 Prague Medical Report / Vol. 125 (2024) No. 1, p. 34–46

Raised First Trimester Thyroid Peroxidase Antibodies May Predict First Trimester Miscarriage: A Case Control Study

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Received October 29, 2022; Accepted January 30, 2024.

Key words: Thyroid autoimmunity – First trimester – Miscarriage

Abstract: Miscarriages constitute a significant aspect of failed pregnancies and a source of worry for the patient and caregiver. Some of the causes of miscarriages remain unknown. Immunological conditions such as thyroid autoimmunity could play significant roles. Our objective was to determine the relationship between raised thyroid peroxidase antibodies and first trimester miscarriages in a low resource setting. This was a case control study at the Gynaecological Clinic of the University of Calabar Teaching Hospital, Nigeria; from 14th February 2020 to 13th January 2021, involving 145 cases who had first trimester miscarriages, and their matched controls who had apparently normal pregnancies, at same gestational ages. Sera of venous blood from both participants and controls were analysed for thyroid peroxidase antibodies using enzyme-linked immunosorbent assay, and analysed using SPSS version 20, and GraphPad Prism 8.4.3 statistical software. Being a civil servant and low social status had significant odds for first trimester miscarriage. Raised thyroid peroxidase antibodies in the first trimester had 10-fold odds for miscarriage. Odds ratio 10.34, 95% CI: 3.22 to 32.98, P-value = 0.0001. The test had a sensitivity of 89.66% and specificity of 54.41%. The positive predictive value was 17.93%, while the negative predictive value was 97.93% and a likelihood ratio of 1.966. Rising thyroid peroxidase antibodies in early pregnancy could be a predictor for miscarriage. This is so because patients with raised thyroid peroxidase antibodies in the first trimester had a 10-fold risk of having a first trimester miscarriage.

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https://doi.org/10.14712/23362936.2024.3

Introduction

First trimester miscarriage is a challenging experience for both the patient and the physician, it is a source of maternal anxiety and yet commonly encountered in clinical practice. Up to 75% of fertilized ova and at least 15% of clinically recognized pregnancies never survive to birth (Jurkovic et al., 2013; Stagnaro-Green, 2015). First trimester miscarriage is defined as the loss of pregnancy before 13 weeks of gestation (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins – Gynecology, 2018). Both ectopic and molar pregnancies are not usually included in this definition. Most miscarriages occur early as seen in a study where over 80% of cohort participants had first trimester pregnancy losses (Lawani et al., 2022) with approximately half occurring before or just after a missed menses. It is thought that an overwhelming majority of miscarriages are the result of chromosomal abnormalities (Jurkovic et al., 2013). In a study in Jos, Nigeria, thyroid peroxidase antibodies were positive in 11.4% of women with first trimester miscarriage as against 4.5% of pregnant women who have had a previous normal delivery without miscarriage (Samson et al., 2018). In India, Bhattacharyya et al. (2015) reported a prevalence of 10.87% of miscarriages among women with positive thyroid peroxidase antibodies as against 4.8% in women who were negative for thyroid peroxidase antibodies.

Considering the fact that, the exact cause(s) of first trimester miscarriage is not known in over 50% of cases (Twig et al., 2012), this has become a topic of consideration by researchers. Several aetiological reasons have been put forward. Immunological disorders are known causes of first trimester miscarriage, these include: rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes mellitus, antiphospholipid antibody syndrome (APS), thyroid disorders among others. There is evidence that thyroid autoimmunity is an important risk factor for miscarriage and preterm birth, as it has been reported that the presence of thyroid autoantibodies is relatively common in women of reproductive age (Stagnato-Green, 2015). Studies have shown that the prevalence of thyroid autoantibodies in women of reproductive age range from 5 to 20%, and in about 22.1% of women seeking fertility in Damascus (Aljarad et al., 2019). Even in women with biochemically normal thyroid function, studies have reported presence of thyroid autoantibodies, particularly thyroid peroxidase (TPO) antibodies in 10–15% of normal individuals (Frohlich and Wahl, 2017). Pregnant women who are euthyroid but who are positive for thyroid peroxidase antibodies are at increased risk for miscarriages, preterm birth, pregnancy-induced hypertension, intrauterine growth restriction, and intrauterine fetal demise (Rajput et al., 2017).

Miscarriages in women with positive thyroid autoantibodies occur within the first trimester of gestation (Lata et al., 2013) when the fetus is critically dependent on maternal thyroid hormones. Therapeutic interventions aiming at modulating the immune system of women with autoantibodies have included intravenous

immunoglobulin administration. This treatment resulted in an increase in the percentage of women who had successful pregnancies (Lata et al., 2013). An earlier study (Negro et al., 2006) divided thyroid autoantibody positive women into two groups. One group was treated with levothyroxine (LT4) in a dose based on the thyroid stimulating hormone (TSH) starting values. The other group was not treated. A third group served as a normal general population control. The TSH values of the untreated group remained significantly higher than those of the other two groups during the entire gestational period. TSH and free thyroxine (FT4) values in the treated group were not significantly different from the control group. The treated group and the controls showed a similar miscarriage rate (3.5 and 2.4%, respectively), which was lower than that of the second group (13.8%) who did not receive LT4. The conclusion of this study was that thyroid autoantibody positive women have an increased risk of miscarriage but when given the benefit of treatment with thyroid hormone, they behave as the normal ones.

It is necessary to study the association of thyroid autoantibodies in early pregnancy and first trimester miscarriages in Calabar.

Aims and Objectives

Specific aim

To determine the relationship between presence of thyroid autoantibodies and first trimester miscarriages at University of Calabar Teaching Hospital.

Specific objectives

1) To study the sociodemographic characteristics of women with first trimester miscarriage and their matched controls.
2) To determine the odds of raised thyroid peroxidase antibody on first trimester pregnancy.
   Null hypothesis: There is no relationship between raised thyroid peroxidase antibody and first trimester miscarriage.
   Alternate hypothesis: A relationship does exist between raised thyroid peroxidase antibody and first trimester miscarriage.

Methods

Study design

This was a case control study.

Study setting

This study was conducted in the Department of Obstetrics and Gynaecology of the University of Calabar Teaching Hospital, Calabar. The hospital is located within

the Calabar metropolis providing tertiary health services to more than 3 million people in Cross River State and also serves as a referral center for adjourning States of Akwa Ibom, Abia, Benue as well as the Republic of Cameroun and Equatorial Guinea. The cases and controls were studied from 14th February 2020 to 13th January 2021.

Participants

The study population comprised 145 consenting women presenting with miscarriage within 12 weeks of gestation in the gynaecological emergency unit of the University of Calabar Teaching Hospital (UCTH), Calabar, Nigeria. These participants are referred to as "cases". The "control" group comprised 145 consenting pregnant women (within 12 weeks of gestation) who have had a previous successful pregnancy, without history of previous miscarriage, matched for maternal age and gestational age with the "cases", and presented for routine antenatal care.

The research was conducted in line with requirement for the conduct of research on human subjects. It was registered with University of Calabar Teaching Hospital Research and Ethics Committee with number NHREC/07/10/2012 and assigned approved protocol number UCTH/HREC/33/692.

Inclusion criteria:

1) Women presenting with miscarriages at or before 12 weeks of gestation.
2) Maternal age and gestational age-matched women with normal pregnancies at or before 12 weeks of gestation.

Exclusion criteria:

1) Women who refuse to give consent.
2) Obese pregnant women.
3) Maternal age more than or equal to 40 years.
4) Women known to have rheumatoid arthritis, chronic renal disease, diabetes mellitus or antiphospholipid syndrome.

Variables

The outcome measure was first trimester miscarriage. The exposure was raised thyroid peroxidase antibody in first trimester pregnancy.

Data sources/sampling method and data collection

Women who presented in the gynaecological emergency unit with miscarriage (≤ 12 weeks) were the case group, while the control group were women matched for age, and gestational age with apparently normal pregnancy at that time. Convenient sampling technique was used in selecting controls to match the cases. Consent was taken from the respondents before data collection.

Test procedure

Blood samples were collected by venepuncture of the antecubital vein aseptically. About 5 ml of blood was collected into a plain vacutainer tube using a 5 ml syringe. It was left undisturbed to clot at room temperature over 15–30 minutes. The sample was centrifuged at 2,500–3,000 rpm for 5–10 minutes, after which it separates into upper liquid layer, and the serum, below the upper layer, was stored at –20 °C before analysis. The product kit used was Accubind-ELISA microwells, Monobind, CA 92630 USA. Assays were done according to the kit's manufacturer's specification. One hundred µl of calibrators, controls and prediluted samples were drawn into the wells, and incubated for 30 minutes at room temperature (20–28 °C). The content of each microwell was discarded and washed 3 times with 300 µl of wash solution. One hundred µl of enzyme conjugate was added into each well and then incubated for 15 minutes at room temperature. The contents of the microwells were discarded and washed 3 times with 300 µl of wash solution; one hundred µl of tetramethylbenzidine (TMB) substrate solution will be added into each well and incubated at room temperature for 15 minutes. The reaction was stopped by adding 100 µl of stop solution to each well of the modules and incubate for 5 minutes at room temperature. Optical density at 450 nm was read and results calculated. The optical density (OD) is proportional to the antibody concentration, which is interpreted using a standard chart. Values above 35 IU/ml are considered positive for the presence of anti-TPO autoantibodies (Loh et al., 2016). However, our laboratory used values above 40 IU/ml as positive.

Quality control for the assays were ensured using pooled sera as control specimen run in duplicate with each assay batch and the inter and intra-batch coefficient of variations computed to examine the analytical precision.

All samples were subjected to the same processing to eliminate bias.

A researcher-administered questionnaire was used to collect information on the sociodemographic characteristics of the participants (cases and controls).

Estimation of sample size

The sample size was estimated using the formula (Charan and Biswas, 2013):

$$n = \frac{\{P_1(1-P_1) + P_2(1-P_2)\} \times (Z_\alpha + Z_\beta)^2}{(P_1-P_2)^2}$$

Where:

n = number of sample size in each of the group

P_1 = proportion of positive TPO autoantibodies among women with miscarriage (0.11 in a similar study) (Samson et al., 2018)

P_2 = proportion of positive TPO autoantibodies in the control group (0.05 in the same study)

$Z\text{-}_{\alpha/2}$ = value of standard normal distribution corresponding to a significance level of alpha (1.96 for two-sided test at the 0.05)
$Z\text{-}_{\beta/2}$ = value of standard normal distribution corresponding to the desired level of power (0.84 for a power of 80%)

$$n = \frac{\{(0.11\times0.89 + 0.05\times0.95)\} \times (1.96 + 0.84)^2}{(0.06)^2} \qquad n \approx 134$$

The sample size was scaled up to 145 for the cases and 145 for the controls.

Analyses of the sociodemographic characteristics of the cases and controls were performed using SPSS software (version 20.0) and presented as frequencies and percentages. Categorical and continuous variables were compared using chi-squares and Fischer's exact tests as appropriate, and P-values are shown in Table 1.

The result of thyroid peroxidase antibodies of the participants (cases and controls) is presented in Table 2. The sensitivity, specificity, positive and negative predictive values as well as the likelihood ratio were also determined using GraphPad Prism software, and the result presented in Table 3.

Apart from age and ethnicity other sociodemographic characteristics were compared by a contingency analysis using GraphPad Prism software. The results are presented in Figure 1.

The result of thyroid peroxidase antibodies was used to dichotomize those with raised antibodies (> 40 IU/ml) from those (≤ 40 IU/ml) between cases and controls. The values as shown in Table 2 were analysed for contingency using GraphPad Prism software version 8.4.3, San Diego, California. Fishers' exact test determined a two-sided P-value between the groups. The odd ratios (OR) and 95% confidence intervals (CI) are shown in Figure 2. A P-value of < 0.05 was considered as statistically significant.

Results

Table 1 shows sociodemographic characteristics of the participants. The mean age of the women with miscarriages and control groups was 29.87 ± 3.84 years. Education of the women was not significantly different at P-value < 0.05, however, the distribution of their occupation, husband's education and occupation and social class were significantly different.

Table 2 shows the distribution of participants according to result of antibody test for the cases and controls. There were 26 patients with miscarriage and 3 in the control group who had thyroid peroxidase antibodies above 40 IU/ml. In Table 3, the values in Table 2 were subjected to contingency analysis for sensitivity, specificity, positive and negative predictive values. The sensitivity of the test was 89.7%, specificity 54.4%, positive predictive value 17.9%, negative predictive value 97.9% and a likelihood ratio of 1.97.

Table 1 – Sociodemographic characteristics of women with first trimester miscarriages (cases) and their matched controls

Variables	Cases (n=145)		Control (n=145)		Chi-square	P-value
	frequency	%	frequency	%		
Age group						
≤ 35	135	93.1	135	93.1		
> 35	10	6.9	10	6.9		
Education						
Primary	32	22.2	19	13.3		
Secondary	84	57.8	103	71.1	5.90	0.0514
Tertiary	29	20.0	23	15.6		
Ethnicity						
Efik	23	15.9	23	15.9		
Ibibio	29	20.0	23	15.9		
Obudu	42	29.0	16	11.0	30.52	<0.00001*
Igbo	26	17.9	19	13.1		
Others	25	17.2	64	44.1		
Occupation						
Housewife	32	22.1	52	35.9		
Student	10	6.9	22	15.2		
Trader	45	31.0	42	28.9	23.05	0.00012*
Civil servant	32	22.1	9	6.2		
Self employed	26	17.9	20	13.8		
Husband education						
Primary	26	17.9	10	6.9		
Secondary	71	49.0	106	73.1	18.70	0.000086*
Tertiary	48	33.1	29	20.0		
Husband occupation						
Self employed	29	20.0	42	29.0		
Civil servant	48	33.1	19	13.1		
Trader	52	35.9	48	33.1	32.09	<0.00001*
Unemployed	10	6.9	6	4.1		
Artisan	6	4.1	30	20.7		
Social class						
Low	61	42.1	12	8.3		
Middle	61	42.0	120	82.8	54.90	<0.00001*
High	23	15.9	13	8.9		

*significant P-value < 0.05

Figure 1 shows a comparison of five sociodemographic characteristics listed in Table 1.

Figure 1A compared participants' occupation. Being a civil servant was at increased risk for miscarriage (OR 4.28, 95% CI 3.06 to 9.44).

Table 2 – Results of thyroid peroxidase antibody among women with first trimester miscarriage and matched controls

Data analysed	Thyroid peroxidase > 40 IU/ml	Thyroid peroxidase ≤ 40 IU/ml	Chi-square	P-value
Cases	26	119		
Controls	3	142	20.2682	<0.00001
Column total	29	261		

Table 3 – Results of sensitivity, specificity, positive and negative predictive values as well as likelihood ratio of the test

Effect size	Value (%)	95% confidence interval (%)
Sensitivity	89.66	73.61 to 96.42
Specificity	54.41	48.34 to 60.34
Positive predictive value	17.93	12.54 to 24.98
Negative predictive value	97.93	94.09 to 99.44
Likelihood ratio	1.966	

Figure 1B compared participants' educational status. There was no increase in odds when primary level of education was compared with other levels, P-value was 0.0635.

Figure 1C compared participants' husbands' level of education. Women whose husbands had only primary level education were at increased odd for miscarriage (OR 2.95, 95% CI 1.38 to 6.04).

Figure 1D compared participants' husbands' occupation. Women whose husbands were civil servants were at increased odd for miscarriage (OR 3.28, 95% CI 1.80 to 6.04).

Figure 1E compared social status of participants. Women of low social status were at increased odd for miscarriage (OR 8.05, 95% CI 4.11 to 15.26).

In Figure 2, there were 26 positive cases within the group of women who had first trimester miscarriage, and 3 among those of matched controls. We identified two groups; one with raised thyroid peroxidase > 40 IU/ml and another with values ≤ 40 IU/ml, which were analysed. The OR was 10.34 with a 95% CI of 3.22 to 32.98, and P-value 0.0001.

Discussion

Social class, husband education and occupation as well as wife occupation are significant risk factors for miscarriage as shown in Table 1. The odd ratios in Figure 1A, D and E, infer that being a civil servant, especially of low socioeconomic

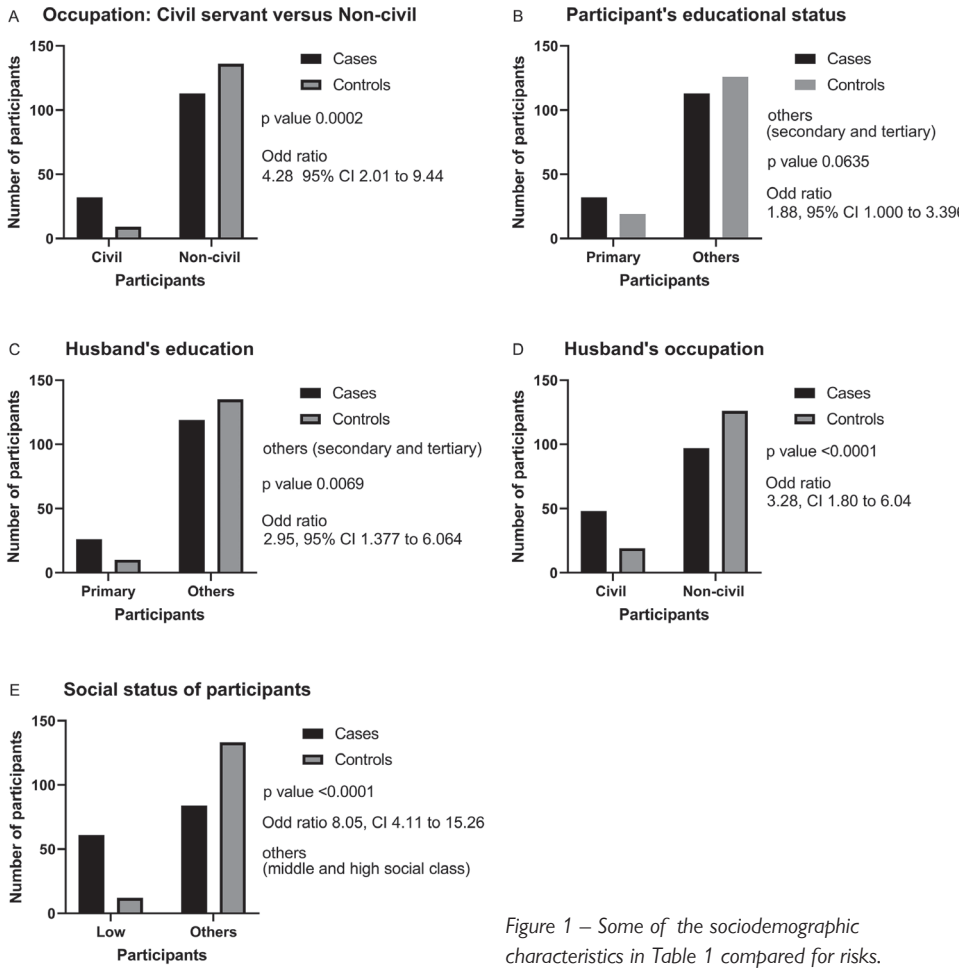

Figure 1 – Some of the sociodemographic characteristics in Table 1 compared for risks.

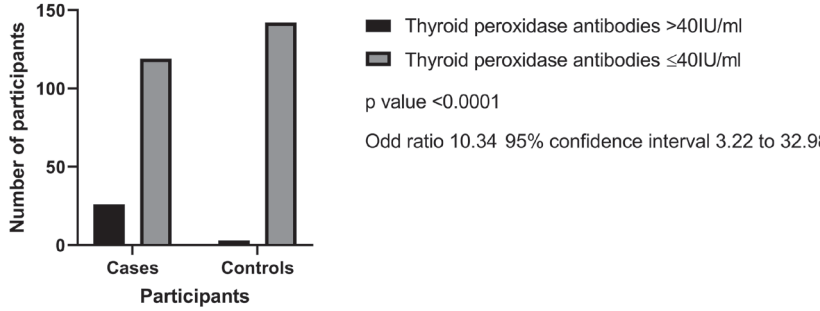

Figure 2 – Bar chart showing the number of participants with raised thyroid peroxidase antibody (levels > 40 IU/ml) among women with first trimester miscarriage (cases) and their matched controls in the University of Calabar Teaching Hospital, Calabar.

status was significantly associated with increased odd for miscarriage. This is a significant finding and a wakeup call for policy implementers in the Nigerian civil service. Low socioeconomic status, on its own, is associated with adverse pregnancy outcomes (Thomson et al., 2021).

In Tables 2 and 3, there were 26 patients with first trimester miscarriage and 3 in the control group who had thyroid peroxidase antibodies above 40 IU/ml. This method of testing has a sensitivity of 89.7% and a negative predictive value of 97.9%. In Figure 2, patients with raised thyroid peroxidase antibodies in the first trimester had a 10-fold odd of having a first trimester miscarriage. It could be inferred that testing for thyroid peroxidase antibodies in early pregnancy could detect those who might be at risk for miscarriage because of thyroid autoimmunity.

One of our study limitation was the challenge of getting pregnant women coming to book at or before 12 weeks of pregnancy. Most pregnant women book after the first trimester, with about 24.8% booking in the first trimester (Oliobi et al., 2019).

In Table 2, thyroid autoimmunity as evidenced by raised thyroid peroxidase antibodies in this study was present in 26 of 145 (17.9%) of women with first trimester miscarriages, and in three of 145 (2.1%) of matched controls. In the study by Lata et al. (2013), the miscarriage rate was 13.8% in the thyroid autoantibody positive group and 2.4% in the antibody negative group. In a similar study, Bhattacharyya et al. (2015) reported a miscarriage of 10.87% among thyroid peroxidase positive pregnant women against 4.8% in the thyroid peroxidase negative pregnant women in the first trimester. Samson et al. (2018) reported autoimmunity of 11.4% in Jos, North Central Nigeria, and 9% prevalence documented by Jibril et al. (2015) in Zaria. Our study design was case control, which is not a prevalence study. However, the prevalence of 17.9% in our study was deduced from a subset of women with miscarriage who had raised thyroid peroxidase antibodies above 40 IU/ml. In addition, our control group were pregnant women who had no previous history of miscarriage rather than those negative for thyroid peroxidase antibodies. Samson et al. (2018) did a case control study using 44 patients with miscarriage at mean gestational age of 11.57 ± 4.3 weeks (cases) and 44 pregnant women with previous history of delivery without miscarriage at mean gestational age of 17.9 ± 4.9 weeks as control. This study compared the thyroid peroxidase antibodies on both groups with finding of 11.4% in cases and 4.5% in the control. The difference was not statistically significant. Our study had a larger population and the participants' ages and gestational ages were matched. Our finding of 17.9% positivity for thyroid peroxidase antibodies in cases and 2.1% in the control group was statistically significant.

In Table 1 the sociodemographic characteristics of the women recruited in this study revealed that level of education of the women was the only factor that was not statistically significant. Poor husband education and occupation may mean

poor feeding (poor iodine intake) and high risk to environmental toxicants, which may affect thyroid function (Brent, 2010). All the twenty-nine patients (including controls) who had raised thyroid peroxidase antibodies were aged 35 or less. This does not refute the fact that thyroid disease can occur at any age as variously reported in Nigeria (Okafor et al., 2019). Our study focused on patients with miscarriage, but tested thyroid peroxidase antibodies in comparison with matched controls.

The patients in the control group who had raised thyroid peroxidase antibodies in first trimester were counselled on the need to take levothyroxine to prevent adverse pregnancy outcome in the second or third trimester. Although raised thyroid peroxidase antibodies in pregnant euthyroid women increased the risk of miscarriages and preterm birth, and treatment with levothyroxine decreased miscarriage rate (Thangaratinam et al., 2011; Dal Lago et al., 2021). However, Dhillon-Smith et al. (2019) in a randomized controlled trial involving 19,585 women in 49 hospitals in the United Kingdom failed to demonstrate significant difference in the pregnancy outcomes. Further research in different communities is necessary to elucidate the role of levothyroxine in preventing adverse pregnancy outcomes in this group of patients.

Conclusion

There was a 10-fold odd of having first trimester miscarriage in pregnant women with raised thyroid peroxidase antibodies. This study buttressed the fact that endocrine disorder is a significant contributor to first trimester pregnancy loss.

This study establishes a local data on thyroid autoimmunity and first trimester miscarriage, which could serve as template for a broad-based and multi-center study on this topic in order to improve on its validity.

Early assay of rising thyroid peroxidase antibody in first trimester may predict a pregnancy that may miscarry if not protected.

Acknowledgements: The authors would like to acknowledge Dr. Ogarekpe of Chemical Pathology who assisted in the test procedures and quality control.

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