The relationship between TSH levels, maternal characteristics and racial group of the aneuploidy screening

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***Abstract*— First-trimester maternal screening is a widely used test for detecting fetal aneuploidies and neural tube defects for over two decades. Human chorionic gonadotropin hormone (beta-hCG) and pregnancy-associated plasma protein A (PAPP-A) are two serum biomarkers that are analyzed in this screening.**
The thyroid hormone is a critical hormone for normal pregnancy and fetal development. During the first half of pregnancy, placental and fetal development depends on the thyroid hormone levels in the mother. Therefore, thyroid abnormalities in the mother can result in unfavorable pregnancy outcomes such as intrauterine growth restriction, miscarriage, hypertensive disorders, premature birth, and an increase in the risk of low IQ in the newborn.
In this study, we analyzed the first-trimester screening data collected from 410 pregnant women who were seen at Yale University Hospital Prenatal Unit; and checked for possible correlations of TSH levels with maternal characteristics, racial group PAPP-A MoM levels.

Keywords*— *Thyroid Stimulating Hormone, PAPP-A, Free ß-hCG

I. INTRODUCTION

Pregnancy-associated plasma protein A (PAPP-A) is a popular biomarker of aneuploidy screenings. Understanding the effect of PAPP-A values in pregnancy is an active research area. Previous studies suggest that women with low maternal PAPP-A concentrations in the first trimester have a higher risk of pregnancy-related problems [1]. A low PAPP-A level may cause undesired pregnancy outcomes such as miscarriage in the mid-trimester, intrauterine fetal death, fetal growth restriction, pregnancy failure, preeclampsia and preterm labor [2,3]. High maternal PAPP-A concentration causes a large for gestational age baby [4]. Different PAPP-A levels have been shown to have an impact on maternal traits in previous research [5].

On the other hand, the thyroid hormone is known as an essential hormone for normal pregnancy and fetal development. Thyroid stimulating hormone (TSH) is produced by the pituitary gland, which is located in the brain. TSH regulates the thyroid gland's function. The thyroid gland is stimulated by TSH to create the thyroid hormone. Human chorionic gonadotropin hormone stimulates this process during the first trimester of pregnancy [6]. Fetal and placental development in the first half of pregnancy depends on the thyroid hormone levels in the mother. Therefore, thyroid abnormalities in the mother can result in unfavorable pregnancy outcomes such as intrauterine growth restriction, miscarriage, hypertensive disorders, premature birth, and an increase in the risk of low IQ in the newborn [7]. However, in literature, there is not much information about the association between TSH levels and ethnicity in pregnancy. Hollowell et al. analyzed the TSH levels in a group of men and nonpregnant females with Caucasion, African and Hispanic American ethnicities [8]. They showed that TSH level is higher in females with increasing age. They also reported that TSH value is greater in Caucasians and Hispanic Americans than in African Americans [8]. Benhadi et al. studied the differences in TSH levels for different ethnicities, and they evaluated whether there is a significant change in TSH values between the first and second trimesters of pregnacy. Benhadi et al. reported that i) Dutch females have the highest TSH levels between four ethnic populations (Moroccan, Turkish, Surinam and Dutch), and ii) in transition from the first trimester to the second trimester, an increase in TSH values is observed in all ethnic groups [9]. Tan et al. analyzed maternal, delivery and infant factors according to the TSH concentrations in different ethnic groups in Singapore. They studied 3 different groups including Chinese, Malay, Indian; and found no correlation between TSH and ethnicity [10]. Lee et al. evaluated TSH values during pregnancy according to race (Caucasians, African, Hispanic, other) and according to ethnicity (hispanic, non-hispanic); and reported that they observed a correlation [11].

The placenta of a pregnant woman produces the hormone known as human chorionic gonadotropin (hCG) [2]. It is possible to detect it in the blood 10 days after the onset of pregnancy. The level of hCG is a crucial

consideration for determining the risk of Down syndrome. Bogart et al. suggested that the concentration of β-hCG is much higher than normal in the blood of expectant mothers carrying a baby with Down syndrome [12]. Some other studies show that the average multiple of the median (MoM) level for β-hCG in pregnant women with Down syndrome is above 2.00 [13].

During the first ten weeks of pregnancy, hCG levels generally increase and then decrease, which causes a decrease in TSH [14]. In literature, some studies reported the TSH hormone values that are measured during pregnancy [15]. This study aims to investigate the association of TSH values with other variables such as ethnicity, maternal characteristics and biochemical values during pregnancy.

II. METHODS AND MATERIALS

In our previous study [16], we used data from 11 824 pregnant women who were followed in the Prenatal Unit of Yale University Hospital (approved by the Yale University Institutional Review Board). In only 410 of the 11 842 pregnant women, TSH values were collected. In this study, initially the minimum and maximum values, mean and median of 410 patients' weight, β-hCG MoM, PAPP-A MoM, TSH and down syndrome risk values were calculated.

As summarized in Figure 1, we perform analyzes in two main categories. Firstly, subgroups of 410 pregnant women with known TSH values were created based on their PAPP-A levels and ethnicity. We determined the mean, median, lowest and maximum values. The significance of the study's variables was examined using the Mann Whitney U test. The 95% level of significance was chosen ($p < 0.05$).

Statistical Analysis: As statistical indicators, the Mann Whitney U Test and Pearson correlation coefficient are employed. The non-parametric Mann Whitney U test is utilized to make a comparison between the means of two independent groups. Our Mann Whitney U test statistical significance is 0.05. Pearson's correlation coefficient is a statistical indicator showing the strength of a linear relationship between two data sets. It accepts values from -1 to 1. For statistical analyses we utilized Statistical Program for Social Sciences.

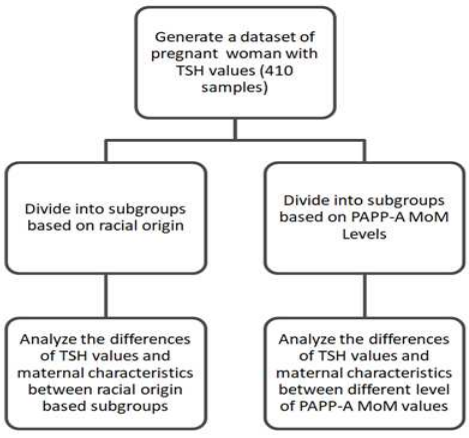

Figure 1. Flowchart of our methodology

III. RESULTS

Focusing on the pregnant woman whose TSH values are present, we generated a dataset including 410 samples (Pregnant women whose TSH values are followed during the first trimester screening). Table 1 shows the calculated percentiles, PAPP-A MoM values, and free BhCG MoM values for these 410 samples. The 1st, 3rd, 5th, 90th and 99th centile PAPP-A values were 0.27, 0.34, 0.43, 2.29, 3.63 MoM (shown in Table 1). Table 2 shows the maternal characteristics of these 410 samples that have TSH values. We further subdivided TSH group according to their PAPP-A MoM values. PAPP-A value of >3.00 MoM were taken as cases (15 patients). We have categorized the values as low if they are lower than 3.00, and as high if they are bigger than 3.00. As observed in Table 2, the down syndrome risk values of the various PAPP-A MoM levels varied significantly in this subgroup ($p = 0.012$, as shown in Table 2). No significant difference was observed between the TSH values of these two subgroups ($p=0.949$ for high vs. low PAPP-A MoM subgroups).

Next, we subdivided TSH group according to their racial origin. As presented in Table 3, weight distribution, PAPP-A MoM and Down Syndrome risk between the Caucasian and Afro-Caribbean groups is found to be significantly different. The TSH values of these three subgroups did not significantly differ from one another.

Percentile	PAPP-A (MoM)	Free Beta HCG (MoM)
1	0.27	0.37
3	0.34	0.44
5	0.43	0.49
10	0.5	0.59
90	2.29	1.65
95	2.84	1.89
97	3.02	2.21
99	3.63	2.58

Table I. Percentiles, PAPP-A MoM, free BhCG MoM (Multiples of the Median) values

In Figures 2(a), 2(b), and 2(c) the correlation between TSH values and BHCG values of pregnant women separated by ethnic group is shown. In all three groups the TSH and BHCG values showed no significant correlation (for Afro-Caribbean ($r = -0.032$), for Caucasian ($r = -0.067$), for other ($r = -0.144$)).

Similarly, the correlation between TSH and BHCG values of pregnant women with low and high PAPP-A MoM values is shown in Figures 3(a) and 3(b). No significant correlation was observed between the TSH measurements and BHCG MoM values in the group with low PAPP-A MoM values ($r = -0.076$) and in the high group ($r = 0.105$).

	All Patients			PAPPA (MoM)>3 (3%) (High)			PAPPA (MoM)<3 (97%) (Low)			*P (mann Whitney U test)*
	N	*Mean (SD)*	*Median (min-max)*	*N*	*Mean (SD)*	*Median (min-max)*	*N*	*Mean (SD)*	*Median (min-max)*	
Weight (kg)	410	77.4±22.1	72.1 (39.7-164.2)	15	81.9±26.5	71.6 (48.8-139.6)	395	77.1±21.9	72.1 (39.7-164.2)	0.518
Down Syndrome risk	410	5337±5766	3000 (4-20000)	15	8526±6214	7500 (1400-20000)	395	5194±5642	3000 (4-20000)	0.012
TSH	410	1.82±3.25	1.22 (0.03-41.8)	15	1.34±0.80	1.32 (0.04-2.89)	395	1.84±3.31	1.22(0.03-41.8)	0.949
Beta HCG MoM	410	1.09±0.45	1.05 (0.33-3.81)	15	1.23±0.58	1.1 (0.5-2.49)	395	1.08±0.4	1.04(0.33-3.81)	0.334

Table II. Maternal characteristics of PAPP-A level-based subgroups

Characteristics	Caucasian Patients (C)			Afro-Caribbean Patients (A)			Patients of Other Ethnicities (O)			p (Mann Whitney U test for racial origin)		
	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	N	Mean (SD)	Median (min-max)	C-A	C-O	A-O
Weight (kg)	227	74.45±19.89	69(43-144)	90	88.67±25.23	82.8(51.5-164)	93	73.35±20.17	68.4(39.6-135.9)	<0.0001*	0.552	<0.0001*
PAPP-A MoM	227	1.19±0.81	0.91(0.26-5.66)	90	1.4±0.9	1.22(0.16-5.67)	93	1.08±0.52	0.98(0.17-2.49)	0.025	0.885	0.036
Down Syndrome risk	227	4562.2±5102.6	2800(25-20000)	90	7370.9±6686.4	5400(11-20000)	93	5168.5±5488.2	3200(4-20000)	0.0003*	0.329	0.021
TSH	227	1.81±2.61	1.28(0.03-33.9)	90	1.73±4.33	1.13(0.03-41.8)	93	1.93±3.42	1.33(0.03-32.1)	0.128	0.918	0.134
Beta HCGMoM	227	1.11±0.49	1.06(0.41-3.81)	90	1.11±0.48	1.06(0.36-3.19)	93	1.01±0.35	0.98(0.33-2.23)	0.953	0.233	0.320

Table III. Maternal characteristics and TSH values of racial origin-based subgroups

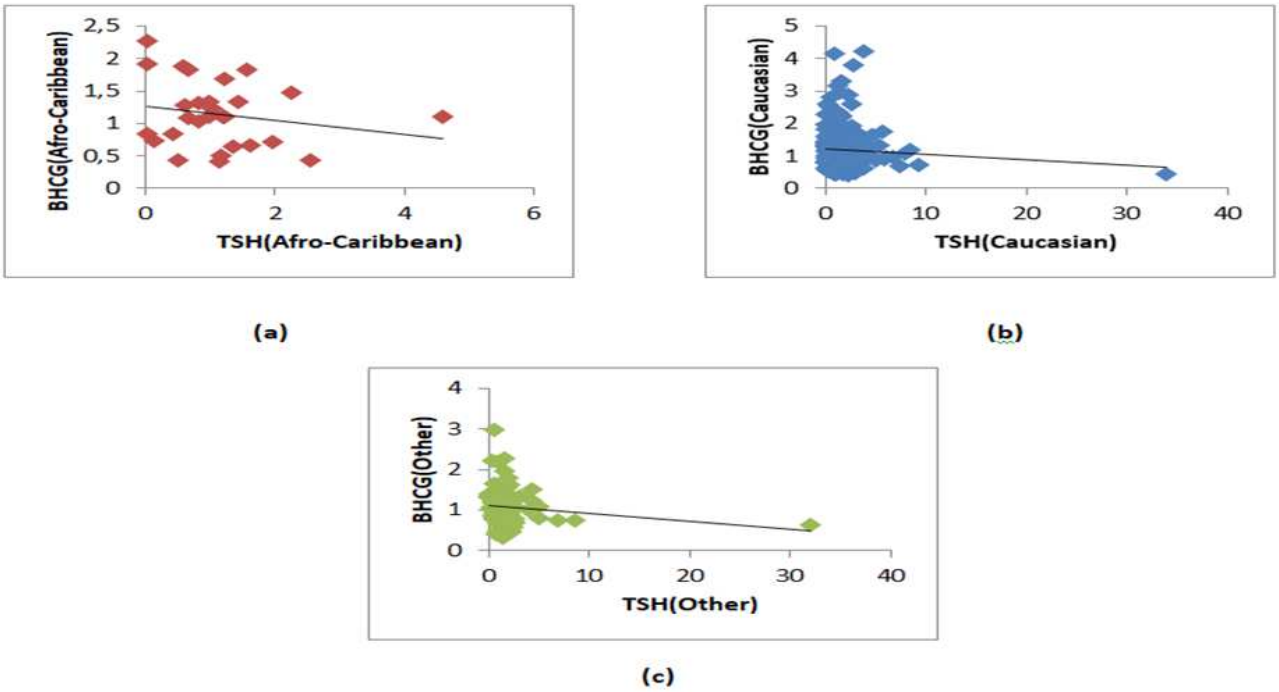

Figure 1. The correlation between BHCG multiples of median (MoM) values and TSH measurements for distinct racial origin categories, (a) Afro-Caribbeans, b) Caucasians, c) Other ethnicities

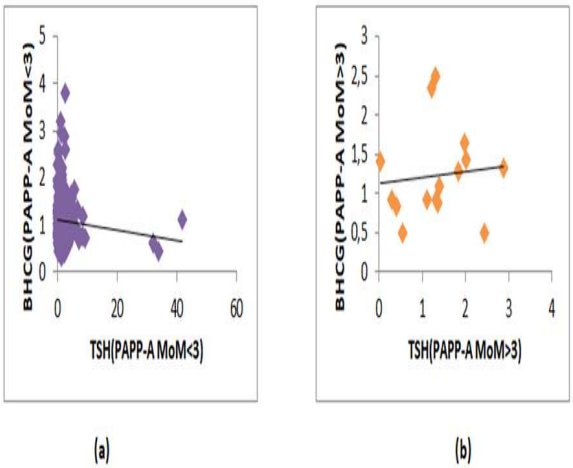

Figure 2. Correlation between BHCG multiples of median (MoM) and TSH values for different PAPP-A MoM levels, (a) PAPP-A MoM<3, b) PAPP-A MoM>3.

IV. DISCUSSION

Physiologically, non-pregnant women have greater TSH than pregnant women. Numerous studies' findings include the creation of reference ranges for TSH in pregnancy that are particular to each trimester. The estimation of thyroid parameter reference intervals during pregnancy is influenced by a number of variables. In this respect, the definition of euthyroidism is the most significant one. Iodine saturation and analytical technique are other related factors. The selection of the test assay platform, clinical heterogeneity and thresholds applied are most likely causes of the statistical variability. The 95th percentile from a cohort of women with a sufficient iodine supply, or selected samples from the community are suggested by the National Academy of Clinical Biochemistry as possible ways to identify the reference ranges that are appropriate for the first trimester of pregnancy [17]. High inter - individual variability exists for TSH and in some cases, FT4 values and the inclined distribution of readings in a group of pregnant women can be taken into account. To determine TSH and FT4 reference intervals, a group of pregnant women must be chosen, from which variables promoting or inhibiting thyroid function must be removed [17].

Immunoassays are commonly utilized to test TSH, TPOAb and FT4 levels in the blood. There are various immunoanalytical systems in use around the world. According to American Thyroid Stimulation, reference intervals should be established not just for each trimester of pregnancy, but also for each distinct geographic area [18], due to the considerable fluctuations in thyroid hormone concentrations during pregnancy [19]. Furthermore, potential differences in analytical procedures should be considered.

Our aim was to look for correlations of other serum markers of pregnancy and TSH to better understand the physiology of thyroid function during pregnancy. We did not find any significant correlation, but our limitation is that we do not know the gestational age when TSH values are collected. It is worth to note that TSH values differ according to gestational age.

V. CONCLUSION

In this research effort, we retrospectively analyzed the effects of distinct variables on PAPP-A levels and racial origin in 410 pregnant women during their first trimester. Additionally, in this group we analyzed the correlation between TSH and β-hCG.

PAPP-A levels are used to predict the course of pregnancies. Therefore, it is crucial to use precise cut-off values that take the patient's characteristics into account. Previous studies [2, 20] have shown that there is a racial difference; i.e. Afro-Caribbeans have higher PAPP-A levels than Caucasians. In this study, we had similar findings. Also, a noteworthy variation in weight and the likelihood of Down syndrome is observed between the Caucasian and Afro-Caribbean groups.

No significant correlation was observed between TSH measurements and β-hCG values for different ethnic groups and for different PAPP-A MoM levels.

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