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Effect of phases of the menstrual cycle on biophysical and biochemical parameters of African black women with breast cancer

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ABSTRACT

INTRODUCTION: Many studies on female breast cancer patients do not consider the differences between the follicular and luteal phases when collecting blood samples for laboratory investigations. Therefore, this study was designed to investigate the effects of the phases of the menstrual cycle on reproductive and thyroid hormones, endocrine disruptors, blood pressure, and body adiposity.

METHODS: Participants (n=107) aged 28-50 years, comprising 54 newly diagnosed breast cancer patients (cases were menstrual phase and age-matched to 53 seemingly healthy women without breast cancer that served as controls. Anthropometric indices and blood pressure (BP) were obtained. Serum hormones-estradiol, progesterone, luteinizing hormone (LH), free triiodothyronine (FT3), thyroid-stimulating hormone (TSH), stimulating follicle hormone (FSH), and free thyroxine (FT4) were quantified by enzyme immunoassay. Endocrine disruptors (EDs)-arsenic, lead and cadmium were quantified by atomic absorption spectrophotometry (AAS). Data were analyzed using Student's t-test and Pearson correlation coefficient with $p<0.05$ considered significant.

RESULTS: Bodyweight, hip circumference, waist-height ratio, and FT3 varied between the luteal and follicular phases, higher in cases than controls. EDs were significantly higher in cases than controls in both phases. Progesterone, estradiol and LH levels were significantly higher in luteal cases and controls when compared with follicular cases and controls.FT3 was significantly lower in luteal controls compared with follicular controls. There were significant direct and inverse correlations among adiposity measures, BP, EDs, and hormones in each phase in both cases and controls.

CONCLUSION: The menstrual cycle appears to influence blood pressure, measures of adiposity, endocrine disruptors, and reproductive hormones in women with normal and cancerous breasts. This requires consideration in the collection of blood samples for investigations of these parameters.

Keywords: Luteal Phase, Follicular Phase, Luteinizing Hormone, Follicle-Stimulating Hormone, Breast Cancer

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INTRODUCTION

Breast cancer is the dominant cancer type in reproducing women [1]. Clinical and experimental studies suggest a relationship between the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-thyroid axes, particularly in breast cancer [2]. Endocrine disruption also results in disorders of the reproductive system, such as altering hormone concentration and the menstrual cycle [3]. Heavy metals: arsenic, lead, and cadmium are recognized endocrine disruptors.

Our previous studies in Black women living in Nigeria showed significant involvement of anthropometry, endocrine disruptors, reproductive and thyroid hormones, as well as their receptors in the pathogenesis of breast cancer [4,5]. Epidemiological studies suggest that menstrual cycle characteristics such as early menarcheal age, as well as late menopausal age, are capable of increasing breast cancer risk via increased exposure to hormones of the ovary [6,7]. Existing data in this regard are inconsistent, while well-controlled studies are also sparse.

The menstrual cycle is the typical variation in the feminine reproductive system regulated by the complex interaction between the hypothalamus-pituitary-ovarian axis [8]. It comprises the follicular and luteal phases. The follicular phase is characterized by low progesterone and increased estrogen levels, whereas both progesterone and estrogen levels are elevated in the luteal phase. The length of the follicular phase varies while the length of the luteal phase is moderately constant [9]. Therefore, females with shorter menstrual cycles spend less time in the follicular phase [10]. Estrogens and progestins increase breast cell proliferation in the luteal phase, thus, increasing breast cancer risk in this menstrual phase [11].

The variations in the menstrual cycle may be the basis of discrepancies in reported outcomes of breast cancer studies. Pre-analytical errors in laboratory testing are well recognized [12]. Standardization in the time of blood collections from pre-menopausal women with breast cancer may enhance breast cancer diagnosis.

Information is sparse on the influence of the menstrual cycle phases on biophysical and biochemical parameters in breast cancer. The effect of menstrual cycle phases on anthropometric indices, endocrine disruptors, reproductive and thyroid hormones in premenopausal Nigerian women with breast cancer was investigated in this study.

METHODS

Study design: The study was a case-control study. Study participants were recruited at the Surgical Oncology Clinic, University College Hospital, Ibadan, Nigeria and its environs

One hundred and seven study participants aged 28-50 years were enrolled in the study. Details of participants' enrollment were reported elsewhere [13, 14]. They comprised 54 newly diagnosed women with breast cancer who were yet to commence treatment (cases). Thirty of the cases were in the follicular phase, while twenty-four were in the luteal phase. They were age and menstrual phase-matched to 53 seemingly healthy women without breast cancer that served as controls; 30 and 23 women in the follicular and luteal phases, respectively.

Newly diagnosed women with breast cancer who had not commenced treatment and given consent, were enrolled in the present study. However, women with bilateral oophorectomy, women on hormone replacement therapy, pregnant and lactating women were excluded from the study [4].

Sampling: The sample size was calculated using the formula for the comparison of two means;

$$N = \frac{(Z\alpha + Z2\beta)^2 (\sigma 12 + \sigma 02)}{(\mu 1 - \mu 0)^2}$$

N=Sample size

μ1-μ0=difference between the means to be detected set at 113.72 and 156

σ12+σ02=Standard deviations set at 16.40 and 19.80

Zα= Standard normal deviation corresponding to the null hypothesis i.e., 1.96

Z2β=Standard normal deviate corresponding to the alternate hypothesis i.e. 1.28,

α=level of significance,

β=type II error.

Further details on sampling have been described elsewhere [13]

Determination of blood pressure was done after participants rested for a minimum of 10 minutes, according to Umohet al [15]. The measurement

was done twice and the average reading reported. Measurement of anthropometric indices, sample collection, hormonal assay, and the heavy metal determination were as previously reported [13, 14].

The major outcome was the possible influence of the variation of the menstrual cycle on the blood pressure, serum levels of sex hormones and endocrine disruptors, and anthropometric indices

Data analysis was done with Statistical Package for Social Scientists (SPSS 18.0) SPP, Inc., Richmond, CA. Comparison of variables was determined by Student's t-test, while Pearson correlation coefficient was employed to determine relationships between variables. A significant level was set at P<0.05.

Information obtained from study participants was kept confidential and was used solely for research purposes. Minimal pain was experienced by the participants at the point of blood sample collection. They were earlier informed of this before they consented to participate in the study.

Approval of the study protocol was granted by the University of Ibadan/University College Hospital Joint Ethical Review Committee (UI/EC/10/0193). Written informed consent was received from each of the study participants.

RESULTS

The comparison of blood pressure, measures of anthropometry, and biochemical indices between women with and without breast cancer

Table 1: Biochemical indices, measures of anthropometry and blood pressure in women with and without breast cancer at the follicular phase

Index	Cases (n=30)	Control (n=30)	t	P
Anthropometric indices				
Height (m)	1.62±0.01	1.57±0.01	2.906	0.005*
Bodyweight (Kg)	66.15±2.64	61.40±1.74	1.504	0.138
BMI (Kg/m^2)	25.03±0.85	24.85±0.68	0.160	0.873
Waist Circumference (cm)	89.30±1.76	77.67±1.62	4.861	0.000*
Hip Circumference (cm)	99.97±1.67	95.57±1.39	2.025	0.048*
Waist hip ratio	0.89±0.01	0.80±0.02	4.575	0.000*
Waist height ratio	55.13±1.16	49.45±1.09	3.572	0.001*
Blood pressure				
Systolic blood pressure (mmHg)	121.00±1.75	117.59±1.69	1.400	0.167
Diastolic blood pressure (mmHg)	80.67±1.26	81.67±1.36	-0.538	0.592
Biochemical Indices				
Progesterone (nmol/L)	1.67±0.14	1.34±0.11	1.912	0.061
Estradiol (pmol/L)	315.04±30.07	303.17±36.07	0.253	0.801
LH (IU/L)	5.47±0.69	4.86±0.51	0.704	0.484
FSH (IU/L)	8.11±0.92	6.86±0.52	1.175	0.245
FT_3 (pmol/L)	3.01±0.09	3.59±0.07	-5.317	0.000*
FT_4 (pmol/L)	17.48±0.72	15.09±0.31	3.024	0.004*
TSH (mIU/L)	1.94±0.25	1.60±0.15	1.152	0.254
Lead (µg/dL)	5.17±0.24	1.71±0.08	13.820	0.000*
Cadmium (µg/dL)	0.04±0.00	0.01±0.00	13.884	0.000*
Arsenic (µg/dL)	0.32±0.02	0.04±0.00	14.900	0.000*

*Values are mean±SE. P=probability value, n= number of participants. Cases= participants diagnosed with breast cancer, controls=apparently healthy women devoid of breast cancer. *=significant value at P<0.05. TSH=thyroid stimulating hormone, LH=luteinizing hormone, FT4=free thyroxine, FT3=free triiodothyronine, FSH=follicle-stimulating hormone, BMI=body mass index*

Table 2: Biochemical indices, measures of anthropometry and blood pressure in women with and without breast cancer at the luteal phase

Index	Cases (n=24)	Control (n=23)	t	P
Anthropometric indices				
Height (m)	1.63±0.02	1.56±0.01	3.196	0.003*
Body weight (Kg)	70.29±2.58	58.50±1.96	3.609	0.001*
BMI (Kg/m^2)	26.54±1.11	24.06±0.77	1.832	0.074
Waist Circumference (cm)	87.58±2.35	79.00±2.18	2.671	0.011*
Hip Circumference (cm)	101.21±2.60	96.52±1.61	1.520	0.136
Waist hip ratio	0.87±0.01	0.82±0.01	3.705	0.001*
Waist height ratio	53.83±1.61	50.63±1.48	1.457	0.152
Blood pressure				
Systolic blood pressure (mmHg)	125.42±2.33	120.87±1.77	1.545	0.129
Diastolic blood pressure (mmHg)	84.58±1.90	80.00±1.54	1.864	0.069
Biochemical Indices				
Progesterone (nmol/L)	25.53±4.72	18.51±4.18	1.109	0.273
Estradiol (pmol/L)	625.09±77.42	597.31±85.42	0.241	0.810
LH (IU/L)	10.54±1.04	6.93±0.90	2.620	0.012*
FSH (IU/L)	5.96±0.47	3.93±0.58	2.726	0.009*
FT_3 (pmol/L)	4.31±0.85	3.34±0.11	1.103	0.276
FT_4 (pmol/L)	18.28±0.89	14.63±0.64	3.305	0.002*
TSH (mIU/L)	1.51±0.21	1.31±0.15	0.771	0.445
Lead (µg/dL)	5.59±0.29	1.81±0.09	12.147	0.000*
Cadmium (µg/dL)	0.04±0.00	0.01±0.00	12.613	0.000*
Arsenic (µg/dL)	0.29±0.02	0.04±0.00	10.098	0.000*

*Values are mean±SE. P=probability value, n= number of participants. Cases= participants diagnosed with breast cancer, controls=apparently healthy women devoid of breast cancer. *=significant value at P<0.05. TSH=thyroid stimulating hormone, LH=luteinizing hormone, FT4=free thyroxine, FT3=free triiodothyronine, FSH=follicle-stimulating hormone, BMI=body mass index*

in the follicular phase are shown in table 1. Free triiodothyronine, free thyroxine, lead, cadmium, arsenic, waist circumference, waist-hip ratio, waist-height ratio, hip ratio, and height were significantly elevated in participants with breast cancer in comparison with controls (P<0.05).

As shown in table 2, lead, cadmium, arsenic, follicle-stimulating hormone, free thyroxine, luteinizing hormone, waist circumference, height, waist-hip ratio, and body weight were significantly elevated in participants with breast cancer at the luteal phase compared with women without breast cancer at the same phase (P<0.05).

The comparison of biochemical indices, blood pressure, and anthropometry measures in participants with breast cancer (cases) at the luteal and follicular phases are shown in table 3. Progesterone, estradiol, and luteinizing hormone were significantly elevated in participants with breast cancer in the luteal phase than follicular phase (P<0.05).

Table 4 shows a comparison of biochemical indices, blood pressure, and measures of anthropometry in participants without breast cancer (controls) at the luteal and follicular phases. Progesterone, estradiol, and luteinizing hormone were significantly higher, while free triiodothyronine was significantly lesser in controls in the luteal phase than controls in the follicular phase (P<0.05).

Correlation of indices; blood pressure, anthropometric and biochemical in participants

Table 3: Biochemical indices, measures of anthropometry and blood pressure in women with breast cancer at the luteal and follicular phases

Index	Follicular Cases (n=30)	Luteal Cases (n=24)	t	P
Anthropometric indices				
Height (m)	1.62±0.01	1.63±0.02	0.483	0.631
Bodyweight (Kg)	66.15±2.64	70.29±2.58	1.105	0.274
BMI (Kg/m^2)	25.03±0.85	26.55±1.11	1.109	0.273
Waist Circumference (cm)	89.30±1.76	87.58±2.35	0.596	0.554
Hip Circumference (cm)	99.97±1.67	101.21±2.60	0.417	0.678
Waist hip ratio	0.89±0.01	0.87±0.01	1.718	0.092
Waist height ratio	55.13±1.16	53.83±1.61	0.675	0.503
Blood pressure				
Systolic blood pressure (mmHg)	121.00±1.75	125.41±2.33	1.545	0.128
Diastolic blood pressure (mmHg)	80.67±1.26	84.58±1.90	1.773	0.082
Biochemical Indices				
Progesterone (nmol/L)	1.67±0.14	25.53±4.72	5.655	0.000*
Estradiol (pmol/L)	315.04±30.07	625.09±77.42	4.034	0.000*
LH (IU/L)	5.47±0.70	10.54±1.04	4.190	0.000*
FSH (IU/L)	8.11±0.92	5.96±0.47	1.926	0.060
FT_3 (pmol/L)	3.01±0.09	4.30±0.85	1.696	0.096
FT_4 (pmol/L)	17.48±0.72	18.28±0.89	0.703	0.485
TSH (mIU/L)	1.94±0.25	1.51±0.21	1.277	0.207
Lead (µg/dL)	5.17±0.24	5.60±0.29	1.151	0.255
Cadmium (µg/dL)	0.04±0.00	0.04±0.00	0.933	0.355
Arsenic (µg/dL)	0.32±0.02	0.29±0.02	0.981	0.331

*Values are mean±SE. P=probability value, n= number of participants. *=significant value at P<0.05. Follicular cases= participants with breast cancer at the follicular phase, Luteal cases= participants with breast cancer at the luteal phase. FT4=free thyroxine, LH=luteinizing hormone, FT3=free triiodothyronine, FSH=follicle-stimulating hormone, TSH=thyroid stimulating hormone, BMI=body mass index*

with and without breast cancer at the follicular and luteal phases are shown in table 5. In follicular cases, progesterone correlated with waist circumference and hip circumference. Furthermore, TSH and arsenic correlated with diastolic blood pressure (P<0.05), whereas in follicular controls, arsenic correlated with waist circumference (P<0.05). Progesterone also correlated inversely with arsenic (P<0.05).

Furthermore, free thyroxine correlated inversely with both lead and cadmium (P<0.05). Systolic blood pressure correlated with diastolic blood pressure while progesterone correlated with estradiol (P<0.05) in luteal cases, whereas LH correlated with FSH while FSH correlated with arsenic (P<0.05) in luteal controls (P<0.05).

DISCUSSION

The menstrual cycle's hormonal stimulation of breast tissues is important in breast carcinogenesis [7]. A system of reproductive hormones controls the menstrual cycle. Estrogen and progesterone are important in developing the mammary glands [16]. Serum levels of progesterone, estradiol, and LH were significantly elevated in women with breast cancer (cases) at the luteal phase in comparison with cases at the follicular phase in this study. A similar observation of significantly

higher estrogen and progesterone levels in the luteal phase than in the follicular phase was reported by Linton et al. [17]. The observation in this study is at variance with a report that found an association between follicular phase estrogen and pre-menopausal breast cancer [18]. Furthermore, serum levels of progesterone, estradiol, and LH were significantly elevated in women without breast cancer (controls) at the luteal phase when compared with controls at the follicular phase in this study. The luteal phase being the second phase of the menstrual cycle, is fixed in time relative to the follicular phase [19]. It is typified by a high level of progesterone stimulated by LH. This is with the view to preparing the corpus luteum and endometrium for implantation of a fertilized ovum. Progesterone sends a response to the anterior lobe of the pituitary gland. This aims to reduce levels of LH, FSH, and, subsequently, estradiol as the luteal phase ends [20]. It thus appears that these hormones are not affected by breast cancer. A significantly raised level of FSH was observed in controls in the follicular phase relative to controls in the luteal phase. This appears physiological. In the follicular phase, estradiol is the main hormone. Its increase is a result of the upregulation of FSH receptors within the follicle [20]. The significantly higher levels of LH and FSH in cases than controls

Table 4: Biochemical indices, measures of anthropometry and blood pressure in women without breast cancer at the luteal and follicular phases

Index	Follicular Controls (n=30)	Luteal Controls (n=23)	t	P
Anthropometric indices				
Height (m)	1.57±0.01	1.56±0.01	0.509	0.613
Body weight (Kg)	61.40±1.74	58.50±1.96	1.103	0.275
BMI (Kg/m^2)	24.85±0.68	24.06±0.77	0.775	0.442
Waist Circumference (cm)	77.67±1.62	79.00±2.18	0.502	0.618
Hip Circumference (cm)	95.57±1.39	96.52±1.61	0.451	0.654
Waist hip ratio	0.80±0.02	0.82±0.01	0.631	0.531
Waist height ratio	49.45±1.09	50.63±1.48	0.658	0.514
Blood pressure				
Systolic blood pressure (mmHg)	117.59±1.69	120.87±1.77	1.329	0.190
Diastolic blood pressure (mmHg)	81.67±1.36	80.00±1.54	0.809	0.422
Biochemical Indices				
Progesterone (nmol/L)	1.34±0.11	18.51±4.18	4.703	0.000*
Oestradiol (pmol/L)	303.17±36.07	597.31±85.42	3.451	0.000*
LH (IU/L)	4.86±0.51	6.93±0.90	2.102	0.041*
FSH (IU/L)	6.86±0.52	3.93±0.58	3.748	0.000*
FT_3 (pmol/L)	3.59±0.07	3.34±0.11	2.136	0.038*
FT_4 (pmol/L)	15.09±0.31	14.63±0.64	0.701	0.486
TSH (mIU/L)	1.60±0.15	1.31±0.15	1.356	0.181
Lead (µg/dL)	1.71±0.08	1.81±0.09	0.820	0.416
Cadmium (µg/dL)	0.01±0.00	0.01±0.00	1.262	0.213
Arsenic (µg/dL)	0.04±0.00	0.04±0.00	1.349	0.183

*Values are mean±SE. P=probability value, n= number of participants. *=significant value at P<0.05. Follicular controls= participants without breast cancer at the follicular phase, Luteal controls= participants without breast cancer at the luteal phase. TSH=thyroid stimulating hormone, LH=luteinizing hormone, FT4=free thyroxine, FSH=follicle-stimulating hormone, FT3=free triiodothyronine, BMI=body mass index*

Table 5: Correlation of biochemical indices, measures of anthropometry and blood pressure in women with and without breast cancer at the follicular and luteal phases

Follicular Phase					
Index	**Index**	**Cases (r- value)**	**Cases (P-value)**	**Control (r-value)**	**Control (P-value)**
WC	HC	0.785	0.000*	0.667	0.000*
WC	BMI	0.443	0.014*	0.670	0.000*
HC	BMI	0.435	0.016*	0.670	0.000*
SBP	DBP	0.405	0.026*	0.472	0.010*
Progesterone	WC	0.483	0.007*	-0.032	0.869
Progesterone	HC	0.504	0.004*	0.080	0.676
TSH	DBP	-0.367	0.046*	0.213	0.257
Arsenic	DBP	-0.373	0.042*	0.299	0.108
Arsenic	WC	-0.265	0.158	0.492	0.006*
Progesterone	Arsenic	-0.159	0.402	-0.411	0.024*
Oestradiol	TSH	0.440	0.015*	0.115	0.545
LH	FSH	0.573	0.001*	0.191	0.312
FT_4	Lead	0.099	0.602	-0.415	0.023*
FT_4	Cadmium	0.083	0.662	-0.429	0.018*
Luteal Phase					
WC	HC	0.914	0.000*	0.947	0.000*
WC	BMI	0.586	0.003*	0.489	0.018*
HC	BMI	0.620	0.001*	0.530	0.009*
SBP	DBP	0.533	0.007*	-0.218	0.318
Progesterone	Oestradiol	0.581	0.003*	0.355	0.096
LH	FSH	-0.389	0.060	0.435	0.038*
FSH	Arsenic	0.103	0.633	0.615	0.002*

*Cases= participants diagnosed with breast cancer, controls=apparently healthy women short of breast cancer, *=significant value at P<0.05, FT4=free thyroxine, LH=luteinizing hormone, TSH=thyroid stimulating hormone, WC= waist circumference, BMI=body mass index, HC=hip circumference, DBP=diastolic blood pressure, and SBP=systolic blood pressure.*

at the luteal phase support our earlier report that implicated gonadotropins in pre-menopausal breast cancer [13]. This could be via alteration of certain genes upon the stimulation of their receptors [21].

The import of thyroid hormones in breast cancer pathogenesis is not clearly defined [22]. The level of FT4 was significantly raised in cases at both follicular and luteal phases compared with their respective controls in this study. This is in tandem with reports that found an association between thyroxine and breast cancer [23, 24]. Conversely, a significantly lower level of FT3 was observed in follicular cases relative to follicular controls in the present study. This observation is similar to reports suggesting a link between low triiodothyronine levels and breast cancer [25, 26]. Activation of estrogen receptors by thyroid hormones as well as the synergistic relationship of estrogen with thyroid hormones in cell proliferation, are plausible mechanisms of thyroid hormones' involvement in breast carcinogenesis [27]. Moreover, the significantly higher FT4 and lower FT3 observed in the follicular cases compared with controls in the present study suggests possible conversion of FT3 to reverse T3 (RT3), which is biologically inactive and present in illnesses [28].

Elevated FT3 level in controls at the follicular phase compared to controls at the luteal phase in this current study suggests the involvement of thyroid hormones in the menstrual cycle. Jacobson et al. reported an association between thyroid hormone levels within normal reference intervals and menstrual cycle outcomes in healthy

premenopausal women [29]. The significantly higher FT3 and FSH in controls in the follicular phase than controls in the luteal phase further suggest the relationship between thyroid hormones and gonadotropins. The occurrence of thyroid hormone receptors on the epithelium of the ovary and the regulation of embryo development, tissue differentiation, and maturation by thyroid hormones are reported mechanisms of this relationship [30, 31]. Therefore, elevated FSH and FT3 in controls in the follicular phase compared with controls in the luteal phase in the current study could be synergistic. This suggests they could be menstrual phase-dependent.

The relationship between environmental levels of heavy metals and the length of the menstrual cycle has been reported [32, 33]. In this study, a comparison of lead, cadmium, and arsenic cases in both luteal and follicular phases showed no significant difference. A similar observation was made between controls in both phases. However, the levels of these heavy metals were considerably higher in the cases in both phases relative to their respective controls. This observation suggests that although heavy metals' role in breast carcinogenesis is not in doubt, as we earlier reported [4], it appears that the menstrual cycle does not affect their serum levels.

Observation in this study, as evidenced by the significantly higher values of some anthropometric indices in cases than controls in both follicular and luteal phases, shows the importance of obesity in breast cancer pathogenesis. This is in tandem with reports linking obesity with increased breast cancer risk [34,35]. The comparison of anthropometric indices between cases in the follicular and luteal phases has shown no difference. A similar observation was made when controls in both phases were compared. This suggests that the menstrual phase may have minimal effect on adiposity. In addition, there was no variation in blood pressure across the different study groups, particularly during the menstrual phases in this study. Arifuddin et al. reported a similar observation [36]. This observation could be due to the ability of homeostatic mechanisms of the cardiovascular system to correct subtle changes in blood pressure attributed to ovarian hormones [36].

The significant positive correlations among the following: BMI and HC, BMI and WC and HC and WC in cases as well as controls in both follicular and luteal phases in this study suggest the relationship between general and central obesity, which have implications for breast carcinogenesis irrespective of menstrual cycle phase. The positive correlation between SBP and DBP in cases and controls in the follicular phase and cases the luteal phase in this study suggests the minimal influence of the menstrual cycle on blood pressure. Furthermore, the positive correlations between LH and FSH in cases in the follicular phase and controls in the luteal phase and the positive correlation between estradiol and progesterone in cases in the luteal phase may relate to physiological events in the respective menstrual cycle phases.

Thyroid-stimulating hormone is a sensitive indicator that shows changes in thyroid function [37]. Diastolic blood pressure was inversely related to TSH in cases in the follicular phase in this study. This observation contradicts reports of a positive association between thyroid hormones and blood pressure [38]. The association of arsenic with blood pressure is controversial [39]. In this current study, a converse association between arsenic and DBP was observed in cases at the follicular phase. A similar inverse relationship between urinary arsenic concentration and blood pressure was reported by Ameer et al. [40]. The subtle relationship of arsenic with DBP might have been due to breast cancer but necessitate further studies

Heavy metals' interference with the endocrine system has been reported [33,41]. FT4 correlated inversely with lead and cadmium in controls in the follicular phase in this study. Pollack et al. reported an alteration in reproductive hormone levels in premenopausal women exposed to environmental levels of heavy metals, including lead and cadmium [41]. This suggests the endocrine-disrupting abilities of these heavy metals. The adverse consequences of arsenic on reproductive hormones have been reported [42,43]. Progesterone inversely correlated with arsenic in controls in the follicular phase, while arsenic correlated positively with FSH in controls in the luteal phase in this study. This implies that the disruptive endocrine of arsenic could either increase or decrease hormones' levels. This requires further studies. The relationship between arsenic and BMI, an index of general obesity, was reported by Castriota et al. [44]. This suggests that arsenic may be important in obesity and obesity-related pathologic conditions.

CONCLUSION

The observations in this study suggest that blood pressure, adiposity, and levels of endocrine disruptors, especially arsenic and reproductive hormones i.e., progesterone, LH and estradiol, may be affected by variations in the menstrual cycles. This may be considered during anthropometric measurements and collection of blood samples in breast cancer investigations and studies.

This study presents some limitations. The small sample size and the non-monitoring of each participant through the menstrual phases/ phases of the menstrual cycle might have limited observations in the study.

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