]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, DMCH, Laheriasarai, Darbhanga, Bihar, India

[2]Senior Resident, Department of Pediatrics, Darbhanga Medical College and Hospital Darbhanga, Bihar, India

Received: 15-02-2023 / Revised: 25-03-2023 / Accepted: 13-04-2023

Corresponding author: Dr. Randhir Kumar Mishra

Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to report the neonatal outcomes and congenital anomalies in pregnancies affected by hypothyroidism.

Methods: We conducted a cross-sectional retrospective chart review of neonates of hypothyroid pregnant patients delivered at the DMCH, Laheriasarai, Darbhanga, Bihar, India for two years (Dec 2020-Dec 2022). Among 532 hypothyroid women recruited, 470 had live births. Out of 470 births, 459 were singleton, 16 were had twin pregnancy and 3 were had triplet pregnancy. Total 500 neonates were in the study. Data was collected by trained medical students.

Results: The mean gestational age at delivery was 37.5 weeks (SD 2.1). Single session phototherapy was required in 16% of neonates. Neonates with total bilirubin <255 mmol/L, requiring phototherapy were total 80. Out of these, 390 had appropriate birth weight and born at term and 105 had low birth weight at term. Women diagnosed before conception had significant association with low birth weight and congenital anomalies in the neonates. However, there was only marginally significant association of premature birth and sepsis in the neonates, with respect to these two groups. Other neonatal outcomes had no clinically significant association with respect to the timings of diagnosis of hypothyroidism in pregnant women.

Conclusion: In conclusion, our study described hyperbilirubinaemia as the most common neonatal outcome and cardiovascular defects as the most common major congenital anomaly. There was significant association of congenital anomalies and low birth weight with the timing of diagnosis of hypothyroidism in women.

Keywords: Hypothyroidism; Congenital Anomalies; Neonatal; Outcomes; Maternal.

Introduction

Hypothyroidism, both overt and subclinical, is common in women of reproductive age and during pregnancy, with frequencies ranging from 0.3% to 2.5%. [1] Hypothyroidism has adverse effects on the course of pregnancy and development of the fetus. [2] Several studies have reported that maternal hypothyroidism is associated with increased risks of abortions, stillbirths, preterm delivery, and pregnancy induced

hypertension. [3-6] Conversely, other reports have shown successful pregnancy outcomes in women who were profoundly hypothyroid. [1] More recently, the potential adverse impact of maternal hypothyroidism and hypothyroxinemia, even when subclinical, on neurodevelopmental outcomes in the offspring has been recognized. [7-9] Hypothyroidism should be corrected before initiation of pregnancy, replacement dosage should be augmented early in pregnancy, and euthyroidism should be maintained throughout. [10] Maternal hyperthyroidism during pregnancy is associated with an increased risk of low birth weight, predisposing to neonatal morbidity and mortality. [11] In addition, Medici et al. [12] have reported that maternal high-normal FT4 levels in early pregnancy are associated with lower birth weight and an increased risk of small for gestational age (SGA) newborns.

Thyroid-stimulating hormone surges soon after birth, resulting in thyroxine (T4) concentrations that are higher in the first postnatal week than at any other time of life and in circulating triiodothyronine (T3) concentrations that are three to four times higher than fetus. Thyroid hormone synthesis is critically dependent on an adequate prenatal and postnatal supply of iodine, which can paradoxically suppress T4 secretion when present in excess, especially in preterm infants and in the presence of iodine deficiency. [13] Congenital hypothyroidism is the most frequent cause of preventable mental retardation. Neonatal hypothyroidism has an incidence of one in 3.000–4.000 births and includes both permanent and transient types. [14]

Congenital hypothyroidism can be caused due to thyroid dysgenesis, disorders of thyroid hormone synthesis, iodine deficiency or excess, as well as trans-placental transfer of maternal antibodies or medications. [5,15] Untreated hypothyroidism is associated with several complications, most notably preeclampsia, abruptio placentae and increased risk of spontaneous miscarriage, perinatal mortality, preterm delivery and low birth weight. Treatment of pregnant mothers with l-thyroxine reduces these complications substantially. [16] Enough evidence has accumulated over the years about the role of thyroxine in normal development of the fetal brain. Congenital hypothyroidism is a preventable cause of intellectual disability. Hence it is important to monitor babies born to mothers with hypothyroidism.

The aim of the present study was to report the neonatal outcomes and congenital anomalies in pregnancies affected by hypothyroidism.

Materials and Methods

We conducted a cross-sectional retrospective chart review of neonates of hypothyroid pregnant patients delivered at the DMCH, Laheriasari, Darbhanga, Bihar, India for two years. Among 532 hypothyroid women recruited, 470 had live births. Out of 470 births, 459 were singleton, 16 were had twin pregnancy and 3 were had triplet pregnancy. Total 500 neonates were in the study. Data was collected by trained medical students. It was randomly double-checked and corroborated by the principal investigator. We reviewed the medical record files of neonates of the mothers who were either a known case of hypothyroidism (overt as well as subclinical) or were diagnosed during their antenatal visits. We determined the timing of diagnosis of hypothyroidism (newly diagnosed as well as previously diagnosed) through data recorded by their primary physicians (endocrinologist or obstetricians) in relation to the gestation during the study period. We started the file review of the most recent case. We noted the data from neonatal files including neonatal TSH level of 2nd or 3rd day of life (whichever available).

We selected neonates born to mothers who were diagnosed hypothyroid according to the following inclusion criteria: All pregnant women attending endocrine and obstetric clinic who had been diagnosed overt [thyrotropin (TSH) > 2.5 mIU/l and low free tetra-iodothyronine (FT4) OR TSH > 10 mIU/l only] or subclinical (TSH 2.5-10 mIU/l and normal FT4) hypothyroidism either before or during pregnancy. Patients were either on levothyroxine replacement or newly started according to their presentation. Maternal characteristics and maternal outcomes of these neonates have already been published in a separate article (MHPO-1). [17] Pregnancies with any abnormal thyroid function tests that did not fit into the overt or subclinical hypothyroidism criteria by American Thyroid Association were excluded from the study. [18]

Statistical analysis

The results of demographic and clinical features are presented as mean ± standard deviation for quantitative variables and number (percentage) for qualitative variables. Proportional differences were assessed by using the Chi-square test or Fisher exact test where appropriate. For the purpose of subgroup analysis, variables of birth weight and gestational age at delivery were recoded dichotomously into low birth weight and premature birth. Unadjusted Odds ratio was calculated for the effect of timing of diagnosis of hypothyroidism on various neonatal outcomes and congenital anomalies.

Results

Neonatal outcomes	**N %**
Gestational age at delivery (weeks)	
Extremely preterm (<28)	5 (1)
Very preterm (28–31)	10 (2)
Late preterm (32–36)	85 (17)
Term (37–42)	400 (80)
Birth weight (g)	
Low (<2500)	105 (21)
Appropriate (2500–4000)	390 (78)
Large (>4000)	5 (1)
Not documented	2 (0.4)
Respiratory complications	40 (8)
Sepsis	35 (7)
Hypocalcaemia	25 (5)
Neonatal Jaundice	50 (10)
Total Bilirubin 1.0–5.0 (mg/dl)	240 (48)
Total Bilirubin 5.1–10.0	150 (30)
Total Bilirubin 10.1–15.0	25 (5)
Total Bilirubin 15.1–20.0	50 (10)
Need for phototherapy	80 (16)
APGAR at 1 min	7.8 (± 0.6)
APGAR at 5 min	8.8 (± 0.4)
Low APGAR at 5 min (Score<7)	2 (0.4)
NICU admission	
Less than 24 h	10 (2)
More than 24 h	55 (11)
Neonatal TSH (at 48 h) (mIU/L)	4.1 (2.4–6.8)

Neonatal death	
Early (<7days)	4 (0.8)
Late (between 7-28)	4 (0.8)

The mean gestational age at delivery was 37.5 weeks (SD 2.1). Single session phototherapy was required in 16% of neonates. Neonates with total bilirubin <255 mmol/L, requiring phototherapy were total 80. Out of these, 390 had appropriate birth weight and born at term and 105 had low birth weight at term.

Table 2: Subgroup analysis of neonatal outcomes and congenital anomalies based on timing of diagnosis of hypothyroidism

Neonatal outcomes	**Diagnosis of maternal hypothyroidism**		**P Value**
	During pregnancy N=50	**Prior to pregnancy N=450**	
Low APGAR at 5 min			
Yes	0	5 (1.12)	1.000
No	50 (100)	445 (98.8)	
Premature birth			
Yes	14 (28)	90 (20)	0.50
No	36 (72)	360 (80)	
Low Birth Weight			
Yes	15 (30)	90 (20)	0.25
No	35 (70)	360 (80)	
Respiratory distress syndrome			
Yes	5 (10)	36 (8)	0.55
No	45 (90)	414 (92)	
Sepsis			
Yes	6 (12)	27 (6)	0.48
No	44 (88)	423 (94)	
Hyperbilirubinemia			
Yes	16 (32)	162 (36)	0.420
No	34 (68)	288 (64)	
Need for Phototherapy			
Yes	5 (10)	68 (15.12)	0.360
No	45 (90)	382 (84.88)	
Hypocalcaemia			
Yes	4 (8)	27 (6)	0.325
No	46 (92)	423 (94)	
NICU admission less than 24 h			
Yes	0	9 (2)	0.410
No	50 (100)	441 (98)	
NICU admission more than 24 h			
Yes	8 (16)	45 (10)	0.120
No	42 (84)	405 (90)	
Neonatal death			
Yes	1 (2)	9 (2)	0.620
No	49 (98)	441 (98)	

Congenital anomalies and conditions			
Yes	20 (40)	90 (20)	.001
No	30 (60)	360 (80)	

Women diagnosed before conception had significant association with low birth weight and congenital anomalies in the neonates. However, there was only marginally significant association of premature birth and sepsis in the neonates, with respect to these two groups. Other neonatal outcomes had no clinically significant association with respect to the timings of diagnosis of hypothyroidism in pregnant women.

Discussion

Hypothyroidism is widely prevalent in pregnant women and the rate of detection, especially in a developing country like India, has not kept pace with the magnitude of the problem. Since hypothyroidism is easily treated, timely detection and treatment of the disorder could reduce the burden of adverse fetal and maternal outcomes, which are very commonly encountered.

Pregnancy influences thyroid function in multiple ways. Maternal hypothalamic-pituitary-thyroid (HPT) axis undergo a series of adjustments, fetus develops its own HPT axis and the placenta plays an active role in iodide and T4 transport and metabolism. Thus, an integrated three-compartment thyroid model exists during gestation. [19] Early in pregnancy estrogen promotes production of a more highly sialylated T4-binding globulin isoform that is less rapidly degraded, resulting in increased serum T4-binding globulin and T4 concentrations. The thyroxine-binding globulin (TBG) begins to increase early in the first trimester, plateaus during midge station, and persists until shortly after delivery. This increased TBG concentration leads to an expansion of the extra-thyroidal pool and results in elevated total T3 and T4 levels. A high circulating HCG level in the first trimester leads to HCG cross-reactivity with the TSH receptor, resulting in temporary increase in free T4 and partial suppression of TSH. The final physiologic change results from placental deiodination of maternal T4, which increases T4 turnover. [20]

In a systematic review by Maraka S et al among pregnant women with subclinical hypothyroidism, it was found that they were at higher risk for pregnancy loss, placental abruption, PROM, and neonatal death compared with euthyroid pregnant women. This emphasizes the importance of screening all the mothers for hypothyroidism. [21] Effects of maternal hypothyroidism on fetal brain development are not well defined, several recent reports indicate that IQ is modestly affected. These studies have increased the concern that even mild hypothyroidism can interfere with normal brain development. A recent cross-sectional study from Bangladesh has reported maternal hypothyroidism to be present in 5.12% of babies born with congenital anomalies. [22] Several studies are reported about the association of congenital maternal hypothyroidism and the risk of neurodevelopment impairment of their children. [23,24] However, data are still conflicting about this strong association in mothers without congenital hypothyroidism; hence, it is difficult to report this from the literature. [25-27]

Thyroxine dose requirement increases during pregnancy and thus close monitoring of thyroid function with appropriate adjustment of thyroxine dose to maintain a normal serum TSH level is necessary throughout gestation. Within a joint endocrine–obstetric clinic, maternal hypothyroidism at presentation and in the third trimester may increase the risk of low birthweight. Derksen-Lubsen et al in a meta-analysis suggested that at least part

of the brain damage in patients with CH was caused in utero and may not be prevented by initiation of early treatment after birth. All studies analyzed by them had shown a trend toward lower IQ and poorer motor skills in congenital hypothyroidism patients compared with controls; meta-analysis showed the deficit to be significant. The most important independent risk factor for the eventual outcome was the severity of congenital hypothyroidism (defined by initial T4 at the moment of diagnosis and skeletal maturation). However, two changes in management, early initiation of treatment, and higher dose l-thyroxine therapy to mother may abrogate or ameliorate any impact of thyroid hormone deficiency on intellectual development. [28] This explains need for screening of all pregnant mothers for hypothyroidism in early part of gestation.

Rovet reported the long-term outcome in a large cohort of Toronto based children with congenital hypothyroidism identified by newborn screening from infancy to adolescence. Early findings revealed a 5-10-point decline in IQ, poorer visuomotor and visuospatial abilities, delayed speech and language development, selective neuromotor deficiencies, and poorer attention and memory skills, which were correlated with different disease and treatment factors. Furthermore, 30% of these adolescent patients were not receiving an adequate l-thyroxine dose. [29] The "Controlled Antenatal Thyroid Screening Study," (CATS) by Lazarus et al, in the United Kingdom, in their ongoing 8-year prospective intervention trial seeks to determine whether universal screening of pregnant women (and levothyroxine treatment, when hypothyroid) prevents adverse outcomes. In their study, serum samples were obtained before 16 weeks gestation, with half of the sera analyzed immediately for free T4 and TSH, and the other half frozen until delivery. Women with a free T4 below the 2.5th percentile and/or TSH above the 97.5th percentile were given levothyroxine therapy. The main outcome measure was development of the unborn child, measured at 3 year of age. With the data available till date universal screening of all pregnant mothers is better than case finding so as to not miss any mother with hypothyroidism thus preventing adverse maternal and fetal outcome. [30,31]

Conclusion

In conclusion, our study described hyperbilirubinaemia as the most common neonatal outcome and cardiovascular defects as the most common major congenital anomaly. There was significant association of congenital anomalies and low birth weight with the timing of diagnosis of hypothyroidism in women. Moreover, premature birth and neonatal sepsis is also associated in this respect with marginal significance. We observed higher congenital anomalies and conditions in neonates born to women diagnosed during pregnancy. As this is a single hospital study, women with known hypothyroidism could have been more likely referred into our hospital for the high-risk obstetrical care with lessor congenital defects.

References

1. Idris I, Srinivasan R, Simm A, Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. Clinical Endocrinology. 2005 Nov;63(5):560-5.
2. M. Abalovich, N. Amino, L. A. Barbour et al., "Clinical practice guideline: management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline," Journal of Clinical Endocrinology and Metabolism, 2007; 92, supplement 8: S1–S47.
3. Montoro MN. Management of hypothyroidism during pregnancy.

Clinical obstetrics and gynecology. 1997 Mar 1;40(1):65-80.
4. L. E. Davis, K. J. Leveno, and E. G. Cunningham, Hypothyroidism complicating pregnancy, Obstetrics & Gynecology, 1988; 72(1): 108–112.
5. Smallridge RC, Ladenson PW. Hypothyroidism in pregnancy: consequences to neonatal health. The Journal of Clinical Endocrinology & Metabolism. 2001 Jun 1;86(6):2349-53.
6. Wasserstrum N, Ananla CA. Perinatal consequences of maternal hypothy roidism in early pregnancy and inadequate replacement. Clinical endocrinology. 1995 Apr;42(4):353-8.
7. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New England Journal of Medicine. 1999 Aug 19;341(8):549-55.
8. R. Z. Klein and M. L. Mitchell, Maternal hypothyroidism and child development, Hormone Research, 1999; 52(2): 55–59, 1999.
9. Pop VJ, Brouwers EP, Vader HL, Vulsma T, Van Baar AL, De Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clinical endocrinology. 2003 Sep; 59 (3):282-8.
10. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. New England Journal of Medicine. 2004 Jul 15;351(3):241-9.
11. Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, Hooijkaas H, de Rijke YB, Tiemeier H, Bongers-Schokking JJ, Visser TJ. Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. The Journal of Clinical Endocrinology & Metabolism. 2013 Jan 1;98(1):59-66.
12. Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, Hofman A, Hooijkaas H, Steegers EA, Tiemeier H, Bongers-Schokking JJ. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. The Journal of Clinical Endocrinology & Metabolism. 2012 Feb 1;97(2):646-52.
13. Feingold SB, Brown RS. Neonatal thyroid function. NeoReviews. 2010 Nov;11(11): e640-6.
14. Benvenga S., Ordookhani A., Pearce E.N., Tonacchera M., Azizi F. and Braverman L.E., 2008. Detection of circulating autoantibodies against thyroid hormones in an infant with permanent congenital hypothyroidism and her twin with transient congenital hypothyroidism: possible contribution of thyroid hormone autoantibodies to neonatal and infant hypothyroidism. Journal of Pediatric Endocrinology and Metabolism, 2008; 21(10):1011-1020.
15. Ozedimir H. Akman I, Coskun S, Demirel U, Turan S, Bereket A et al. Maternal thyroid dysfunction and neonatal thyroid problems. Int J Endocrinol. 2013.
16. Montoro MN. Management of hypothyroidism during pregnancy. Clin Obstet Gynecol. 1997; 40:65-80.
17. Kiran Z, Sheikh A, Malik S, Meraj A, Masood M, Ismail S, Rashid MO, Shaikh Q, Majeed N, Sheikh L, Islam N. Maternal characteristics and outcomes affected by hypothyroidism during pregnancy (maternal hypothyroidism on pregnancy outcomes, MHPO-1). BMC pregnancy and childbirth. 2019 Dec;19(1):1-2.
18. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the american thyroid association for the diagnosis

and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27(3): 315–389.
19. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med. 1994; 331:1072-8.
20. Sahay RK, Nagesh VS. Hypothy roidism in pregnancy. Indian Journal of Endocrinology and Metabolism. 2012;16(3):364-370.
21. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Ospina NM, T O'Keeffe D, De Ycaza AE, Rodriguez-Gutierrez R, Coddington CC, Stan MN. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. Bmj. 2017 Jan 25; 356.
22. Fatema K, Das T, Mannan A, Zaman SM. Frequency, Distribution of Congenital Anomaly and Associated Maternal Risk Factors. Mymensingh Medical Journal: MMJ. 2017 Jul 1;2 6(3):658-66.
23. Amr NH. Thyroid disorders in subjects with down syndrome: an update. Acta Bio-Medica: Atenei Parmensis. 2018; 89(1):132–139.
24. Pierce MJ, LaFranchi SH, Pinter JD. Characterization of thyroid abnormalities in a large cohort of children with Down syndrome. Horm Res Paediatr. 2017;87(3): 170–178.
25. Nazarpour S, Tehrani FR, Simbar M, Tohidi M, Majd HA, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. European journal of endocrinology. 2017 Feb 1;176(2):253 -65.
26. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, Azizi F. Effects of levothyroxine on pregnant women with subclinical hypothyroidism, negative for thyroid peroxidase antibodies. The Journal of Clinical Endocrinology & Metabolism. 2018 Mar;103(3):926-35.
27. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, Reddy UM, Wapner RJ, Thorp Jr JM, Saade G, Tita AT. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. New England Journal of Medicine. 2017 Mar 2;376(9):815-25.
28. Derksen-Lubsenb G, Verkerk PH. Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. Pediatr Res. 1996; 39:561-6.
29. Rovet JF. Congenital hypothyroidism: long-term outcome. Thyroid. 1999 Jul; 9(7):741-8.
30. Taylor P, Lacey A, Thayer D, Draman M, Tabasum A, Muller I, Marsh L, Poacher A, Roberts A, Ludgate M, Rees A. Controlled antenatal thyroid screening study. obstetric outcomes. InEndocrine Abstracts 2016 Oct 14; 44: Bioscientifica.
31. Sanoussi M, N., Brahim B., Derkaoui, A., Abdelkrim S., & Mohammed K. Facteurs De Risques Du Sepsis Chez Les Traumatises Craniens Graves. Journal of Medical Research and Health Sciences, 2022; 5(1): 1653–1657.