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Assessment of Changes in Sex Hormones, Cortisol and White Blood Cells during Menstrual Cycle in Female Asthmatic Students at NAU, Nnewi, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author RUN designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors RUN, NUS and NMI managed the literature searches and analyses of the study performed the spectroscopy analysis and managed the experimental process. Authors COC and EAJ did the statistical analysis and proof read the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms due to triggers to which the patients are sensitive. Due to the hormonal variations in monthly cycles, women are at risk of increased asthma exacerbations which require close monitoring of those patients to ensure better control and management of the condition.

Aims of Study: This study was designed to assess the changes in sex hormones (progesterone and estradiol), cortisol and white blood cells in asthma female students in Nnamdi Azikiwe University, Nnewi Campus Nigeria.

Materials and Methods: A total of 120 female students with regular menstrual cycle, within the age bracket of 18-35 were randomly recruited for the study. 60 female participants were students who have been diagnosed of asthma exacerbations and use synthetic therapy (Inhaled corticosteroid therapy), while the remaining 60 female participants were apparently healthy control females students. The eligible female students were classified based on menstrual phases as: (i) Follicular asthma females (n=60), (ii) Luteal asthma females (n=60), (iii) Follicular control females (n=60) and (iv) Luteal control females (n=60). Blood samples were collected consecutively from each of the participant at the mid-follicular (4^{th}-13^{th}) and mid-luteal (14-23^{rd}) phases of their menstrual cycle for determination of progesterone, estradiol and cortisol, using ELISA kit method and white blood cell indices using Sysmex K21N Hematology analyzer.

Results: 40 (66.7%) of the Asthma students reported increased exacerbations with reduced activities at mid-luteal phase of their menstrual cycle while 20 (33.3%) reported increased exacerbations with reduced activities at mid-follicular phase of menstrual cycle. The mean serum progesterone, and cortisol in asthma female subjects at follicular phase were significantly lower compared with the values at luteal phase of menstrual cycle (*P=.05*). Progesterone level was lower in asthma females compared with control females at luteal phase of menstrual cycle (*P=0.05*). Estradiol level was significantly higher at follicular phase compared with the value at luteal phase of menstrual cycle in asthmatic females (*P=0.05*). Estradiol level was significantly lower in asthma females compared with control females at both phases of menstrual cycle (*P=0.05* respectively). The percentage neutrophils was significantly lower in asthma female subjects when compared with the value in control female subjects at both follicular and luteal phases of menstrual cycle (*P=.05* respectively).

Conclusion: The changes noted in this study vary according to the phases of the menstrual cycle which may be indicative of a link between respiratory symptoms and hormonal changes through the menstrual cycle. This may be attributed to inhibitory effects of the synthetic glucocorticoids on hypothalamo-pituitary-adrenal axis and on the proliferation, growth and migration of white blood cells in asthma female students.

Keywords: Asthma; menstrual cycle; synthetic therapy; steroid hormones.

1. INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm [1]. The syndrome is characterized by wheezing, chest tightness, dyspnea, and/or cough, and results from widespread contraction of tracheobronchial smooth muscle (bronchoconstriction), hypersecretion of mucus, and mucosal edema, all of which narrow the caliber of the airways [1-3]. Asthmatics usually experience exacerbation of symptoms, which may be mild, intermediate or severe and normally occur when they are exposed to triggers, such as dust, emotional stress, irritant chemicals, dust, and smoke. Also Inflammation of the airways increases, further narrowing the airways and with the production of more mucus, the flow of air is undermined as well [2,3]. Inflammation involves various cells and mediators, including eosinophils, mast cells, T-lymphocytes, neutrophils and cytokines [3]. Thus, chronic inflammatory state of the airways is considered the hallmark of asthma [4].

Asthma affects about 235 million people worldwide [5]. The incidence of asthma has been growing over the past 30 years due to changing environmental factors, particularly in the low- and middle-income countries that are predominantly affected. Asthma causes an estimated 250,000

deaths annually (1 in 250 deaths worldwide) [5,6]. The World Health Organization estimates that around 15 million disability-adjusted life years (DALYs) are lost annually through this disease [6]. Fifty years ago asthma was uncommon in Nigeria, however recent reports from different parts of Nigeria have shown a prevalence of adolescent and adult asthma in excess of 10% and a rising trend in the prevalence of asthma [5-9].

The incidence, severity, and prognosis of asthma can be affected by a number of factors, including the patient's sex and age. Adult onset of asthma has been reported to be more severe than childhood-onset asthma [10,11].

Asthma is associated with the proliferation in blood of chronic inflammatory cells such as eosinophils, neutrophils and mast cells and may also be mediated by inflammatory cytokines hence corticosteroids have been generally accepted as ideal anti-inflammatory agents used in the control/treatment of asthmatic patients. The delivery of topically active corticosteroids directly to the airways by inhalation has revolutionized the anti-inflammatory treatment of asthma [12]. The use of corticosteroids in the treatment of asthma in females may significantly affect the hormonal profile in these females during menstruation and also alter the composition of inflammatory cells in affected females. The present study was therefore designed to evaluate these changes and their clinical implication.

2. MATERIALS AND METHODS

2.1 Study Area

The study was conducted at college of Health Sciences, Nnamdi Azikiwe University (NAU), Nnewi Campus, Nigeria. This case-control study was carried out in asthma female students and apparently healthy students of college of Health Sciences, Nnamdi Azikiwe University, Nnewi.

2.2 Study Population and Design

A total of 120 female participants within the age group of 18-35 years were randomly recruited for the study. 60 out of the 120 female participants were asthma females who have been on synthetic therapy (glucocorticoids-beclomethasone and fluticasone) while the remaining 60 participants were apparently healthy control female students. They were grouped based on phases of the menstrual cycle as (i) follicular asthma females (n=60), (ii) luteal asthma females (n=60), (iii) follicular control females (n=60) and (iv) luteal control females (n=60)

A well structured questionnaire was used to obtain the details concerning asthma symptoms, history of their menstrual cycle and exacerbations during the two phases of the menstrual cycle and the types of drugs used.

2.3 Sample Collection and Analysis

From each subject, 5ml of blood collected consecutively at mid-follicular (7^{th} to 13^{th} day) and luteal (14^{th} to 23^{rd} day) phases of menstrual cycle respectively. 3 ml was dispensed into a plain container, allowed to clot, centrifuged, separated and stored frozen at -20 until assayed for sex hormones (estradiol and progesterone) and cortisol. The remaining 2 ml was dispensed into EDTA container for differential white cell count (neutrophils, eosinophils and lymphocytes).

2.4 Exclusion and Inclusion Criteria

Pregnant women, postmenopausal, females with history of contraceptives and females with greater than 28 days menstrual cycle or incomplete reproductive history were excluded. Also Asthma female students with malaria parasite infection were excluded from the study.

2.5 Methods

Determination of Estradiol, Progesterone and Cortisol were done using Enzyme Linked Immunoassay kits (Glory Science Laboratory USA).

Determination of white blood cells (neutrophil, eosinophils and Lymphocytes percent) were done using Sysmex K21N Hematology analyzer and the results recorded directly from the instrument.

2.6 Statistical Analysis

Continuous variables and categorical data were analyzed using independent sample *t*-tests and analysis of Variance using version 17 of SPSS package. The variables were expressed as mean (±SD) and post-hoc (LSD) were used to assess significant mean differences. All *P*-values were two-tailed, and a *P*-value *=.05* was considered statistically significant.

3. RESULTS

3.1 Determination of Progesterone pg/ml, Estradiol (pg/ml), Cortisol (µg/ml) in Asthmatic and Control Females at Follicular and Luteal Phases of Menstrual Cycle

The mean ± SD serum progesterone and cortisol levels in asthmatic females were significantly lower at follicular (1.56±0.75, 19.02±12.56) compared with luteal (5.02±3.89, 27.02±15.97) phase of menstrual cycle (*P=.05*). The mean serum estradiol in asthmatic females was significantly higher at follicular (44.05±23.02) compared with luteal (28.11±11.63) phase of menstrual cycle (*P=.05*). The mean ± SD serum progesterone in control females was significantly lower at follicular (1.94±1.34) compared with luteal (8.11±2.33) phase of menstrual cycle (*P=.05*). The mean serum estradiol concentration in control females was significantly higher at follicular (65.28±20.13) phase compared with luteal (38.37±15.55) phase of menstrual cycle (*P=.05*).

However, there was no significant difference in the mean cortisol level in control females between follicular (25.44±8.72) and luteal (25.63±8.25) phases of menstrual cycle (*P>.05*). Similarly, the mean progesterone level was not significantly different at follicular (1.56±0.75) phase in asthmatic females when compared with follicular (1.94±1.34) phase of menstrual cycle in control females subjects (*P>.05*). Progesterone level was significantly lower in asthmatic females at luteal (5.02±3.89) compared with luteal (8.11±2.63) phase in control female subjects (*P=.05*). Similarly, the mean estradiol level was significantly lower in asthmatic females (28.11±11.63, 44.05±23.02) when compared control females (65.28±20.13, 38.37±15.55) at both phases of menstrual cycle (*P=.05* respectively).

3.2 Determination of Blood Concentration of Neutrophil (%), Eosinophil (%) and Lymphocyte (%) in Asthmatic and Control Females at Follicular and Luteal Phases of Menstrual Cycle

The result showed that the mean ± SD blood concentration of neutrophils was significantly lower in asthmatic females (40.90±4.78, 42.25±3.44) compared with control female subjects (44.05±5.03, 45.45±4.65) at both follicular and luteal phases of menstrual cycle (*P=.05* respectively). Contrastingly, the mean blood concentration of eosinophils and lymphocytes were not significantly different between asthmatic females (1.05±0.19, 56.15±6.20) and control female subjects (1.20±1.15, 54.05±4.87) at follicular phase of menstrual cycle, (*P>.05*).

Similarly, the mean blood concentration of eosinophils and lymphocytes were not significantly different between asthmatic females (0.88±0.68, 55.50±3.96) and control female subjects (1.20±1.15, 52.80±5.39) at luteal phase of menstrual cycle, (*P>.05* respectively).

There was no significant difference in the mean ± SD blood concentration of neutrophils, eosinophils and lymphocytes in asthmatic female subjects at follicular phase (40.90±4.78, 1.05±0.19, 56.15±6.20) compared with the value (42.25±3.44, 0.88±0.68, 55.50±3.96) at luteal phase of menstrual cycle (*P>.05* respectively).

The mean blood concentration of neutrophils, eosinophils and lymphocytes were not significantly different in control female subjects between follicular (44.05±5.03, 1.20±1.15, 54.05±4.78) and luteal (45.45±4.65, 1.10±0.96, 52.80±5.39) phases of menstrual cycle (*P>.05* respectively) (See Table 2).

4. DISCUSSION

Asthma is a very common disease in our community and there are trends in asthma prevalence and severity, which seem to coincide with key transition points in a woman's reproductive life. The present study revealed that most of the female asthmatic patients had more symptom flare ups during the mid- luteal phase when compared to the mid follicular phase. This finding is consistent with previous reports which have shown that there is a correlation between hormones and asthma symptom flare-ups [13,14]. Asthmatic flare-ups have been linked to high responsiveness of the airways which are triggered when victims are exposed to different substances such as smokes, dust, irritant odours, anxiety, stress and indoor allergens as was reported by some researchers [15-18]. Ferenc [19] also documented a similar report. Studies have shown that certain disease conditions such as multiple sclerosis, asthma or systemic lupus erythematosis (SLE), may have exacerbations during specific periods of the menstrual cycle [20-22]. It has been reported that asthma exacerbations at different phases of menstrual cycle may be more severe and fatal [23,24,14].

Table 1. Mean (±SD) serum estradiol, progesterone and cortisol in asthmatic females and control females at follicular and luteal phases of menstrual cycle

Parameters	Progesterone (pg/ml)		P-value	Estradiol (pg/dl)		P-value	Cortisol (µ/dl)		P-value
groups	Follicular	Luteal		Follicular	Luteal		Follicular	Luteal	
Asthma females (n=60)	1.56±0.75	5.02±3.89	0.000	44.05±23.02	28.11±11.63	0.039	19.02±12.56	27.02±15.97	0.046
Control females (n=60)	1.94±1.34	8.11±2.63	0.000	65.28±20.13	38.37±15.55	0.033	25.44±8.72	25.63±8.25	0.944
F-value	0.666	-0.866		-0.961	-1.282		0.450	2.678	
P-value	0.509	0.039		0.002	0.028		0.655	0.320	

Table 2. Mean (±SD) blood concentration of neutrophils, lymphocytes and eosinophils in asthmatic females and control females at follicular and luteal phases of menstrual cycle

Parameters	Neutrophil (%)		P-value	Lymphocyte (%)		P-value	Eosinophil (%)		P-value
groups	Follicular	Luteal		Follicular	Luteal		Follicular	Luteal	
Asthma females (n=60)	40.90±4.78	42.25±3.44	0.313	56.15±6.20	55.50±3.96	0.695	1.05±0.19	0.88±0.68	0.183
Control females (n=60)	44.05±5.03	45.45±4.65	0.368	54.05±4.78	52.80±5.39	0.447	1.20±1.15	1.10±0.96	0.768
F-value	2.028	2.464		1.190	-1.803		-0.405	1.707	
P-value	0.050	0.018		0.241	0.079		0.688	0.096	

The study showed that the mean serum level of progesterone was significantly lower while estradiol was significantly higher in asthmatic subjects at follicular phase compared to luteal phase. This may be due to the circadian rhythmical variations in the secretion of progesterone and estradiol at different phases of the menstrual cycle as reported by Guyton and Hall, [25]. The increases in progesterone and estradiol in healthy control females is said to have effect on glucocorticoid treatments on asthma subjects [26-28]. This is probably due to the role of sex hormones on bronchial smooth muscle and β_2-adrenergic receptor function. Progesterone has been shown to potentiate the relaxation effect of β_2-agonists on bronchial smooth muscle *in vitro*. Also, female sex hormones have effects on several cells and cytokines involved in inflammation. For instance, the peripheral blood total white blood cell counts are increased, and there is a marked deviation of the T_{H1}/T_{H2} balance toward T_{H2}.

The significant decrease in the sex hormones (progesterone and estradiol) in Asthma female participants compared with control female counterparts at both phases of menstrual cycle may also be attributed to the inhibitory effects of synthetic glucocorticoids on reproductive function. These have been reported previously, suggesting that glucocorticoids act to prevent binding of sex hormones with their specific receptors at target tissues [29]. It has also been reported that glucocorticoids therapies inhibit uterine and thymus growth. These effects are mediated by decreasing cytoplasmic and nuclear receptors which have specialized affinity to estrogen hormone. Moreover, these changes are unrelated with receptors specialized with progesterone hormone [30]. Previous experimental study which involved injection of glucocorticoids led to inhibition of reproductive axis through decrease of follicle stimulating hormone (FSH) and luteal hormone (LH) and gonadotrophic releasing hormone (GnRH). These effects are mediated by blocking of estradiol receptors at target tissues or by inhibition of HPA [31].

The insignificant difference in the mean serum cortisol level observed between asthmatic females and control counterparts at both phases of menstrual cycle showed that there was no impact of asthma on adrenal glands. This may be due to conventional doses of glucocorticoids consumed by these patients during the course of treatment showing some benefits of these steroids to reduce stress in these patients. This finding is consistent with the study done by Breborowicz and Niedziela [32]. The authors stated that the use of fluticasone or the equivalent of budesonide as long-term treatment of children with severe asthma did not substantially affect their adrenal function. Similarly, in a study conducted by Kapoor and colleagues [33], it was shown that the hypothalamo-pituitary-adrenal axis functions normally in asthmatics with acute exacerbation and increase in cortisol levels corresponds to the degree of stress relating to asthma severity.

The present study showed that the mean blood concentration of neutrophils (%) was significantly reduced in asthmatic individuals at both phases of menstrual cycle compared with the control subjects. This finding contradicts previous reports [34-36]. The significant reduction in neutrophils observed in the present study may therefore be attributed to the anti-inflammatory/inhibitory effects of the synthetic glucocorticoid therapy used by these subjects. Other authors also corroborate this finding [37]. The inhibitory mechanisms originate from several interactions among signal transduction or among membrane receptors and of transcription of ribonucleic acid (RNA).

The insignificant difference of mean blood concentrations of eosinophils and lymphocytes between asthmatic females and control counterparts at both phases of menstrual cycle may be due to influx of the eosinophils and lymphocytes to the airways or reduced exacerbation of asthma symptoms as a result of response to inhaled corticosteroids [38]. However, studies have shown that there is incidence of eosinophilia in airway lavages and induced sputum samples [39,40]. Contrastingly, many previous studies using glucocorticoids showed significant increase of total white blood cells and the authors associated the changes with inhibition of leukocytes attraction and retention of lymphocytes within lymphatics [41].

5. CONCLUSION

In conclusion, the present study showed that changes observed in some of the studied parameter may be attributed to the action of glucocorticoids administered to these female students exerting some inhibitory effects on the hypothalamo-pituitary-adrenal axis and on the proliferation and migration of leukocytes in the

asthmatic subjects. Adjusting asthma medication according to a woman's menstrual cycle might therefore greatly improve its efficacy and help reduce exacerbations and the costs of care. Further longitudinal study on relationship of sex hormones, menstrual cycle and asthma therapies is recommended on women particularly during different phases of menstrual cycle for better management.

CONSENT

All author(s) hereby declare that written informed consent was obtained from all the students who participated in this study.

ETHICAL APPROVAL

All author(s) hereby declare that all experiment and procedure have been examined and approved by the appropriate board of ethics committee of College of Health Sciences, Nnamdi Azikiwe University Nnewi, Nigeria, and research have therefore been performed in accordance with the standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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