EVALUATING THYROID FUNCTIONS IN MOTHERS WITH SMALL FOR GESTATIONAL AGE AND APPROPRIATE FOR GESTATIONAL AGE NEONATES: INSIGHTS FROM A PAKISTANI CASE-CONTROL STUDY

Zakia Rehman[1], Safia Rahman[2], Nida Khan[3], Sadia Fatima[4] Ehtesham[4], Rubina Nazli[4]

ABSTRACT

Objective: To evaluate differences in maternal thyroid hormone levels between mothers of Small for gestational age (SGA) and Appropriate for gestational age (AGA) newborns in Pakistan.

Methods: This case-control study was conducted among AGA and SGA mothers at Lady Reading Hospital and KMU in Peshawar. After screening 300 postnatal mothers and applying inclusion and exclusion criteria, 63 participants were enrolled, including 32 SGA mothers and 31 AGA mothers. The sample size was determined using the online software OpenEPI, assuming a confidence interval of 95%. The sampling technique used was a non-probability, purposive technique. Healthy mothers of AGA and SGA newborns were included. Thyroid Profiles were compared to the baby's gestational ages. Mothers' socio-demographic, socioeconomic, and reproductive history were all gathered through questionnaires. Anthropometric measurements were done. Blood sampling was done to estimate the thyroid profile of the participant mothers, including TSH, fT4, and fT3. Data Analysis was done using SPSS version 26.

Results: In the present study, differences in the thyroid hormone profile, including fT3, fT4, and TSH, were explored in sixty-three (1-7 days postnatal) mothers aged between 16-35 years (Mean ± SD; 24.75 ±5.06 years). The results showed no difference in the Means of fT4, fT3, and TSH among the two study groups. The Body Mass Index (BMI) of 44.4% of mothers was in the normal range. The frequency of SGA babies' mothers with normal BMI was less than the mothers of AGA babies (SGA=34.4%, AGA=54.8 %). Upon comparison with AGA mothers, SGA mothers were found to be of short stature. A comparison of previous SGA history was also found to be significant.

Conclusion: There was no appreciable difference between the thyroid hormone levels of mothers of the two groups.

Keywords: TSH, fT4, fT3, Appropriate for gestational age, small for gestational age.

INTRODUCTION

Recent studies indicate that globally, over 30 million mothers give birth to babies who are small for gestational age (SGA), with poor countries having the highest prevalence.[1] 26% infant mortality is reported in South Asia, where 34% of babies born are small for gestational age.[2] However, it has been reported that 3–10% of pregnancies in Pakistan result in SGA newborns [3]

[1] NUST School of Health Sciences, Islamabad
[2] Khyber Medical College, Peshawar
[3] Women's University, Swabi
[4] Institute of Basic Medical Sciences, Khyber Medical University

Address for Correspondence
Dr. Safia Rahman
Assistant Professor, Department of Pathology, Khyber Medical College, Peshawar, Pakistan
dr.safiarahman75@gmail.com
0092 335 9793682

A Fetus having a weight less than the tenth percentile of appropriate weight for that specific gestational age is defined as Small for Gestational Age or "SGA". Another criterion of SGA is when the mother's fundal height during pregnancy is 2.5 cm less than normal or if the baby is underweight i.e. less than 2500 grams immediately after birth.[4, 5] Genetic, hormonal, and environmental factors play a great role in the growth of the fetus, [6,7] and subsequent development of the child.[8] Low birth weights are common in constitutionally normal SGA newborns, probably because of genetic traits such as maternal height, weight, ethnicity, and parity. [9]

During gestation, endocrine dysfunctions like thyroid disorders can result in unfavorable outcomes for both the fetus and the mother. Mothers with poor general health, low socioeconomic status, being underweight, short height, low energy intake, Asian ethnicity, hypertension, diabetes, chronic asthma, anti-phospholipid syndrome, and thyroid dysfunction are recognized as risk factors for SGA. [10] According to recent studies, thyroid

hormones have been reported to have a direct impact on placental formation and development and are found to be essential for the neurodevelopment of the fetus.[11] During the second and third trimesters, thyroid hormones accelerate intrauterine growth by increasing fetal metabolism, stimulating the secretion of growth factors and growth hormone, and playing a role in the maturation and differentiation of Fetal organs.[12] The frequency of thyroid hormone derangement is relatively high in pregnant women. About 10% of pregnancies suffer from subclinical hypothyroidism.[13] Collective data clearly show a strong correlation between the probability of unfavorable outcomes and low maternal T4 levels. [14] The adverse outcomes for the fetus may be in the form of cognitive impairment, neurological problems, respiratory distress, increased perinatal morbidity, premature birth, and low birth weight. .[15]

Due to the high occurrence of thyroid dysfunction during gestation[16] and the associated risks to the growing fetus, this study is carried out to compare the thyroid profile of mothers of small for gestational age (SGA) and appropriate for gestational age (AGA) babies.

MATERIALS AND METHODS

After obtaining approval from the Research Ethical Committee and Advanced Study Research Board of KMU No: KMU/IBMS/IRBE/2023/680, this study was conducted at Lady Reading Hospital in Peshawar. The study duration was 6 months, from 1st Feb 2023 to 30 August 2023. The sampling technique used a non-probability, purposive technique. The sample size was determined using the online software Open EPI, assuming a confidence interval of 95%.

After screening 300 postnatal mothers, and applying inclusion and exclusion criteria, 63 participants were enrolled, including 32 SGA mothers and 31 AGA mothers. Healthy mothers of AGA and SGA newborns, aged 16 to 35 years, who were 1-7 days postnatal were included. Mothers with a history of twin pregnancy, pre-eclampsia, and other systemic illnesses like diabetes, chronic kidney disease, and heart and liver disease were excluded. Informed consent was taken from all those who were taking part in the study. Level 4 of Brighton's Scale was used for SGA babies' identification. [3]

Socio-demographic information, reproductive history, and anthropometric details were collected from participants. Three milliliters of blood were drawn by a 5 ml disposable syringe, by aseptic technique from each subject, and shifted to (Lithium- Heparin) Gel tubes. Serum was separated from whole blood through centrifugation at 4000 rpm for 15 minutes. Before centrifugation, clot formation was confirmed. Using calibrated micropipettes serum was transferred into pre-labelled sterilized Eppendorf tubes. The serum was then stored for further analysis.

The serum sample was analyzed for Thyroid Profile, including fT4, fT3, and TSH Assay. TSH assay was performed on, Chemiluminescent Microparticle Immunoassay (CMIA) using the Architect TSH 7K62 Kit. Free T3 and fT4 were measured using Architect free T3 7K63 kit and free T4 7K65 kit, respectively on the same principle of CMIA.

SPSS 26 was used for statistical data analysis. The normality of data was determined using the K-S test (Kolmogorov Smirnov test), which showed that TSH data was not normally distributed, while data for fT3 and fT4 were normally distributed. An Outlier was removed to make TSH data normal. Numerical data was analyzed using means and standard deviations. However, frequencies and percentages were measured for categorical data. Independent sample t-test was applied to compare numerical data with normal distribution. For, categorical data chi-square test was used.

RESULTS

Table 1: Anthropometric Data of SGA and AGA Mothers

	AGA No =31	SGA No =32	Total No = 63	P-value
	Mean ±SD	Mean ±SD	Mean ±SD	
Maternal Weight (kg)	62.47 ± 13.01	60.89 ± 11.29	61.67 ± 12.10	0.607
Height (m)	1.56 ± 0.13	1.48 ± 0.14	1.52 ± 0.14	0.026**
Age (yrs)	24.32 ± 5.42	24.31 ± 4.76	24.32 ± 5.04	0.99
BMI (kg/m^2)	25.73 ± 5.73	28.30 ± 7.19	27.03 ± 6.57	0.13
Newborn Weight (kg)	3.31 ± 0.58	2.11 ± 0.26	2.70 ± 0.74	0.000***

Significant difference: ***P value < 0.001, ** P value < 0.01

The anthropometric measurements, which include newborns' weight, height, BMI, and age were compared and the difference in the height (P value < 0.026) was found significant, and the difference in the weight of newborns (P <0.000) was highly significant, as illustrated in Table 1.

Table 2: Reproductive History of SGA and AGA Mothers

	Total n=63	SGA n=32	AGA n=31	P value
Parity				
Primipara (1)	11(17.5%)	5(15.6%)	6(19.4%)	0.687
Multipara (>1)	52(82.5%)	27(84.4%)	25(80.6%)	
Weight Increase During Pregnancy				
Mild	23(36.5%)	17(27.0%)	6(9.5%)	0.027
Moderate	30(47.6%)	12(19.0%)	18(28.6%)	
Severe	10(15.9%)	3(4.8%)	7(11.1%)	
Interval During Pregnancies				
<1.5 years	32(50.8%)	18(56.3%)	14(45.2%)	0.289
>1.5 years	31(49.2%)	14(43.8%)	17(54.8%)	
Past History of SGA				
Positive	23(36.5%)	19(59.4%)	4(12.9%)	0.000
Negative	40(63.5%)	13(40.6%)	27(87.1%)	

SGA and AGA mothers, reproductive history e.g. Parity, Gap during pregnancies, and previous SGA babies history and weight gain of the mother during pregnancy were analyzed, which showed that the difference between both groups was significant, in terms of previous SGA history (P value <0.000) and weight gain during pregnancy (P value <0.017) as illustrated in Table 2.

Table 3: Comparison of Thyroid Hormone levels in SGA and AGA Mothers

	AGA N=31	**SGA N=32**	**Total N=63**	**P value**
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
TSH	1.62 ± 1.03	1.47 ± 0.96	1.54 ± 0.99	0.540
fT4	0.90 ± 0.11	0.96 ± 0.14	0.93 ± 0.13	0.058
fT3	2.82 ± 0.45	2.96 ± 0.54	2.89 ± 0.50	0.267

Thyroid profiles were compared among both groups, as shown in Table 3, Mean TSH levels were not found to be significant among the two groups (P value = 0.054), and the difference between the mean free T3 was also not significant (P value > 0.267). The free T4 mean of mothers was found to be insignificant (P value = 0.058).

Table 4: Odds Ratio

	Abnormal thyroid levels	Normal thyroid level	Odds ratio
SGA Mothers	3	29	1.50
AGA Mothers	2	29	

SGA mothers had 1.5 times higher odds of abnormal thyroid values than AGA mothers.

The risk estimation, however, is not statistically significant (p = 1.00)

DISCUSSION

The prevalence of births of babies who are small for gestational age in low-income nations is reported to be very high.[16] Despite this, related studies on the Pakistani population are very scarce. The most important reason is the lack of "antenatal data 'throughout pregnancy.[14] Thyroid dysfunction as a risk factor for growth restriction observed in SGA is unclear. Due to the paucity of literature in Pakistan that explicitly examines the factors causing SGA, the current study was conducted to estimate the thyroid profiles of SGA and AGA mothers by analyzing the serum levels of fT3, fT4, and TSH in both groups. Our study favors the results of a research study by Sarah Feigl et al in which there was no correlation among the mother's thyroid hormone levels, including TSH, T3, T4, and SGA.[17] The results of a study by Mannisto et al. who analyzed the perinatal outcome and anthropometric measurements of infants regarding the mother's thyroid status, were in concordance with the findings of the current study results, proving no correlation between maternal thyroid-stimulating hormone and the baby's length and weight. The reason may be the differences in other environmental and nutritional factors during pregnancy.[18]

It is evident from the literature that fetal growth is affected by maternal thyroid hormones. Cia et al. found a positive association between fT3 and fetal development. Furthermore, a negative correlation was determined between fetal growth and fT4, but no association was found between adverse fetal outcomes and TSH.[19] Likewise, a research study by John et al. established a significant positive association between the baby's weight and fT3, and an inverse association was discovered between fT4 and the baby's weight.[15] Marco Medici et al. investigations on the effect of thyroid hormones on the birth weight of babies established that levels of fT4 in the upper normal range are associated with increased risk of SGA, but, not for TSH. These results do not favor the results of our study. [20] Given that another study by Zhu et al. found that increased fT4 hormone levels are directly related to the risk of SGA and LBW, the reason is the possible difference in population characteristics. [21]

This study has a few limitations. Since there was a small sample size, it does not apply to the whole population. Furthermore, postpartum mothers were enlisted to determine the thyroid dysfunction between the SGA and AGA groups. Another limitation was that the sole way to identify SGA and AGA babies was by their birth weight (level 4 of the Brighton Scale) because there was no data available regarding ultrasound findings of SGA during the antenatal period in our region. Furthermore, neither tertiary care hospitals nor the peripheral healthcare system adheres to the RCOG recommendations for early identification of SGA. Large-scale studies with big sample sizes and more antenatal data are required to identify the effects of thyroid dysfunction on the risk of SGA births.

CONCLUSION

There was no appreciable difference between the thyroid hormone levels of mothers of the two groups.

Recommendations: A multicenter trial with a large sample size should be conducted. In high-risk cases, thyroid hormone levels should be measured during antenatal checkups. Mothers should also be given proper nutritional support, guidance, and counseling.

AUTHORS CONTRIBUTIONS:

1. Zakia Rehman: Conceived and designed the analysis, data collection, statistical analysis, and literature search.
2. Safia Rahman: Study design, data collection, statistical analysis, literature search.
3. Nida khan: Data Collection
4. SadiaFatima: literature search
5. Ehtesham: Data analysis
6. Rubina Nazli: Conceived and designed the study.

CONFLICT OF INTEREST: The authors declared no conflict of interest.

ETHICAL CONSIDERATION: The study was approved by the Ethical board of Khyber medical university.

REFERENCES

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013; 382(9890):427-51.
2. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health. 2013; 1(1):e26-e36.
3. Schlaudecker EP, Munoz FM, Bardají A, Boghossian NS, Khalil A, Mousa H, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization

safety data. Vaccine 2017; 35(48Part A):6518.
4. Badshah S, Mason L, McKelvie K, Payne R, Lisboa PJ. Risk factors for low birth weight in the public hospitals at Peshawar, NWFP-Pakistan. BMC Public Health. 2008; 8(1):1-10.
5. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The Lancet. 2013; 382(9890):427-51.
6. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health. 2013; 1(1):e26-e36.
7. Gill C. Evaluation and management of small for gestational age [SGA] Fetus. Medicine Today. 2004; 2(2):59-64.
8. Khadilkar VV, Mandlik RM, Palande SA, Pandit DS, Chawla M, Nadar R, et al. Growth status of small for gestational age Indian children from two socioeconomic strata. Indian journal of endocrinology and metabolism. 2016; 20(4):531.
9. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health. 2013; 1(1):e26-e36.
10. Black RE. Global prevalence of small for gestational age births. Low - Birthweight baby: born too soon or too small. 81: Karger Publishers; 2015.1-7.
11. Lundgren EM, Tuvemo T. Effects of being born small for gestational age on long-term intellectual performance. Best Practice & Research Clinical Endocrinology & Metabolism. 2008; 22(3):477-88.
12. Sahay RK, Nagesh VS. Hypothyroidism in pregnancy. Indian journal of endocrinology and metabolism. 2012; 16(3):364.
13. Lucaccioni L, Ficara M, Cenciarelli V, Berardi A, Predieri B, Iughetti L. Long-term outcomes of infants born by mothers with thyroid dysfunction during pregnancy. Acta Bio Medica: Atenei Parmensis. 2021;92(1).
14. Johns LE, Ferguson KK, Cantonwine DE, Mukherjee B, Meeker JD, McElrath TF. Subclinical changes in maternal thyroid function parameters in pregnancy and fetal growth. The Journal of Clinical Endocrinology & Metabolism. 2018;103(4):1349-58.
15. Mahadik K, Choudhary P, Roy P. Study of thyroid function in pregnancy, its feto-maternal outcome; a prospective observational study. BMC Pregnancy and Childbirth. 2020;20(1):1-7.
16. Delitala AP, Capobianco G, Cherchi PL, Dessole S, Delitala G. Thyroid function and thyroid disorders during pregnancy: a review and care pathway. Archives of gynecology and obstetrics. 2019;299(2):327-38.
17. Feigl S, Obermayer-Pietsch B, Klaritsch P, Pregartner G, Herzog SA, Lerchbaum E, et al. Impact of Thyroid Function on Pregnancy and Neonatal Outcome in Women with and without PCOS. Biomedicines. 2022;10(4):750.
18. Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab. 2009 Mar;94(3):772-9. doi: 10.1210/jc.2008-1520. Epub 2008 Dec 23. PMID: 19106271.
19. Cai C, Chen W, Vinturache A, Hu P, Lu M, Gu H, et al. Thyroid hormone concentrations in the second trimester of gestation and birth outcomes in Shanghai, China. The Journal of Maternal-Fetal & Neonatal Medicine. 2021;34(12):1897-905.
20. Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, et al. Maternal thyroid hormone parameters during early pregnancy and birth weight: the Generation R Study. The Journal of Clinical Endocrinology & Metabolism. 2013;98(1):59-66.
21. Zhu Yd, Han Y, Huang K, Zhu Bb, Yan Sq, Ge X, et al. The impact of isolated maternal hypothyroxinaemia on the incidence of large- for-gestational-age infants: the Ma'anshan Birth Cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2018;125(9):1118-25.