

Thyroid autoimmunity and early pregnancy loss in Jos, Nigeria

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ABSTRACT

Background: Early pregnancy loss is a challenging experience for both the patient and the physician; it is unfortunately a common complication of human gestation. Early pregnancy loss is defined as the termination of pregnancy before 20 weeks of gestation or with a fetal weight of <500 g. Immunological disorders have been attributed to early pregnancy loss in addition to chromosomal abnormalities. Thyroid autoimmunity is one of the immunological causes of early pregnancy loss that has been poorly studied in sub-Saharan Africa.

Objective: This study was aimed at determining the relationship between early pregnancy loss and thyroid autoimmunity in Jos, North-Central Nigeria.

Patients and Methods: This was a case-control study involving 44 women with a current history of miscarriage at an average gestational age of 11.57 ± 4.3 weeks (cases) and 44 pregnant women with previous history of delivery with no history of miscarriage(s) at a mean gestational age of 17.9 ± 4.9 weeks (controls). Serum thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were assayed by Electro-chemiluminescence immunoassay (ECLIA) using Cobas e411 auto analyzer (by Roche). The data obtained were analyzed using SPSS version 16.0.

Results: TgAb was neither present in the cases nor in the control group. The prevalence for TPOAb was 11.4% for the cases and 4.5% for the controls. The difference in proportion was not statistically significant ($P = 0.434$).

Conclusion: There was no statistically significant relationship between thyroid autoimmunity and early pregnancy loss.

Key words: Autoimmunity; pregnancy loss; thyroid.

Introduction

Early pregnancy loss is a difficult situation for both the patient and physician; unfortunately, it is a common complication of human gestation. Up to three-quarters of fertilized ova and about 15% of clinically recognized pregnancies end as miscarriages.^[1,2] Majority of spontaneous pregnancy losses occur early, with approximately half occurring before or just after a missed period^[3] whereas the rest occur before 10 completed weeks of gestation; in both situations, chromosomal abnormalities are the most common causes.^[2]

Early pregnancy loss is defined as the termination of pregnancy before 20 weeks of gestation or with a fetal weight

of <500 g.^[4] This definition excludes ectopic and molar pregnancies. Considering the fact that the exact cause (s) of early pregnancy loss is not known in over half of the cases,^[5] this has become a topic of consideration by researchers.


Apart from idiopathic early pregnancy loss, several etiological reasons have been proposed. Immunological disorders are a known cause of early pregnancy loss. These include rheumatoid arthritis, systemic lupus erythematosus, type-1

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diabetes mellitus, antiphospholipid antibody syndrome (APS), and thyroid disorders among others. Thyroid autoimmunity in pregnancy is associated with increased rates of miscarriage, preeclampsia, placental abruption, growth restriction, prematurity, and stillbirths.^[6] The presence of thyroid autoantibodies is relatively common in women of reproductive age.^[7] In an “unselected” population of women, the prevalence ranges from 6% to 20%,^[8] and it is higher in women with a history of recurrent pregnancy loss from 17 to 33%,^[9-11] and in women with a history of sub-fertility from 10 to 31%.^[12-14]

In industrialized nations, thyroid autoimmunity is the main cause of hypothyroidism, which itself results in poor obstetric outcomes. Even in women with biochemically normal thyroid function, the studies have reported an association between the presence of thyroid autoantibodies, particularly thyroid peroxidase antibodies, and adverse pregnancy outcomes, including miscarriage, preterm birth, and adverse neurodevelopmental sequelae in children.^[15-18]

In Nigeria, hypothyroidism is relatively common mainly in Plateau state, north-central Nigeria.^[19,20] Although most of the cases of hypothyroidism have been attributed to iodine deficiency, little is known about the role of thyroid antibodies in thyroid dysfunction and pregnancy outcomes in Nigerian women.^[21-23] Considering that thyroid antibody testing is not routinely available in developing countries and only a few studies have measured thyroid antibodies in Africans,^[21,24,25] this study was designed to examine the association between thyroid antibodies and pregnancy loss in Nigerian women.

Materials and Methods

This study was carried out between March 2015 and September 2015. The study population comprised all consenting pregnant women presenting with a history of spontaneous early pregnancy loss (≤ 20 weeks). The control group comprised consenting pregnant women (≤ 24 weeks) with at least one successful pregnancy and no history of miscarriages who presented for routine antenatal care (ANC).

The study recruited 44 cases and 44 controls. A structured questionnaire was administered and blood sample was collected for thyroid antibody screening for both cases and controls. A sample of 5 ml of blood was collected into a plain vacutainer tube. The collected sera were stored at -20°C before analysis.

Thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were assayed by Electro-Chemiluminescence Immuno Assay (ECLIA) using Cobas e411 auto analyzer (by Roche). Significant antibody titre for TPOAb and TgAb were

derived from the kits manufacturers’ reference values for pregnant women in the second trimester.^[26]

Quality control was assured by proper calibration of the auto-analyzer and running commercial controls at two levels (supplied by kits manufacturers). The control values were within the prescribed limits.

All statistical analyses were performed using SPSS software (version 16.0). Frequencies and percentages were computed for sociodemographic characteristics of the cases and controls. The relationship between presence of thyroid autoantibodies and early pregnancy loss was tested using Chi-square and odds-ratio. A *P* value of <0.05 was considered as statistically significant.

Ethical clearance was obtained from the appropriate Ethical Committee and consent was also obtained from the participants before they were enrolled in the study.

Results

A total of 88 participants (44 cases and 44 controls) were involved in this study. The sociodemographic characteristics of women that participated in the study are shown in Table 1. The cases and control groups were comparable in terms of maternal age. The mean age of women that comprised the cases was 29.3 ± 5.0 years and the control group was 29.1 ± 5.2 years. The overall mean age was 29.2 ± 5.1 years. A total of 52% of cases and 57% of controls were below age 30 years.

The mean gestational age of presentation was 11.6 ± 4.3 weeks for the cases whereas the controls presented at an average gestational age of 17.9 ± 4.9 weeks. The combined average gestational age at presentation for both the cases and the controls was 14.7 ± 4.5 weeks.

The mean parity was 1.9 ± 1.6 and 1.9 ± 1.2 for the cases and the controls, respectively, with an overall mean parity of 1.9 ± 1.4 for both groups. Both maternal age and parity in both cases and the control groups were comparable.

Anthropometric and clinical characteristics as summarized in Table 2 showed that the average maternal weight was 63.5 ± 16.2 kg for the cases and 69.1 ± 8.1 kg for the controls. The controls significantly had higher mean weight than the cases ($P = 0.043$). The mean weight for both groups was 66.3 ± 13.0 kg.

From Table 2, the height and systolic and diastolic blood pressures were comparable in both cases and controls. The

mean height was 1.61 ± 0.06 m for the cases, 1.58 ± 0.06 m for the control with an overall mean height of 1.6 ± 0.05 m for both groups. Blood pressure pattern was within normal range for all participants, as shown in Table 2 below.

In Table 3, overall average of TgAb and TPOAb were higher among the controls than cases; however, the observed differences were not significant ($P = 0.673$ and $P = 0.450$ for TgAb and TPOAb, respectively).

Two different cutoff values were used to determine significant titer of TgAb as shown in Table 4. The kit manufacturer^[26] proposed a cutoff value of 116 IU/mL for pregnant population (second trimester), whereas the study-derived reference interval using the control in this study was 43 IU/mL (corresponding to the 95th percentile). Using the cutoff value of 116 IU/mL, none of the cases and controls were found to have a significant antibody titer. However, using the cutoff value of 43 IU/mL, none of the cases had a significant titer, but in 2 (4.5%) of the controls, notwithstanding, this was not statistically significant ($P = 0.494$).

Table 1: Demographic characteristics of subjects

Variable	Cases <i>n</i> =44(%)	Control <i>n</i> =44(%)	Total <i>n</i> =88(%)
Age group (years)			
<30	23 (52.3)	25 (56.8)	48 (54.5)
30+	21 (47.7)	19 (43.2)	40 (45.5)
Mean±SD	29.3±5.0	29.1±5.2	29.2±5.1
Parity			
0	8 (18.1)	0 (0.0)	8 (9.1)
1	16 (36.4)	21 (47.7)	37 (42.0)
2-4	16 (36.4)	21 (47.7)	37 (42.0)
5+	4 (9.1)	2 (4.5)	6 (6.8)
Mean±SD	1.9±1.6	1.9±1.2	1.9±1.4
Gestation age (weeks)			
≤10	23 (52.3)	4 (9.1)	27 (30.7)
11-20	20 (45.5)	28 (63.6)	48 (54.5)
>20	1 (2.3)	12 (27.3)	13 (14.8)
Mean±SD	11.6±4.3	17.9±4.9	14.7±4.5

Table 2: Anthropometric and clinical characteristics

Variable	Cases	Control	Overall	t-test	P
Weight (kg)	63.5±16.2	69.1±8.1	66.3±13.0	2.054	0.043
Height (m)	1.61±0.06	1.58±0.06	1.6±0.05	2.928	0.004
SBP (mmHg)	115.6±12.4	111.7±14.9	113.6±13.8	1.330	0.187
DBP (mmHg)	73.8±9.9	68.8±11.5	71.3±10.9	2.181	0.032

Table 3: Chemical characteristics

Variable	Cases IU/mL	Control IU/mL	Overall IU/mL	t-test	P
TgAb	20.4±6.8	21.2±8.7	20.8±7.7	0.423	0.673
TPOAb	38.1±9.6	39.4±6.5	38.7±8.2	0.759	0.450

Also, two different cutoff values were used to determine significant titer of TPOAb as shown in Table 5. The kit manufacturer^[26] has a value of 51 IU/mL, whereas the study-derived reference interval using the control in this study was 54 IU/mL (corresponding to the 95th percentile). Using both cutoff values of 51 IU/mL^[26] and 54 IU/mL, 5 (11.4%) of the cases and 2 (4.5%) of the controls had significant antibody titer. However, this disparity in TPOAb is not statistically significant ($P = 0.434$).

Discussion

For now, there is no agreed cutoff value for thyroid autoantibodies; this could be the basis for differences in the studies on the subject matter.^[21] In this study, two different cutoff values were used to determine significant levels of TgAb and TPOAb. Cutoff values for TgAb were 116 IU/ml from the manufacturer's manual^[26] and 43 IU/ml as the derived upper reference limit from the control group of the study population (corresponding to the 95th percentile).

The study-derived cutoff value was much lower than the quoted values from the manufacturer, which was derived from largely Caucasian population. Although there was no significant difference between the prevalence of autoimmunity among cases and controls at the different cutoff values, no significant autoimmunity was found among cases and controls with the manufacturer's cutoff, whereas 4.5% of controls had significant TgAb titre with the study-derived cutoff values; this was found not to be statistically significant ($P = 0.494$).

For TPOAb, cutoff values of 51 IU/ml from the manufacturer's manual^[26] and 54 IU/ml as derived reference interval were comparable. In this study, using both the kit manufacturer's

Table 4: Thyroid autoimmunity based on different cutoffs of TgAb

Cut-off IU/mL	Cases		Control		Total		χ^2 , P
	Autoimmunity Yes	No	Autoimmunity Yes	No	Autoimmunity Yes	No	
116	0 (0.0)	44 (100.0)	0 (0.0)	44 (100.0)	0 (0.0)	88 (100.0)	0.494*
43	0 (0.0)	44 (100.0)	2 (4.5)	42 (95.5)	2 (2.3)	86 (97.7)	

Table 5: Thyroid autoimmunity based on different cutoffs of ATPO

Cut-off IU/mL	Cases <i>n</i> =44		Control <i>n</i> =44		Total <i>n</i> =88		χ^2 , P
	Autoimmunity Yes	No	Autoimmunity Yes	No	Autoimmunity Yes	No	
51	5 (11.4)	39 (88.6)	2 (4.5)	42 (95.5)	7 (8.0)	81 (92.0)	0.434*
54	5 (11.4)	39 (88.6)	2 (4.5)	42 (95.5)	7 (8.0)	81 (92.0)	0.434*

and study-derived cutoff, TPOAb autoimmunity was present in 2 (4.5%) of the controls and in 5 (11.4%) of the cases. Though TgAb prevalence was higher among the control group and a higher prevalence of TPOAb in the cases, these were found not to be statistically significant ($P = 0.434$). This study utilized ECLIA to analyze TPOAb and TgAb levels as against ELISA, which was the method in similar studies.^[21–23] ECLIA has a higher sensitivity and precision when compared to ELISA.

From related studies in Nigeria, Okosieme *et al.*^[23] found TPOAb in 7% and TgAb in 4% of the patients in a general endocrine clinic. From a population of normal pregnant women, El-Bashir *et al.*^[22] noted TPOAb in 9% of the population whereas Kayode *et al.*^[21] reported a TPOAb prevalence of 25% from another group of pregnant women. TPOAb prevalence is comparatively higher in these studies as against 4.5% from this study.

The findings from our study concerning the association between TPOAb or TgAb and pregnancy loss is similar to the reports of some earlier studies.^[27–29] Esplin *et al.*^[27] studied 74 non-pregnant women with a history of recurrent pregnancy loss and from 75 healthy, fertile control subjects of similar gravidity for thyroglobulin and thyroid peroxidase antibodies by means of radioimmunoassay kits. It was found that women with a history of recurrent pregnancy loss are no more likely than the fertile control subjects to have circulating thyroid autoantibodies.

Furthermore, Russworth *et al.*^[28] concluded that the future risk of pregnancy loss in women with unexplained recurrent miscarriages is not affected by their thyroid antibody status. Kusum *et al.*^[29] found that the prevalence of thyroid autoimmunity was higher in pregnant women with a history of recurrent abortion compared with healthy pregnant control population. There was no difference in the prevalence of miscarriage or obstetric outcomes between recurrent miscarriage and healthy pregnant women group irrespective of TPO status.

However, some studies have shown significant relationship between pregnancy loss and both thyroid autoimmunity and hypothyroidism.^[30–33] The exact mechanism of an association of thyroid autoimmunity with miscarriage remains largely unknown; it is still a postulate of theories.

Although thyroid hormones and thyroid stimulating hormones (TSH) were not analyzed in this study, the similar thyroid antibodies between the case and control groups would suggest that any differences in frequency of hypothyroidism in these groups is unlikely to be related to

thyroid antibodies. One cannot, however, rule out the role of other effects of hypothyroidism, including subclinical hypothyroidism, in the etiology of early pregnancy loss in our environment. The finding from this study has probably helped by leaving one question less among the several questions that have been asked regarding the role of thyroid antibodies and thyroid abnormalities in early pregnancy losses in our environment.

Conclusion

This study suggests that routine testing for thyroid autoantibodies is unlikely to be cost-effective in the evaluation of patients with pregnancy loss in our environment. Notwithstanding, this study might have been limited by its small sample size, hence the need to study a larger population of women.

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Conflicts of interest

There are no conflicts of interest.

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