International Journal of TROPICAL DISEASE & Health
19(2): 1-7, 2016, Article no.IJTDH.27963
ISSN: 2278–1005, NLM ID: 101632866

SCIENCEDOMAIN *international*
www.sciencedomain.org

Neonatal Outcomes of Mothers with Hypothyroidism in the Third Trimester

Ehimen Phyllis Odum[1,2*] and Ngozi Clare Orazulike[3,4]

[1]Department of Chemical Pathology, University of Port Harcourt, Port Harcourt, Rivers State, Nigeria.
[2]Department of Chemical Pathology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria.
[3]Department of Obstetrics and Gynaecology, University of Port Harcourt, Port Harcourt, Rivers State, Nigeria.
[4]Department of Obstetrics and Gynaecology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author EPO did the study design and wrote the protocol. Authors EPO and NCO did the statistical analysis and literature searches while analyses of study was by author NCO. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2016/27963
Editor(s):
(1) Ajay Halder, Department of Obstetrics and Gynecology, All India Institute of Medical College, Bhopal, India.
(2) Nicolas Padilla-Raygoza, Department of Nursing and Obstetrics, Division of Health Sciences and Engineering, Campus Celaya Salvatierra, Mexico.
(3) Shankar Srinivasan, Department of Health Informatics, University of Medicine & Dentistry of New Jersey, USA.
Reviewers:
(1) Magdy Abdelrahman Mohamed, Sohag University, Egypt.
(2) Wong Sze Lyn Jeanne, Putrajaya Hospital, Malaysia.
Complete Peer review History: http://www.sciencedomain.org/review-history/16337

Original Research Article

Received 27th June 2016
Accepted 20th September 2016
Published 26th September 2016

ABSTRACT

Aims: To determine the relationship between maternal hypothyroidism and preterm birth, neonatal low birth weight and neonatal thyroid stimulating hormone (TSH) levels.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Obstetrics and Gynaecology in a tertiary hospital in Rivers State, Southern Nigeria from June 2014 to November 2014.
Methodology: Serum TSH and free thyroxine (FT4) were analyzed in pregnant women before delivery and cord blood TSH was analyzed in their babies immediately after delivery. Maternal hypothyroidism was defined as serum TSH > 3.0 mIU/L in the third trimester according to the

**Corresponding author: Email: phyldion@yahoo.com;*

American Thyroid Association (ATA) recommendation.
Results: Out of 168 pregnant women, 25 (14.9%) women had subclinical hypothyroidism. None had overt hypothyroidism. They had babies with lower birth weight (*P* = .037) and lower Apgar scores at 1 minute (*P* = .003) and 5 minutes (*P* = .001) compared to mothers without hypothyroidism. A total of 17 (10%) babies had low birth weight. Fourteen (8.3%) babies were preterm. Thirteen (7.7%) babies were admitted into the neonatal intensive care unit (NICU) and among them babies born to mothers with hypothyroidism had a higher frequency of admission into NICU (*P* = .002), lower gestational age (*P* = .006) and higher mean TSH (*P* = .015) than babies born to mothers without hypothyroidism.
Conclusion: Maternal subclinical hypothyroidism was associated with neonatal low birth weight, low Apgar scores, preterm birth and high neonatal TSH. Timely detection and treatment of maternal hypothyroidism could reduce the burden of adverse neonatal outcomes.

Keywords: Hypothyroidism; neonatal outcomes; low birth weight; preterm birth.

1. INTRODUCTION

Thyroid disorders are encountered frequently during pregnancy and postpartum period. Thyroid disease is the second most common endocrine condition encountered in women of childbearing age after diabetes mellitus [1,2]. Hypothyroidism is relatively common with subclinical disease having a much higher prevalence than overt disease [1]. Symptoms of hypothyroidism usually masquerade common pregnancy symptoms and a high index of suspicion is required to make early diagnosis [2]. Most of the conditions that cause hypothyroidism are treatable and may adversely affect the foetus if left undiagnosed or not treated appropriately [1,2]. Maintaining thyroid stimulating hormone (TSH) and therefore thyroid hormones at physiological levels is essential for optimal foetal development [3,4].

Hormonal and physiological changes during pregnancy cause demand for thyroid hormones to increase as pregnancy advances [2]. This places a higher demand on the thyroid gland with concomitant increased synthesis of the thyroid hormones and increased requirement for iodine [3,5,6]. The thyroid hormones utilized by the growing foetus in the first trimester are primarily from maternal sources [7,8]. Thereafter, the foetus requires iodine from the mother to synthesize thyroid hormones [3,8]. Thyroid hormones are essential for foetal growth, neurodevelopment and myelination of the brain and nerve tissues, and also for maintenance of the basal metabolic rate [4,9]. Deposition of foetal fat and facilitation of the corticosteroid-dependent maturation necessary for extra-uterine survival has been found to be dependent on thyroid hormones, thus slight changes in maternal thyroid hormone and iodine levels will interfere with foetal growth and maturity [3,4,9].

Causes of hypothyroidism during pregnancy include, most commonly, iodine deficiency worldwide and autoimmune (Hashimoto's) thyroiditis in iodine-sufficient regions of the world [2,10]. Other causes include overtreatment of a hyperthyroid woman with antithyroid medications, radioiodine ablation or thyroidectomy, use of drugs like rifampicin and phenytoin which accelerate thyroid metabolism, and rarely, central hypothyroidism (pituitary and hypothalamic disorders) [2,10,11]. Combined maternal and foetal hypothyroidism is commonly due to endemic iodine deficiency and occasionally TSH receptor-blocking antibodies [4]. Pregnant women with hypothyroidism have been found to have poor foetal outcomes which include spontaneous abortion, preterm birth, low birth weight, foetal distress, mental retardation, congenital malformations, congenital hypothyroidism, increased perinatal morbidity and mortality [1-4,12]. It is therefore apparent that imbalances in maternal thyroid hormone levels would affect the morbidity and mortality of the foetus and newborn.

This study sought to determine if there is an association between maternal hypothyroidism and neonatal TSH level, neonatal low birth weight (Birth weight < 2.5 Kg), and preterm birth (Babies born before 37 completed weeks of gestation).

2. METHODOLOGY

The study was carried out in the Department of Obstetrics and Gynaecology in a tertiary hospital in Rivers State, Southern Nigeria from June 2014 to November 2014. Approval was obtained from the Ethical Committee of the hospital and apparently healthy women that came into the labour ward for delivery were sequentially

recruited after obtaining informed written consent. Sample size was calculated based on an average prevalence rate of hypothyroidism in Nigerian pregnant women of 10% gleaned from previous studies [13] and was estimated at 154 using the formula $n = z^2pq/d^2$ and making allowance for an attrition rate of 10% [14]. A questionnaire was administered to these women. It had segments for biodata, dietary history, family and medical history of thyroid disease, medication and co-morbidities. All women with multiple pregnancies, known thyroid disorders or associated medical conditions and those on antithyroid drugs, levothyroxine or any medication that could affect thyroid function as well as women that were delivered by caesarean section as a result of complications such as foetal distress, obstructed labour and prolonged ruptured membrane were excluded from the study.

Venous blood specimen was obtained from the cubital fossa or dorsum of the hand. Aseptic techniques were applied. A vacutainer bottle was used to collect the specimen. The venous blood was sent to the laboratory, left to stand for one hour to allow for proper clotting centrifuged at 3500 rpm and separated. The serum was then stored at -20℃ and assayed within two weeks. Immediately after delivery, the new born babies of these women were cleaned, examined and their anthropometric measurements taken. Birth weight was measured using an infant weighing scale and recorded in kilograms. Cord blood specimens were obtained from the babies under aseptic techniques and assayed for TSH.

Serum TSH and free thyroxine (FT4) were analysed by the Vitros ECi/ECiQ immunodiagnostic autoanalyser which uses an immunometric immunoassay technique for TSH and competitive immunoassay technique for FT4.

The trimester-specific TSH limit of 3.0 mIU/L proposed by the American Thyroid Association (ATA) [8] was used for the definition of hypothyroidism in the third trimester. Maternal overt hypothyroidism (OH) was defined as TSH level greater than 3.0 mIU/L with a FT4 concentration below the reference range and subclinical hypothyroidism (SCH) was defined as TSH > 3.0 mIU/L with a normal FT4 concentration [1]. The assay-specific, pregnancy (third trimester) FT4 reference range of 8.0 – 19.6 pmol/L was used.

2.1 Statistical Analysis

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc. Chicago, Illinois, U.S.A.). Frequencies and percentages were obtained for categorical variables. Differences in proportions were analyzed using the chi-squared test. Kolmogorov-Smirnov test revealed a skewed distribution of maternal TSH, FT4, and neonatal TSH. The means of normally distributed continuous variables were compared using unpaired students t test and the means of skewed continuous variables were compared using Mann-Whitney U test and expressed as mean ± standard deviation (SD). Spearman's correlation statistics was used to assess the relationship between variables. P-values ≤ 0.05 were considered significant in all analyses.

3. RESULTS

Out of one hundred and seventy-eight pregnant women, 168 delivered live singleton neonates and had complete data for mother-baby pairs. One hundred and thirty-one (78%) women had spontaneous vaginal deliveries and 37 (22%) were delivered by elective caesarean section. The babies' mean birth weight, height and head circumference were 3.2 ± 0.7 Kg, 49.0 ± 4.0 cm and 34.6 ± 2.8 cm respectively. Ninety-five (56%) were males and 73 (44%) were females. A total of 17 (10%) babies had low birth weight. Fourteen (8.3%) babies were preterm.

Baseline characteristics of mothers with hypothyroidism and mothers without hypothyroidism are outlined in Table 1. It revealed similarities in maternal age, gestational age and free T4 levels. Twenty-five (14.9%) women had subclinical hypothyroidism. None had overt hypothyroidism. They had babies with lower birth weight (*P* = .037) and lower Apgar scores at 1 minute (*P* = .003) and 5 minutes (*P* = .001) compared to mothers without hypothyroidism (Table 2). There was no significant difference between the mean TSH values (*P* = .51) of all the babies of mothers with hypothyroidism and all the babies of mothers without hypothyroidism (Table 2).

Thirteen babies (7.7%) were admitted into the neonatal intensive care unit (NICU). Babies born to mothers with hypothyroidism had a higher frequency of admission into NICU (*P* = .002), lower gestational age (*P* = .006) and higher mean TSH (*P* = .015) than babies born to mothers without hypothyroidism (Table 3).

Table 1. Comparison of baseline characteristics of mothers with and without hypothyroidism

Maternal characteristics	Mothers with hypothyroidism (N=25) Mean (SD)	Mothers without hypothyroidism (N=143) Mean (SD)	*P*
Age (Years)	30.5 (6.3)	29.3 (4.9)	.29
Gestational age (Weeks)	36.0 (3.2)	38.8 (1.8)	.09
Maternal TSH (MIU/L)	4.5 (.7)	1.4 (.8)	.00*
Median TSH (MIU/L)	4.8	1.4	
Maternal FT4 (PMOL/L)	.9 (.2)	.9 (.3)	.84
Median FT4 (PMOL/L)	.8	.8	

** P-values ≤ .05 significant*

Table 2. Neonatal outcomes of mothers with and without hypothyroidism

Neonatal outcome	Mothers with hypothyroidism (N=25) Mean (SD)	Mothers without hypothyroidism (N=143) Mean (SD)	*P*
Birth weight (KG)	3.0 (0.7)	3.3 (0.6)	.037*
Apgar score (1 Minute)	5.5 (2.3)	7.6 (1.2)	.003*
Apgar score (5 Minutes)	6.8 (3.0)	9.0 (0.8)	.001*
Neonatal TSH (MIU/L)	6.4 (6.0)	6.0 (3.5)	.514
Median TSH (MIU/L)	4.7	5.0	

** P-values ≤ .05 significant*

Table 3. Admissions into Neonatal Intensive Care Unit (NICU)

NICU admissions	Babies born to mothers with hypothyroidism (N = 25)	Babies born to mothers without hypothyroidism (N = 143)	*P*
Number (%)	4 (16.0)	9 (6.3)	.002*
Mean gestational age (SD) (weeks)	34.0 (1.2)	38.0 (0.8)	.006*
Mean TSH (SD) (MIU/L)	9.8 (2.9)	4.8 (2.9)	.015*
Median TSH (MIU/L)	9.8	4.7	

** P-values ≤ .05 significant*

Maternal TSH correlated negatively with neonatal birth weight (r = -.199, *P* = .01), and negatively with Apgar scores at 1 minute (r = -.271, *P* = .04) and 5 minutes (r = -.305, *P* = .02). Neonatal birth weight correlated positively with gestational age (r = .559, *P* < .001), and Apgar scores at 1 minute (r = .411, *P* = .002) and 5 minutes (r = .463, *P* < .001).

4. DISCUSSION

A firm association between overt hypothyroidism in pregnancy and adverse obstetric complications, including increased risk of placental abruption, pre-eclampsia, gestational diabetes mellitus, miscarriage, preterm birth, neonatal low birth weight (LBW), increased neonatal respiratory distress, congenital hypothyroidism, neurocognitive deficits and foetal death, has been clearly demonstrated [4,6,9,10]. In comparison, data regarding subclinical hypothyroidism has been variable but some studies have revealed an association between subclinical hypothyroidism and several adverse obstetric outcomes like placental abruption, gestational hypertension, gestational diabetes mellitus, pre-labour rupture of membranes (PROM), preterm delivery, LBW, intrauterine growth restriction (IUGR), low Apgar scores and foetal neurodevelopmental disorders [6,9,10,15]. In this study, maternal subclinical hypothyroidism was found to be associated with neonatal LBW and low Apgar scores. When the total number of babies born to mothers with and without hypothyroidism was considered, maternal hypothyroidism was not associated with neonatal prematurity or neonatal TSH levels. However, when the subset of babies admitted into NICU was evaluated, it was observed that babies born to mothers with hypothyroidism had a higher

prevalence of NICU admissions, lower mean gestational age and higher mean TSH.

Thyroid hormones facilitate general foetal growth and development of individual foetal tissues via direct and indirect mechanisms [16]. Direct effects include increased foetal oxygen consumption and glucose metabolism. Indirect effects include regulation of bioavailability and effectiveness of several hormones and growth factors that influence foetal development, such as the catecholamines and insulin-like growth factors [16]. Thyroid hormones are critical for the maturation of several foetal tissues, particularly close to term, and these include the brain, skeleton, lungs, heart and intestines. Synthesis of surfactant and lung maturation, normal maturation of cardiomyocytes and the cardiovascular system, and activation of hepatic gluconeogenesis and non-shivering thermogenesis in the neonate at birth are all dependent on thyroid hormones [16,17]. Thyroid hormones are essential for development of foetal skeleton, attainment and maintenance of peak bone mass, and bone maturation [16,18].

Disruption of the hypothalamic-pituitary-thyroid axis during growth has been demonstrated to interfere with normal linear growth and skeletal maturation significantly. Evidence suggests that maternal hypothyroidism delays foetal skeletal development by reducing normal bone deposition. This reduced bone turnover impairs bone formation and mineralization [15,18] and adversely affects foetal bone maturation towards the end of foetal life [3].

Some earlier studies have reported a positive correlation between maternal TSH and cord blood TSH [17]. Kharb et al. [17] observed that pregnant women with subclinical hypothyroidism had babies with higher cord blood TSH values compared to controls. Findings from this study among babies admitted to the NICU are consistent with data from these previous studies. Maternal as well as foetal thyroid hormones are essential for normal neuropsychological development. Maternal and foetal thyroid insufficiency may predispose the baby to neurologic impairment and mental retardation [3,6].

LBW (Birth weight < 2500 g) may be due to preterm birth (birth before 37 completed weeks of gestation) or IUGR (small for gestational age; birth weight below the 10th percentile for the appropriate gestational age) [19,20]. Several investigators have reported that high maternal TSH levels were significantly associated with higher risk of small for gestational age (SGA), preterm and lower birth weight neonates [3,9,15,17]. Casey and colleagues demonstrated a 2-fold higher incidence of preterm delivery at or before 34 weeks of gestation in women with subclinical hypothyroidism [6]. Similarly, in this study, among neonates admitted into the NICU, maternal subclinical hypothyroidism was observed to be associated with preterm birth at 34 weeks of gestation. Reports from a prospective study of women with singleton pregnancies during the second trimester in an iodine-sufficient country indicated that subclinical hypothyroidism and overt hypothyroidism increased the risk of IUGR by about 2-fold and 5-fold respectively [9]. Chen et al. [3] observed that maternal subclinical hypothyroidism was associated with 3-fold and 4-fold higher incidence of neonatal LBW and IUGR respectively in the third trimester but they did not observe this association in the first or second trimesters. In this study it was also discovered that maternal subclinical hypothyroidism was associated with low birth weight. LBW is an important cause of neonatal morbidity and mortality and a risk factor for early neonatal complications like hypoglycaemia, respiratory distress syndrome and birth asphyxia, as well as long-term outcomes like poor neurointellectual development [15,19,20].

The Apgar scoring system is used to assess the clinical condition of the newborn infant immediately after birth, to evaluate the baby's response to resuscitation and may help to determine the need for continued resuscitation [20,21]. Total scores of 7 to 10 are regarded as normal or good, between 4 to 6 fairly low and 3 or less is critically low. It is usually done at 1 and 5 minutes after delivery. The 5-minute score is a better predictor of survival. Infants with Apgar scores that remain critically low for longer than 5 minutes are predisposed to higher risks of neonatal morbidity and mortality, and long-term neurological complications [20,21]. In this study, babies of mothers with hypothyroidism had low Apgar scores below 7 at 1 and 5 minutes whereas babies of mothers without hypothyroidism had significantly better Apgar scores above 7 at 1 and 5 minutes respectively. Saki et al also observed an association between subclinical hypothyroidism and Apgar score below 7, and demonstrated that subclinical hypothyroidism increased the risk of low Apgar score at one minute by more than 2-fold [9].

A low Apgar score may be due to several factors including maternal medications (analgesic agents, sedatives or anaesthesia), severe preeclampsia, placental abruption and praevia, preterm birth (due to immature lungs and hypoglycaemia), IUGR, respiratory distress syndrome, birth asphyxia, and congenital malformations of the respiratory, circulatory and central nervous systems [20,22]. One or more of these factors may have contributed to the low Apgar scores observed in neonates born to mothers with hypothyroidism in this study. Previous studies have shown that infants born to mothers with hypothyroidism have higher prevalence of respiratory distress syndrome and higher rates of NICU admission than neonates of euthyroid mothers [6,8]. Subclinical hypothyroidism and overt hypothyroidism have been linked to a higher risk of foetal distress, which may be a consequence of inadequate utero-placental circulation resulting in chronic hypoxia in the foetus and reduced ability to tolerate the stress of delivery [9,22,23]. Bari et al. [20] noted that low birth weight babies had lower Apgar scores and a higher requirement for resuscitation and did not respond as well as normal birth weight babies to resuscitative efforts.

5. CONCLUSION

Maternal subclinical hypothyroidism was associated with neonatal LBW, low Apgar scores, preterm birth and high neonatal TSH in this study. Deficiency of thyroid hormones affects maturation of several foetal tissues, particularly close to term, and may result in impaired foetal growth, preterm birth, LBW, neonatal respiratory distress syndrome, low Apgar scores and subsequently neurocognitive deficits. Since hypothyroidism is easily treated, timely detection and treatment of this disorder could reduce the burden of adverse neonatal outcomes.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

ACKNOWLEDGEMENTS

Special thanks and appreciation go to Dr. Ochuko Otokunefor for her invaluable assistance with the data collection for this study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ramprasad M, Bhattacharyya SS, Bhattacharyya A. Thyroid disorders in pregnancy. Indian J Endocr Metab. 2012; 16(Suppl S2):167-70.
2. Carney LA, Quinlan JD, West JM. Thyroid disease in pregnancy. Am Fam Physician. 2014;89:273-78.
3. Alvarez-Pedrerol M, Guxens M, Mendez M, Canet Y, Martorell R, Espada M, et al. Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. Eur J Endocrinol. 2009;160:423-429.
4. Smallridge RC, Ladenson PW. Hypothyroidism in pregnancy: Consequences to neonatal health. J Clin Endocrinol Metab. 2001;86:2349-53.
5. Glinoer D. The regulation of thyroid function in pregnancy: Pathways of endocrine adaptation from physiology to pathology. Endocrine Rev. 1997;18:404-33.
6. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol. 2005;105:239-45.
7. Medici M, Timmermans S, Visser W, Keizer-Schrama SM, Jaddoe VW, Hofman A, et al. Maternal thyroid hormone parameters during early pregnancy and birth weight: The generation R study. J Clin Endocrinol Metab. 2013;98:59-66.
8. Mannisho T, Mendola P, Reddy U, Laughon SK. Neonatal outcomes and birth weight in pregnancies complicated by maternal thyroid disease. Am J Epidemiol. 2013;178:731-40.
9. Saki F, Dabbaghmanesh MH, Ghaemi SZ, Farouhari S, Omrani GR, Bakhshayesh KM. Thyroid function in pregnancy and its influences in maternal and foetal outcomes. Int J Endocrinol Metab. 2014;12(4):e19378.
DOI: 10.5812/ijem.19379

10. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081-125.
11. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. Indian J Endocrinol Metab. 2012;16(3): 364-370.
12. Casey BM, Leveno KJ. Thyroid disease in pregnancy. Obstet Gynaecol. 2006;108:1283-92.
13. Abdusalam K, Yahaya I. Prevalence of thyroid dysfunction in gestational hypertensive Nigerians. Sub-saharan Afr J. Med. 2015;2:19-27.
14. Araoye MO. Research methodology with statistics for health and social sciences. Ilorin: Nathadex Publishers; 2004;118-122.
15. Chen LM, Du WJ, Dai J, Zhang Q, Si GX, Yang H, et al. Effects of subclinical hypothyroidism on maternal and perinatal outcomes during pregnancy: A single-center cohort study of a Chinese population. PLoS One. 2014;9:e109364. DOI: 10.1371/journal.pone.0109364
16. Forhead AJ, Fowden AL. Thyroid hormones in foetal growth and prepartum maturation. J Endocrinol. 2014;221:87-103.
17. Kharb S, Singla P, Nanda S. Maternal serum TSH value in early pregnancy and its relation with pregnancy outcome. Research Journal of Obstetrics and Gynecology. 2014;7:14-22.
18. William GR. Actions of thyroid hormones in bone. Pol J Endocrinol. 2009;60:380-88.
19. Goldenberg RL, Culhane JF. Low birth weight in the United States. Am J Clin Nutr. 2007;85(Suppl):584S-90S.
20. Bari MI, Ullah MA, Khatun M. Morbidity and mortality of low birth weight baby. TAJ. 2008;21:35-39.
21. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. N Engl J Med. 2001;344:467-71.
22. Chen Zi-Li, Liu J. Interpretation of the Expert's Consensus on the criteria for the diagnosis and grading of neonatal asphyxia in China. Transl Pediatr. 2013;2:59-63.
23. Tudosa R, Vartej P, Horhoianu I, Ghica C, Mateescu S, Dumitrache I. Maternal and foetal complications of the hypothyroidism-related pregnancy. Maedica. 2010;5:116-123.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16337