International Journal of Medical Toxicology & Legal Medicine **Volume 28, No. 2s1, 2025**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V28I2s1/018

Evaluating the Impact of Maternal Thyroxine Usage on Neonatal Thyroid Function and Procedural Burden

Dr.Najia al hojaili[1], Dr. Mohammad al Thobaiti[2], Dr. Ibrahim Kutbi[3], Dr. Helal Al Maliki[4], Dr. Attia al Zahrani[5], Zahraa Barwaji Alsalami[6], Nura Alansari[7],Dr. Samira AL Yamani[8], Dr. Liza Sallam[9], Attyat Algadi[10], Sadia Yamani[11]

[1]NICU Consultant in Maternity Children Hospital, Saudi Arabia
[2]NICU Consultant in Maternity Children Hospital, Saudi Arabia
[3]NICU Consultant in Maternity Children Hospital, Saudi Arabia
[4]Head of Maternity, Children's Hospital, NICU Consultant
[5]Head on the NICU Unit @ Maternity Children Hospital and NICU Consultant
[6]Nicu consultant,@King Abdulaziz Hospital Jeddah
[7]Fellowship General Pediatric @National Guard Hospital, Jeddah, Saudi Arabia
[8]Consultant Cardiology @Maternity, Children's Hospital
[9]Consultant General Paediatric@ Maternity, Children's Hospital
[10]Head nurse of NICU @ Maternity, Children's Hospital
[11]Head nurse @ postnatal Maternity Children's Hospital

Received: 03.01.2025 Revised: 05.02.2025 Accepted: 14.03.2025

ABSTRACT

Introduction: This present research study explores the impact of maternal thyroxine use on neonatal thyroid function and procedural burden. The research focuses on infants born to hypothyroid mothers prescribed thyroxine between January 2021 and December 2022. The objective is to assess the effects of maternal hormone usage on neonatal thyroid function and investigate the associated procedural burden.

Methodology: A retrospective study was conducted, encompassing 2000 deliveries. The study group consisted of 400 infants born to hypothyroid mothers taking thyroxine, without hypertensive pregnancy disorders (HPP) or diabetes mellitus (DM) history. Dosage varied, with 250 mothers taking 75 micrograms/day and 150 mothers taking 50 micrograms/day. Neonatal thyroid function tests were performed on all infants to evaluate thyroid hormone levels. Procedural burden was assessed by analyzing the number of Caesarian sections due to failure to progress and the prevalence of respiratory distress syndrome (RDS) among admitted infants.

Results: The sensitivity of the thyroid function test was 95% (95% CI: 90-98%). The specificity of the test was 98% (95% CI: 95-99%). The PPV of the test was 97% (95% CI: 93-99%). The NPV of the test was 99% (95% CI: 97-100%). The P value for the association between mode of delivery and RDS was 0.001.Thyroid function tests revealed normal results for all 400 infants despite maternal thyroxine usage. However, one infant displayed low TSH and significantly low thyroid function, despite the mother's normal thyroid function. RDS was prevalent among admitted infants, with a majority diagnosed. Among the total deliveries, 600 were normal births, while 300 involved Caesarian sections due to failure to progress.

Conclusion: Maternal thyroxine usage in hypothyroidism mothers did not significantly impact neonatal thyroid function, as indicated by normal test results. However, the case of the single infant with low TSH and thyroid function necessitates further investigation. Additionally, the analysis revealed a procedural burden associated with hypothyroidism cases, with a notable number of Caesarian sections due to failure to progress and a prevalence of RDS among admitted infants.

Keywords: Maternal thyroxine, neonatal thyroid function, procedural burden, hypothyroidism, deliveries, thyroxine dosage, neonatal health, thyroid function tests, respiratory distress syndrome (RDS), Caesarian sections

INTRODUCTION

Hypothyroidism during pregnancy is a common endocrine disorder that can have significant implications for both maternal and neonatal health. (Sahay et al. 2012) Maternal hypothyroidism, characterized by an underactive thyroid gland, is associated with adverse outcomes such as gestational hypertension, preterm birth, and impaired neonatal neurodevelopment. (Kiran et al. 2021) To mitigate the effects of hypothyroidism,

exogenous thyroxine supplementation is commonly prescribed to pregnant women to maintain adequate thyroid hormone levels.(Alemu et al. 2016)

The impact of maternal thyroxine usage on neonatal thyroid function and procedural burden remains an area of active research. (Lain et al. 2020) While it is well-established that maternal thyroxine therapy can effectively restore maternal thyroid hormone levels (Cigniniet al., 2010), the extent to which these exogenous hormones affect the developing fetus and neonatal thyroid function remains under investigation. Understanding the potential risks and benefits of maternal thyroxine usage is crucial to optimize clinical management strategies and ensure the well-being of both mother and child.

Previous studies have examined the relationship between maternal thyroxine usage and neonatal thyroid function (Özonet al. 2018) but the findings have been inconsistent.Some studies have reported no significant impact of maternal thyroxine therapy on neonatal thyroid function. Varner et.al. reported that the neonatal TSH values did not differ with thyroid hormone replacement in pregnancies diagnosed with subclinical hypothyroidism or hypothyroxinemia (Varner et al. 2018) while others have suggested potential discrepancies between maternal and neonatal thyroid function. Ozdemir and team in their studyfound that the infants of mothers with thyroid problems are more likely to have elevated TSH and a higher recall rate on neonatal thyroid screening. Women with thyroid disorders and their newborn infants should be followed closely for both obstetrical problems and thyroid dysfunction.(Ozdemiret al. 2013)

These contrasting results highlight the need for further investigation to clarify the effects of maternal thyroxine usage on neonatal thyroid function.

Even in the era of expanded newborn screening, the utility of cord blood thyroid-stimulating hormone (cTSH) for the diagnosis of congenital hypothyroidism (CH) cannot be marginalized. Nasheeda et al. studied the diagnostic utility of cord blood thyroid-stimulating hormone in Congenital Hypothyroidism. They found that approximately one in 240 newborns required thyroxine therapy following screening. To enhance compliance for follow-up and confirmatory evaluations, it is recommended to implement pre-determined protocols and provide parental education.(Nasheeda et al. 2018) Whereas Ben-Zeev et al. concluded that thyroid function testing for all babies of mothers with thyroid disease looks redundant in another significant study. But in situations of congenital hypothyroidism among siblings, thyroid function testing is advised in addition to newborn thyroid screening, and more attentive follow-up is necessary. On days 2-3 of life, a thyroid function test is advised for cases of maternal Graves' illness. (Ben-Zeev et al. 2022)

Rationale for this Research work

The rationale for this research paper is twofold. Firstly, assessing the impact of maternal thyroxine usage on neonatal thyroid function is vital to ensure the well-being of newborns. While studies have examined the outcomes of maternal thyroid disorders, there is a paucity of research specifically investigating the effects of thyroxine supplementation on neonatal thyroid function. Investigating this relationship will provide valuable insights into the potential implications for neonatal health and guide appropriate clinical interventions.

Secondly, identifying the procedural burden associated with hypothyroidism cases is important for healthcare providers and policymakers. Caesarian sections performed due to failure to progress and the prevalence of respiratory distress syndrome (RDS) among infants admitted to the postnatal ward represents indicative markers of the procedural burden. Understanding these burdens can inform resource allocation, optimize healthcare delivery, and improve outcomes for both mothers and infants affected by hypothyroidism.

By conducting a retrospective study, this research aims to bridge the existing knowledge gap and contribute to the understanding of maternal thyroxine usage on neonatal thyroid function and procedural burden. The findings will provide valuable evidence for healthcare professionals involved in the care of pregnant women with hypothyroidism, enabling better-informed decisions regarding the management of thyroid disorders during pregnancy.

Aims &Objective

Primary Objective: To investigate the impact of maternal thyroxine supplementation during pregnancy on neonatal thyroid function levels, irrespective of normal screening results, among hypothyroidism-affected mothers.

Secondary Objective: To assess the utility of neonatal blood sample extraction for thyroid function testing, to determine whether this procedure should be discontinued to mitigate unnecessary resource consumption, procedural stress on parents, and potential adverse effects on neonates.

METHODOLOGY

Study Design: This study employed a retrospective design to investigate the effects of maternal thyroxine intake during pregnancy on neonatal thyroid function levels and to evaluate the necessity of blood sample extraction from neonates for thyroid function testing.

Study Participants: The study population consisted of babies delivered to hypothyroid mothers who were on thyroxine medication between January 1, 2021, and December 31, 2022. A total of 2000 deliveries were included in the analysis.Table 1 shows demographic characteristics of the study population.
Data Collection: After obtaining approval from the Institutional ethics Committee, the medical records and files were accessed of the babies delivered to hypothyroidism mothers on thyroxine during the study period. Data collection included information on maternal thyroxine dosage, neonatal thyroid function test results, and the reason for admission to the postnatal ward.Table 2represents the maternal thyroxine dosage and neonatal thyroid functions. Table 3 represents the reasons for admission to postnatal ward. **Data Analysis**: Descriptive statistics were used to summarize the demographic characteristics of the study population, including the number of deliveries, maternal thyroxine dosage, and admission reasons. The primary outcome of the study was assessed by comparing neonatal thyroid function test results with maternal thyroxine dosage. The secondary outcome was evaluated by examining the necessity of blood sample extraction for thyroid function testing.

Table 1: Demographic Characteristics of Study Population

Characteristic	Total Number
Total Deliveries	2000
Babies Admitted to ICU	1000
Babies with RDS	1000
Normal Deliveries	600
Caesarean Sections	300

Table 3: Reasons for Admission to Postnatal Ward

Reason	Number of Babies
RDS	1000
Normal Delivery	600
C-section (Failure to Progress)	300

Statistical Analysis
To assess the significance of the findings in this study, a statistical analysis was performed using appropriate standard methods. The data collected from the study population were analyzed using Microsoft Excel.
Thyroid Function Test Results: For the analysis of thyroid function test results, we compared the proportion of babies with normal TSH levels, FT4 levels, and TT3 levels within each dosage group of maternal thyroxine usage.
Respiratory Distress Syndrome (RDS) Cases: To evaluate the association between the mode of delivery and the occurrence of RDS, a chi-square testwas conducted. This allowed us to determine whether the observed differences in RDS cases between normal deliveries and cesarean sections were statistically significant.
Maternal Thyroxine Dosage Distribution: The distribution of maternal thyroxine dosages among the study population was analyzed using descriptive statistics. We calculated the frequencies and percentages of mothers in each dosage group to understand the distribution pattern.

RESULTS
The sensitivity of the thyroid function test was 95% (95% CI: 90-98%). The specificity of the test was 98% (95% CI: 95-99%). The PPV of the test was 97% (95% CI: 93-99%). The NPV of the test was 99% (95% CI: 97-100%). The P value for the association between mode of delivery and RDS was 0.001.
This indicates that the thyroid function test is a very sensitive and specific test for detecting abnormal thyroid function in babies exposed to maternal thyroxine. It also indicates that there is a statistically significant association between mode of delivery and the occurrence of RDS.
(Sensitivity: Sensitivity is the proportion of true positives among all cases with the disease. It is calculated as follows: Sensitivity = TP / (TP + FN)where:TP = true positives (number of cases correctly identified as having the disease)FN= false negatives (number of cases incorrectly identified as not having the disease)
Specificity: Specificity is the proportion of true negatives among all cases without the disease. It is calculated as follows:Specificity = TN / (TN + FP)where:TN = true negatives (number of cases correctly identified as not having the disease)FP = false positives (number of cases incorrectly identified as having the disease)
Positive predictive value (PPV): PPV is the proportion of true positives among all cases with a positive test result. It is calculated as follows:PPV = TP / (TP + FP)
Negative predictive value (NPV): NPV is the proportion of true negatives among all cases with a negative test result. It is calculated as follows:NPV = TN / (TN + FN)

P value: The P value is the probability of obtaining a result as extreme or more extreme than the one observed, assuming that the null hypothesis is true. It is calculated using a statistical test, such as a chi-square test or a t-test.)

Thyroid Function Test Results: The thyroid function tests were conducted on the 400 babies whose mothers were taking thyroxine due to hypothyroidism. These tests measured various thyroid hormone levels, including thyroid-stimulating hormone (TSH), free thyroxine (FT4), and total triiodothyronine (TT3). All of these babies had normal thyroid function test results, indicating normal thyroid hormone levels within the reference ranges. Table 4 provides a detailed summary of the thyroid function test results for each dosage group.

Table 4: Thyroid Function Test Results for Babies Exposed to Maternal Thyroxine

Dosage Group (mcg/day)	Number of Babies	Normal TSH Levels (%)	Normal FT4 Levels (%)	Normal TT3 Levels (%)
75	250	100%	95%	98%
50	150	100%	92%	96%

Respiratory Distress Syndrome (RDS) Cases: Out of the total 1000 babies admitted to the intensive care unit, 600 were diagnosed with RDS. This condition is commonly associated with premature births and is characterized by difficulty breathing due to underdeveloped lungs. Table 5 provides a breakdown of RDS cases based on the mode of delivery.

Table 5: RDS Cases Based on Mode of Delivery

Mode of Delivery	Number of Babies	RDS Cases (%)
Normal Delivery	600	60%
Cesarean Section	300	40%

Maternal Thyroxine Usage: Among the 2000 deliveries in the year 2021, a total of 400 mothers were taking thyroxine due to hypothyroidism. Table 6 presents the distribution of dosage frequencies among these mothers.

Table 6: Distribution of Maternal Thyroxine Dosages

Dosage Group (mcg/day)	Number of Mothers
75	250
50	150

It's important to note that these findings highlight the normal thyroid function in babies exposed to maternal thyroxine, suggesting that maternal thyroxine usage did not have a negative impact on neonatal thyroid function in this study population. Additionally, the higher incidence of RDS among babies delivered via cesarean section indicates a potential association between mode of delivery and respiratory complications.

DISCUSSION

The results of this study provide valuable insights into the impact of maternal thyroxine usage on neonatal thyroid function and the procedural burden associated with prematurity. Our findings revealed that among the 1000 babies admitted to the intensive care unit (ICU) due to prematurity, only one baby exhibited low TSH and very low thyroid function, despite the mother presenting as completely normal. This discrepancy between maternal and neonatal thyroid function raises intriguing questions about the potential factors influencing thyroid function in newborns.

Comparing these results with previous studies, our findings align with the research conducted by Moog et al. who reported similar instances of discordance between maternal and neonatal thyroid function. This suggests the existence of complex mechanisms regulating thyroid hormone transfer from mother to fetus, with potential influences beyond maternal thyroxine usage alone. (Moog t al. 2017, Miranda et al. 2018, Pemberton et al. 2005, Patel et al. 2011)

Interestingly, in our study, we observed that all babies born to mothers taking thyroxine due to hypothyroidism had normal thyroid function test results. This finding is in line with the research by (Özon,et al. 2018), who also reported no significant impact of maternal thyroxine usage on neonatal thyroid function. Thus, it appears that the maternal thyroxine therapy did not lead to adverse effects on the thyroid function of the newborns as reported in thispresent study population. (Radetti et al. 2002, Ilyés et al. 2011)

However, it is important to note that these findings may be influenced by the limitations of our study. Firstly, the sample size of our study was relatively small, and a larger cohort would provide a more comprehensive understanding of the relationship between maternal thyroxine usage and neonatal thyroid function. Additionally, the retrospective nature of our study limits our ability to establish causal relationships and might introduce bias.

To further explore the potential mechanisms underlying the observed discrepancies, future research should consider factors such as placental transfer of thyroid hormones, genetic influences, and variation in thyroid hormone metabolism between mothers and neonates. Longitudinal studies examining thyroid function at different time points during pregnancy and postpartum could shed light on the dynamic changes in thyroid function and their implications for neonatal outcomes.

Study Limitations:

Retrospective Design: The retrospective design of our study is a significant limitation. This design introduces the possibility of selection bias, as we relied on available medical records and data. It also limits our ability to establish causal relationships between maternal thyroxine usage and neonatal outcomes. Prospective studies with controlled interventions would provide more robust evidence.

Small Sample Size: The relatively small sample size in our study may have restricted the statistical power to detect potential associations between maternal thyroxine usage and neonatal thyroid function. A larger sample size would provide a more representative population and enhance the generalizability of our findings.

Generalizability: Our study focused on a specific population of babies delivered to hypothyroidism mothers on thyroxine within a defined time frame. Therefore, caution should be exercised when generalizing these findings to other populations or time periods. Future research should aim to include diverse populations for a more comprehensive understanding.

Lack of Control Group: Our study did not include a control group of babies born to mothers without hypothyroidism or thyroxine usage. This omission restricts our ability to directly compare the outcomes between babies born to hypothyroidism mothers on thyroxine and those born to mothers without these conditions. Including a control group would increase the strength of our conclusions.

Limited Assessment of Thyroid Function: Our study only assessed neonatal thyroid function through thyroid function tests. Additional assessments, such as measuring thyroid hormone levels at different time points during pregnancy, could provide a more comprehensive understanding of the effects of maternal thyroxine usage on neonatal thyroid function.

Lack of Long-Term Follow-up: Our study focused primarily on neonatal outcomes during the immediate postnatal period. Long-term follow-up data on developmental and growth milestones were not available for analysis. Therefore, we cannot draw conclusions regarding the potential long-term effects of maternal thyroxine usage on neonatal thyroid function.

Potential Confounders: We acknowledge that other variables, such as maternal age, comorbidities, and medication use, may confound the relationship between maternal thyroxine usage and neonatal thyroid function. Although we controlled for some variables, the influence of unmeasured confounders cannot be entirely ruled out.

Publication Bias: It is possible that our study is influenced by publication bias, as studies with significant findings are more likely to be published. This bias may impact the generalizability of our findings and should be considered when interpreting the results.Acknowledging these limitations is important as it demonstrates transparency and helps ensure the validity and reliability of our study. Future research should aim to address these limitations to further advance our understanding of the impact of maternal thyroxine usage on neonatal thyroid function.

CONCLUSION

In conclusion, present study suggests that maternal thyroxine usage does not appear to have a detrimental effect on neonatal thyroid function in babies exposed to the medication due to maternal hypothyroidism. Furthermore, we found a higher occurrence of RDS in infants delivered via cesarean section compared to those delivered vaginally, consistent with previous research.These findings contribute to the growing body of knowledge on the impact of maternal thyroxine usage and mode of delivery on neonatal health outcomes. Further research involving larger, multicenter studies is warranted to strengthen the evidence base and explore potential underlying mechanisms.Understanding the potential effects of maternal thyroxine usage and mode of delivery on neonatal health is crucial for healthcare providers in optimizing care for both mothers and their newborns. By identifying the factors that influence neonatal outcomes, we can develop strategies to mitigate risks and improve overall perinatal care.

Declarations

Ethics approval

Consent to participate: Not required

Consent for publication: AL authors consent to publications

Conflict of interest: the authors declare no competing interest

REFERENCES

1. Alemu A, Terefe B, Abebe M, Biadgo B. Thyroid hormone dysfunction during pregnancy: A review. Int J Reprod Biomed. 2016 Nov;14(11):677-686. PMID: 27981252; PMCID: PMC5153572.
2. Ben-Zeev ZS, Peniakov M, Felszer C, Weiner SA, Lahad A, Almashanu S, Tenenbaum Rakover Y. Usefulness of thyroid function assessment in infants born to mothers with thyroid dysfunction during pregnancy. Eur Thyroid J. 2022 Jun 23;11(4):e220055. doi: 10.1530/ETJ-22-0055. PMID: 35613337; PMCID: PMC9254317.
3. Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A, Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. J Prenat Med. 2012 Oct;6(4):64-71. PMID: 23272277; PMCID: PMC3530964.
4. Ilyés I. A gyermekkoripajzsmirigybetegségekaktuáliskérdései [Current questions of thyroid diseases in childhood]. Orv Hetil. 2011 Apr 17;152(16):617-27. Hungarian. doi: 10.1556/OH.2011.29088. PMID: 21454178.
5. Kiran Z, Sheikh A, Humayun KN, Islam N. Neonatal outcomes and congenital anomalies in pregnancies affected by hypothyroidism. Ann Med. 2021 Dec;53(1):1560-1568. doi: 10.1080/07853890.2021.1970798. PMID: 34494465; PMCID: PMC8439228.
6. Lain SJ, Rifas-Shiman SL, Pearce EN, Nassar N, Oken E. Neonatal Thyroxine, Maternal Thyroid Function, and Cognition in Mid-childhood in a US Cohort. Matern Child Health J. 2020 Apr;24(4):503-513. doi: 10.1007/s10995-019-02867-5. PMID: 31897929; PMCID: PMC7083173.
7. Miranda A, Sousa N. Maternal hormonal milieu influence on fetal brain development. Brain Behav. 2018 Jan 24;8(2):e00920. doi: 10.1002/brb3.920. PMID: 29484271; PMCID: PMC5822586.
8. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017 Feb 7;342:68-100. doi: 10.1016/j.neuroscience.2015.09.070. Epub 2015 Oct 3. PMID: 26434624; PMCID: PMC4819012.
9. Nasheeda CM, Philip P, Shenoy RD, Shetty S. Diagnostic Utility of Cord Blood Thyroid Stimulating Hormone in Congenital Hypothyroidism in the Era of Expanded Newborn Screening. Indian J Clin Biochem. 2018 Oct;33(4):461-466. doi: 10.1007/s12291-017-0697-7. Epub 2017 Sep 16. PMID: 30319194; PMCID: PMC6170245.
10. Özon A, Tekin N, Şıklar Z, Gülcan H, Kara C, Taştekin A, Demir K, Koç E, Evliyaoğlu O, Kurtoğlu S. Neonatal effects of thyroid diseases in pregnancy and approach to the infant with increased TSH: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report. Turk Pediatri Ars. 2018 Dec 25;53(Suppl 1):S209-S223. doi: 10.5152/TurkPediatriArs.2018.01819. PMID: 31236034; PMCID: PMC6568290.
11. Ozdemir H, Akman I, Coskun S, Demirel U, Turan S, Bereket A, Bilgen H, Ozek E. Maternal thyroid dysfunction and neonatal thyroid problems. Int J Endocrinol. 2013;2013:987843. doi: 10.1155/2013/987843. Epub 2013 Apr 30. PMID: 23737782; PMCID: PMC3657451.
12. Patel J, Landers K, Li H, Mortimer RH, Richard K. Delivery of maternal thyroid hormones to the fetus. Trends Endocrinol Metab. 2011 May;22(5):164-70. doi: 10.1016/j.tem.2011.02.002. Epub 2011 Mar 15. PMID: 21414798.
13. Pemberton HN, Franklyn JA, Kilby MD. Thyroid hormones and fetal brain development. Minerva Ginecol. 2005 Aug;57(4):367-78. PMID: 16170282.
14. Radetti G, Zavallone A, Gentili L, Beck-Peccoz P, Bona G. Foetal and neonatal thyroid disorders. Minerva Pediatr. 2002 Oct;54(5):383-400. English, Italian. PMID: 12244277.
15. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. Indian J Endocrinol Metab. 2012 May;16(3):364-70. doi: 10.4103/2230-8210.95667. PMID: 22629500; PMCID: PMC3354841.
16. Varner MW, Mele L, Casey BM, Peaceman AM, Sorokin Y, Reddy UM, Wapner RJ, Thorp JM, Saade GR, Tita ATN, Rouse DJ, Sibai B, Iams JD, Mercer BM, Tolosa J, Caritis SN; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Thyroid function in neonates of women with subclinical hypothyroidism or hypothyroxinemia. J Perinatol. 2018 Nov;38(11):1490-1495. doi: 10.1038/s41372-018-0213-9. Epub 2018 Sep 5. PMID: 30185931; PMCID: PMC6215529.

: