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Serum levels of oxytocin in pregnancy, parturition and postpartum for Nigerian females in Zaria, Nigeria

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Oxytocin is a hormone involved with adjustment of pregnancy, the process of delivery, breastfeeding, social recognition and bonding. This study aimed at determining the serum levels of oxytocin in pregnancy, during labour, and in the puerperium for Nigerian females in Zaria. It was a cross-sectional study of one hundred and twenty women aged 18 to 45 years from four hospitals in Zaria. The women were grouped into four groups comprising non-pregnant women (control), pregnant women (first, second, and third trimester), women in labour and in their first week after delivery. Questionnaires were administered to the women and their blood samples collected via venipuncture between 09.00 and 13.00 h. After centrifuging the blood samples, the sera were analyzed with human oxytocin ELISA kits at the Department of Chemical Pathology, Ahmadu Bello University Teaching Hospital, Shika. Results were presented as frequencies, percentages and mean ± standard deviation (SD) while data was analyzed using one-way analysis of variance (ANOVA), Tukey post-hoc test and the reference range (defined as 95% confidence limits) was determined. A statistical significance of $p<0.05$ was selected. Serum oxytocin levels (non-pregnant controls: 82.80 ± 23.68 pg/ml; 95% Confidence Interval (CI): 73.02 to 92.58 pg/ml) rose progressively with advancing gestation (first trimester: 167.56 ± 24.17 pg/ml, 95% CI: 148.98 to 186.13 pg/ml; second trimester: 377± 53.113 pg/ml, 95% CI 358.50 to 396.17 pg/ml), but there were no significant differences in serum oxytocin concentration for women in their third trimester (499.06 ± 42.06 pg/ml; 95% CI: 483.64 to 514.49 pg/ml) as compared to women during labour (525.0 ± 35.98 pg/ml; 95% CI: 497.35 to 552.65 pg/ml) and the puerperium (spontaneous vaginal delivery: 532.25 ± 29.93 pg/ml; 95% CI: 507.23 – 557.27 pg/ml; caesarean section: 502.40 ± 42.34 pg/ml; 95% CI: 449.83 to 554.97 pg/ml), $p>0.05$. Maternal serum oxytocin levels at spontaneous vaginal delivery (532.25 ± 29.93 pg/ml; 95% CI: 507.23 to 557.27 pg/ml) were higher than those at caesarean section (502.40 ± 42.34 pg/ml; 95% CI: 449.83 to 554.97 pg/ml) though not statistically significant ($p>0.05$). In conclusion, it appears that maternal oxytocin levels in Nigerian females though following the pattern in other studies had higher values.

Key words: Enzyme immunoassay, lactation, pregnancy hormone, reference range, serum oxytocin, Zaria.

INTRODUCTION

The neurohormone oxytocin (OTC) is known for its involvement in the process of delivery, reproductive behavior and its physiological role in the onset and maintenance of lactation (Thackare et al., 2006; Zamiri et al., 2001; Argiolas and Gessa, 1991). Oxytocin has also been linked to metabolic, analgesic, anxiolytic and health-

promoting cardiovascular effects (Grewen et al., 2008; Ring et al., 2006; Holst et al., 2002; Petersson et al., 1999).

Maternal OTC concentrations have been associated with autism related disorders (Nyffeler et al., 2014; Bartz and Hollander, 2008). Lower blood oxytocin levels in autistic children were associated with higher social deficits (Parker et al., 2014; Andariet al., 2010; Modahl et al., 1998). The two comparison groups of the study by Parker et al. (2014), consisted of children with autistic siblings and those without autistic siblings. All the groups demonstrated social skills correlating with their oxytocin levels. Variants of the oxytocin receptor also correlated with social ability and are suggested to serve as predictors of attachment in human infants (Chen et al., 2011).

Beyond these roles, OTC plays a major role in adjustment to pregnancy, maternal behavior and bonding (Wittig et al., 2014; Bartz et al., 2010; Feldman et al., 2007; Curley and Keyerne, 2005; Bartz and Hollander, 2006; Kendrick, 2000). Higher postpartum maternal-fetal attachment scores were observed in women with an OTC rise between the first and third trimester compared to women with stable or decreasing patterns of OTC (Levine et al., 2007). Another study revealed the development of postpartum depression in women having lower oxytocin concentration in mid-pregnancy (Skrundz et al., 2011). Variants of the oxytocin receptor have been associated with depressive symptomatology (Saphire-Bernstein et al., 2011).

OTC also plays a role in the social behavior of humans (Meyer-Lindenberg et al., 2011; Ebstein et al., 2010). In other subjects, OTC was observed to promote interpersonal relationships and enhance feelings of love and trust (Krueger et al., 2012). Evidence suggests that more intimate, positive social affiliations may protect and prolong good health (Kiecolt-Glaser and Newton, 2001; Berkman, 1995). Intra-nasally administered OTC was also found to increase adult attention to the eye region of faces and to facilitate their recognition of positive social words (Unkelbach et al., 2008; Guastella et al., 2008a).

In medical practice, measurement of hormone concentrations is important for the evaluation and treatment of diseases. Ethnic variations in hormone reference ranges exist (Sachidhanandam et al., 2010; Pinheiro et al., 2005; Potischman et al., 2005). Considering the relevance of oxytocin concentration to several physiological parameters and social behaviors, this study aimed at determining the reference range of serum oxytocin for Nigerian women in Zaria. A difference was expected in the reference ranges of serum oxytocin of Nigerian women in pregnancy, labour and the puerperium.

METHODOLOGY

Study site

The study was conducted among women in Zaria, Northern Nigeria. Zaria is a town located within latitude 11°3´N and longitude 7° 42´E. The town is comprised of 2 local government areas with an altitude of 610 m, an annual rainfall of 1056.6 mm and a mean annual temperature of 27°C (Mortimore, 1970).

Study design

The study was a cross-sectional, multicenter study. Women were recruited from antenatal clinics, delivery rooms and lying-in wards of five hospitals in Zaria. They consisted of Primary Health Centre, Samaru; Comprehensive Health Centre, SabonGari; Salama Hospital and Maternity, Kwangila; St Luke's Hospital, Wusasa; and Ahmadu Bello University Health Centre, Samaru, Zaria. While the control subjects consisted of individuals from Ahmadu Bello University (students and staff). Approval for the study was obtained from the Ethical Committee on Human Study of the Kaduna State, Ministry of Health. All participants provided informed consent.

Participants

A total of one hundred and twenty healthy female subjects participated in the study. Twenty-five subjects served as controls for the study. They were non-pregnant, non-lactating women in their reproductive age who were not on hormonal contraceptives. A total of ninety-five women were either pregnant, in labour or in the puerperium. All pregnancies were dated to the last menstrual period. Nine women were in their first trimester, 33 women were in their second trimester while thirty-one women were in their third trimester. Nine women were in labour and 13 were women in puerperium; eight of which had spontaneous vaginal delivery (SVD) and five had a caesarean section (CS). Subjects were screened for the following exclusion criteria: (1) medical complications, such as diabetes mellitus or hypertension; (2) smoking.

Sociodemographic variables

A questionnaire was administered to all participants to obtain bio-socio-demographic data about age, educational level, marital status, parity and ethnicity from self-report.

Weight, height and body mass index (BMI) assessment

The weights of the subjects were measured while wearing light clothing to the nearest 0.2 kg with a calibrated weighing scale. Height (without shoes and head attire) was measured to the nearest 0.5 cm with a stadiometer. The BMI was calculated as weight (kg)/height (m^2) (Guyton and Hall, 2006).

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Blood pressure measurement

The subjects were seated for 5 min with legs uncrossed, while a mercury sphygmomanometer (Acosson, A. C. Cossor & Son (surgical) LTD, London) and a 3M Littmann Classic II S.E. Stethoscope (3M Health Care, U.S.A) was used to determine the blood pressure by auscultation (Pickering et al., 2005).

Blood sample collection

Participants were instructed about the procedure on arrival at the health facility, they rested quietly for a minimum duration of 30 min to 1 h. Other parameters were also obtained on the same day (some participants had to proceed for their antenatal visits thereafter). The blood samples were taken between 09.00 and 12.00 h. Participants were seated on an examining couch while5 ml of venous blood was collected at the cubital fossa using a 5 ml syringe and a 23G needle. The sample were then transferred to clean, plain and dry bottles which were kept cold and centrifuged using a bench centrifuge at 1,000 × g for 15. The serum was pipetted into plain bottles and frozen at -8°C until analysis.

Blood sample analysis

Samples were analyzed at the Department of Chemical Pathology, Ahmadu Bello University Teaching Hospital, Shika, Zaria. Using Human Oxytocin, OT ELISA kit (EIAab). The principle of the test employed the quantitative sandwich enzyme immunoassay technique. Serum concentration of OTC was determined according to the protocol of the commercial kits and by measuring the detectable color intensity using a Microwell reader at 450 nm (Tietz, 1995). Assay sensitivity was <11.7 pg/ml with a detectable range of 15.6 to 1000 pg/ml specificity was for recombinant and human oxytocin with no significant cross-reactivity (Tiezts et al., 2000).

Data analysis

Results were presented as frequencies, percentages and mean ± standard deviation (SD). Data was analyzed using one-way analysis of variance using SPSS version 22, followed by a Tukey Post-hoc test and the reference range (defined as 95% confidence limits) was determined as arithmetic mean ± 2 SD. Results were considered statistically significant with $p<0.05$.

RESULTS

The following result is for 120 subjects comprising of non-pregnant controls, women in their first, second, and third trimesters, women in labour and the puerperium. The data presented includes the socio-demographic details, the anthropometric parameters and the serum oxytocin (central 95 percentile) concentration of apparently healthy Nigerian women in Zaria (Tables 1, 2 and Figure 1). Women in the age range of 21 to 25 years constituted the highest proportion of the study subjects. A large proportion of the subjects were Hausa women (49%) while all the women had some form of education with the tertiary education group constituting the highest proportion (38%). Most of the subjects were housewives (35%) while the least were artisans (5%).

There was a significant difference in weight of the pregnant women and women in labour as compared to the non-pregnant control ($p<0.05$). There was nosignificant difference in the height and BMI of the women across all groups. Mean systolic blood pressure, diastolic blood pressure and mean arterial blood pressure was significantly increased in women in labour and the puerperium as compared to the non-pregnant control ($p<0.05$). There was however no significant difference in the blood pressure parameters of pregnant women as compared to the non-pregnant control ($p>0.05$). There was no significant difference in the age of the women across all groups ($p>0.05$). There was a progressive increase in mean serum oxytocin level across the trimesters of pregnancy into the puerperium ($p<0.05$). However, this increase was not significant between the 3rd trimester, labour and postpartum groups ($p>0.05$).

DISCUSSION

The range of OTC concentration found in our sample of participants, is in line with the findings of Prevost et al. (2014). In their study, they had a range of 32.3 to 2297.6pg/ml. In our study, there was a large inter-individual differences in OTC levels (minimum = 55 pg/ml; maximum = 591 pg/ml respectively). However, other studies have observed a much lower value for peripheral OTC levels in women (Bick and Dozier, 2010; Grewen et al., 2010). The pulsatile release of OTC, laboratory variation in assay methods and variation in sample processing could explain the variations from one study to another.

In line with our hypothesis, it could be shown that OTC concentration showed fluctuations at different stages of gestation and the postpartum period. An observed increase in OTC concentration with increasing trimester was demonstrated (Figure 1). Our findings are in agreement with studies by Feldman et al. (2007), Stock et al. (1991), and deGeest et al. (1985). The prepartum elevated levels of OTC is contributed by maternal pituitary production, maternal uterine sources and fetal pituitary production. On a molecular level, the amount of freely available oxytocin measured by the antibody-based assay might vary due to the amount of albumin circulating (Abduljalil et al., 2012). As albumin (a protein likely to bind oxytocin) levels decrease as pregnancy progresses more, oxytocin becomes available for the assay. This mechanism could explain how oxytocin levels rise during pregnancy. The increase in oxytocin level is in preparation for delivery sequelae to which the later stage of pregnancy is also characterized by an increase in the number of oxytocin receptors (Maggi et al., 1990). In the study by Prevost et al. (2014), women who were pregnant with their first child had higher oxytocin levels in the third trimester and showed larger increases in

Table 1. The sociodemographic parameters of the participants.

Variable	Groups				Totals
	Non-pregnant (n=25)	Pregnant (n=73)	Labour (n=9)	Puerperium (n=13)	
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	
Age group (years)					
<20	5 (20)	19 (76)	0 (0)	1 (4)	25
21-25	10 (27)	22 (59.5)	1 (2.7)	4 (10.8)	37
26-30	4 (13.8)	22 (79.9)	2 (6.9)	1 (3.4)	29
>31	6 (20.7)	10 (34.5)	6 (20.7)	7 (24.1)	29
Ethnicity					
Hausa	2 (3.4)	43 (72.9)	5 (8.5)	9 (15.3)	59
Igbo	3 (30)	5 (50)	2 (20)	0 (0)	10
Yoruba	9 (52.9)	7 (41.2)	0 (0)	1 (5.9)	17
Others	11 (32.4)	18 (52.9)	2 (5.9)	3 (8.8)	34
Educational Status					
Qur'an	0 (0)	19 (76)	3 (12)	3 (12)	25
Primary	0 (0)	3 (37.5)	2 (25)	3 (37.5)	8
Secondary	3 (7.5)	28 (70)	4 (10)	5 (12.5)	40
Tertiary	22 (47.8)	23 (50)	0 (0)	1 (2.2)	46
Nil	-	-	-	-	-
Occupation					
Civil Servant	8 (53.3)	7 (46.7)	0 (0)	0 (0)	15
Trader	0 (0)	17 (73.9)	2 (8.7)	4 (17.4)	23
Student	17 (50)	16 (47.1)	0 (0)	1 (2.9)	34
House Wife	0 (0)	30 (71.4)	5 (11.9)	7 (16.7)	42
Artisan	0 (0)	3 (50)	2 (33.3)	1 (16.7)	6

Table 2. The mean age, anthropometric measurement and blood pressure of the participants.

Parameter (mean±SD)	Non-pregnant women (n=25)	Pregnant women (n=73)	Women in labour (n=9)	Women in puerperium (n=13)
Age (years)	25.53±5.14	25.30±5.14	32.78±5.12	30.00±6.65
Height(m)	162.69±7.96	163.65±11.28	165.5±1.41	161.30±2.14
Weight(kg)	58.04±10.14	64.08±18.08*	78.38±3.11*	65.45±5.26
BMI (kg/m²)	21.87±4.41	24.25±5.58	28.25±0.07	25.12±2.14
Systolic B.P(mmHg)	112.36±11.26	109.30±10.19	135.71±19.88*	131.82±19.40*
Diastolic B.P(mmHg)	76.20±9.05	71.69±9.14	87.14±11.13*	90.0±13.42*
Mean Arterial B.P (mmHg)	88.25±8.82	84.23±8.62	103.33±13.19*	103.94±15.26*

B.P: Blood pressure; BMI: body mass index. *p<0.05.

oxytocin levels from the first to the third trimester as compared to mothers who already had one or more children. The rise in prepartum OTC with increasing weeks of gestation is also associated with higher postpartum maternal-fetal attachment scores (Levine et al., 2007). Plasma OTC concentrations during pregnancy, have been found to be positively associated with a set of maternal bonding behaviors. Behaviors are like positive effect and gaze in interactions, as well as cognitive attachment representations towards the newborn in the

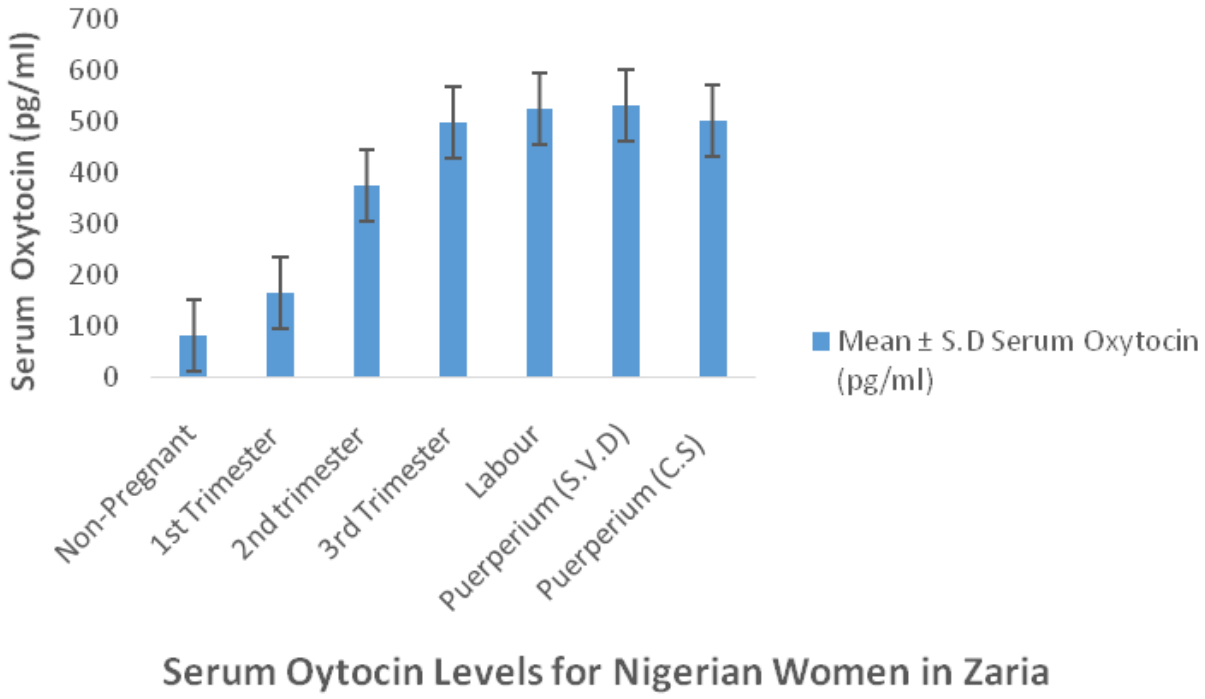

Figure 1. Serum oxytocin levels in non-pregnant, pregnant, in labour and postpartum Nigerian women in Zaria. SVD: Spontaneous vaginal delivery; CS: caesarean section.

early postpartum period (Feldman et al., 2007). While lower OTC levels in pregnancy was found to be associated with a risk for the development of postpartum depression (PPD) (Skrundz et al., 2011). Their study findings suggest that prepartum oxytocin levels could be used to identify women at risk for PPD. The mechanisms behind the observed association between OTC and PPD symptoms remain to be elucidated. Correspondingly, animal studies report deficits in social memory, decreased vocalization and increased aggressiveness in oxytocin knockout mice, while oxytocin knockout rats exhibited deficits in maternal behavior (Winslow and Insel, 2002).

Group comparisons revealed that though maternal OTC levels rose progressively with advancing gestation; there was however no significant difference in the concentration of OTC among women in their third trimester, labour and postpartum (Figure 1, $p>0.05$). The present findings are also in agreement with the human study by Kuwabara et al. (1987). Their study revealed a lack of significant difference in OTC concentration around the onset of labour. There is however a 100 fold increase in oxytocin receptor concentrations during pregnancy. This accounts for the increased sensitivity of the myometrium during the second half of pregnancy which peaks during early labour (Fuchs et al., 1982). This effect is reversed eventually as shown by the observed decrease in oxytocin receptors in the postpartum uterus in rats (Soloff et al., 1979).

Maternal oxytocin levels at spontaneous delivery were higher than those at Caesarean section (Figure 1). This was however not significant ($p>0.05$). This is at odds with a previous report, where significantly higher maternal oxytocin concentration was observed in women that had spontaneous delivery as compared to women that had caesarean section delivery (Kuwabara et al., 1987). Our finding might be due to our subjects comprising of both elective and emergency caesarean section cases.

The findings of this study need to be confirmed in future studies by longitudinal studies assessing OTC over the course of pregnancy, labour and puerperium. Single sample per subject was assayed more than one sample per assessment giving a more accurate measure. The sample consisted predominantly of women of Hausa origin. Consequently, studies need to be replicated with a more heterogenous population of Nigerian women. Studies involving the effect of peripheral OTC on social behavior of children and adult mothers though elucidated in other populations (Caucasian and African-American samples) should be explored in a Nigerian sample. The use of women in the first week of puerperium could be extended to include further weeks postpartum.

In summary, the findings of this study suggest that serum OTC concentration progressively increase with

increasing weeks of gestation, does not significantly increase during labour and the early postpartum period and the reference ranges for maternal oxytocin levels in Nigerian females, though following the pattern in other studies had higher values. Does this suggest higher maternal-infant attachment scores in Nigerian women? Is a question to be explored in further studies.

Conflict of Interests

The authors have not declared any conflict of interests.

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