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Original Article

Cortisol plays central role in biochemical changes during pregnancy

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ABSTRACT

Background: Pregnancy is known to alter the feedback effect of cortisol on ACTH secretion and reduce the effectiveness of cortisol in inhibiting ACTH response to hypertension. The mechanism and physiological significance of these changes in maternal plasma cortisol level is not fully understood. This study is the first attempt to investigate the levels of serum cortisol during three stages of pregnancy and its associated physiological significance in Nigeria women. **Aim:** Serum cortisol in the three stages of pregnancy was measured and correlated with reproductive hormones and electrolyte levels. **Methods:** 200 volunteers consisted of 50 women in each of the three trimesters and 50 non-pregnant apparently healthy controls were recruited. Demographic data were obtained by questionnaire. Serum cortisol, progesterone and prolactin levels were measured by ELISA, chloride and bicarbonate by titration methods, Na^+ and K^+ by flame photometry and other analytes by conventional colorimetric methods. **Results:** While glucose and protein levels were significantly decreased, the total cholesterol concentrations increased progressively in pregnancy. Serum cortisol increased significantly in the first trimester reached a peak in the second and declined in the third trimester. Progesterone and prolactin levels were significantly higher in pregnancy in all stages of pregnancy. Serum cortisol correlates positively with chloride and potassium inversely with bicarbonate. **Conclusion:** Cortisol plays a central role in biochemical changes that occurs in pregnancy. It increase is an indicator of emotional stress and physiological challenges in pregnancy and also, possible risk signal. The concurrent increases in progesterone and prolactin levels are compensating mechanisms. It may therefore be of clinical relevance to monitor serum cortisol levels and some of the associated variables, especially in women experiencing threatened pregnancy.

Keywords: Cortisol, pregnancy, progesterone, prolactin, electrolytes

INTRODUCTION

Pregnancy is a period marked by profound changes in a woman's hormonal status and metabolism.[1] It is also a condition of chronic volume overload in which hypervolemia is the result of active sodium and water retention primarily induced by the activation of the rennin-angiotensin system.[2] The ability to regulate nutrient balance during this period is critical to the health of the mother and the growing foetus.[3]

It is known that normal human pregnancy lasts for about 40 weeks as measured from

the day of the last menstrual cycle (LMP).[4] Pregnancy is usually divided into three intervals called trimesters with each one beginning a little longer than 13 weeks.[5] The first trimester ends at the beginning of the 13th week, which is the three completed months of pregnancy. The second trimester usually ends at the end of the 27th week. The third trimester can end anywhere between the 38th and 42nd week.[5]

Santiago *et al*.[6] reported secretion of large amount of estrogen, progesterone, prolactin and corticosteroids during pregnancy which is believed to affect various metabolic, physiologic and endocrine systems. Several of these hormones exhibit 24 hour rhythms, some of which have been observed during pregnancy. Changes in rhythm, distribution and serum levels of some of these hormones, particularly cortisol have been described in pregnancy.[6] Most factors that increase cortisol binding protein (CBG) will decrease free cortisol levels, pregnancy being an exception due to displacement of cortisol by a large quantity of progesterone.[6] Pregnancy alters the feedback effect of cortisol on ACTH secretion and may decrease the effectiveness of cortisol to inhibit an ACTH response to hypertension.[7] However, the mechanism and the physiological significance of this chronic increase in maternal plasma cortisol level is not fully understood. Progesterone also circulates in blood and is bound to binding globulin (CBG). About 90-98% of the circulating hormone is bound while the remaining portion, the free progesterone, is assumed to be the active steroid.[8] In pregnancy, placental progesterone induction rises rapidly to the levels of 10 to 20 times those of the luteal phase peak.[9] To a certain extent the increase in plasma cortisol levels reported may be due to increased plasma aldosterone and deoxycorticosterone concentrations.[10,11]

Fluid and electrolyte changes also constitute one of the most fundamental changes in normal pregnancy. Fluid retention accounts for between 9 and 10 kg of the average maternal weight gain.[12] It has been shown that electrolyte concentration may increase in the third day after conception accompanied by a rise in renal ionic excretion. It has also been shown that a net retention of sodium, chloride and potassium does not occur until the final week of pregnancy when the urinary output of these ions is reduced.[13,14] Atherton *et al.*,[14] also reported that sodium and total osmolality were reduced during the last week of pregnancy despite salt retention, suggesting increased foetal usage. In our review of literature, the possible influence of cortisol in fluid and electrolyte changes in pregnancy has not been investigated in Nigeria population.

Cholesterol concentrations have been found to be elevated in a wide range of stressful situations including pregnancy.[15] These authors reported serum cholesterol levels to be higher in pregnancy than in controls. Also, pregnancy has been reported to reduce protein and albumin levels and that such decreases probably result from the increased protein demand by the growing child.[4] Koski *et al* [16] reported that an increase in glucose levels during pregnancy promotes optimal growth, development of the foetus and prevent excessive maternal weight gain, a common phenomenon observed in gestational diabetes. High protein diet has been associated with an increased cortisol levels.[17] Also, high foetal exposure to cortisol may lead to elevated blood pressure and therefore have a negative effect on pregnancy.[11]

This study is the first to describe the postulated important role that cortisol is believed to play in pregnancy and its associated effects on other biochemical parameters in Nigeria pregnant women. The study was designed to investigate the levels of serum cortisol during the three stages of pregnancy and to relate changes observed with other reproductive hormones and biochemical parameters among Nigerian pregnant women compared to control group.

METHODOLOGY

Study Population

A total of 200 voluntary individuals participated in the study. Of these, 150 were pregnant women attending the antenatal clinic of Our Ladies of Apostle, Oluyoro Catholic Hospital, Ibadan, Nigeria. The 150 pregnant women consist of 50 women in each of the three stages of pregnancy while 50 others were age matched non-pregnant, non-lactating women who are staff and students at

the hospital and served as a control group. A longitudinal study of the same group of women before and during pregnancy, at regular intervals though desire, was difficult to implement in our study setting. Compare three carefully selected groups of women in different stages of pregnancy with a group of non-pregnant woman of similar socioeconomically and ethnical background was the best alternative. The selected volunteers consist of apparently healthy patient with no history of chronic communicable or non-communicable diseases. Also, anemic subjects, hepatitis and HIV positive patients were excluded from the study. All subjects were required to give their informed consent. Ethical approval was granted by the ethical committee of the Oyo State Ministry of Health, Nigeria.

Data and sample collection

Demographic data were obtained by using a semi-structured questionnaire. Ten milliliters of 9.00am fasting blood sample was drawn from the ante cubital vein of each consented patients. Five milliliters of the blood was placed in lithium heparin tubes for the estimation of electrolytes, urea and creatinine while 2 mls was placed in a fluoride oxalate tubes for blood glucose estimation and 2 mls into sodium EDTA tubes for the measurement of packed cell volume (PCV) and lipids. The remaining 1 ml was used for the screening of hepatitis B virus (HBV) and Human Immunodeficiency Virus (HIV-I & II) using ELIZA (Human diagnostic Laboratory, Wiesbaden, Germany).

Measurement of serum hormones

Serum cortisol, progesterone and prolactin levels were estimated by using a commercially prepared Eliza Kit (Human Diagnostic Laboratory, Wiesbaden, Germany).

Evaluation of serum electrolytes

Potassium and sodium were estimated as described by Mencaly *et al* [18] using cunning flame photometer. Serum bicarbonate was estimated by titrimetric method as described by Mencaly *et al.*[18] Serum chloride was estimated by colourimetric method as described elsewhere by Visweswariah *et al.*[19]

Measurement of other biochemical parameters

Serum urea was estimated by colorimetric enzymatic method described by Tussky *et al.*[20] Serum creatinine was estimated by the Jaffe's reaction using a commercially prepared kit (Randox Laboratory Limited, Antrim, United Kingdom). Serum protein was estimated by colourimetry method based on biuret reaction, using a commercially prepared kit (Randox Laboratory Limited Antrim, United Kingdom). Plasma glucose was estimated by glucose oxidase enzymatic method using a commercially prepared kit (Randox Laboratory Limited, Antrim, United Kingdom). Serum cholesterol was estimated using the Liebermann- Burchardt technique as described by Allain *et al.*[21]

Statistical analysis

The Statistical Package of Science and Social Sciences Version 15.0 (SPSS Inc.; Chicago, IL 60606-6412, United States) software was used in all statistical analyses. All values in this study were expressed as mean $\pm$ standard error of mean (SEM). Statistical differences among the three groups were analysed by one-way ANOVA then by LSD test. Student t-test was used to determine the statistical differences between two variables. Pearson's correlation was used to determine the relationship between the parameters.

RESULTS

Demographic characteristic of the study population

The vital signs and the demographic data of pregnant women and control group (non-pregnant) are presented in Table I. There were no significant differences in the age and height of all the study groups. However, the weights of the pregnant women were significantly higher than that of the control (59.36 $\pm$ 1.20) ($P < 0.05$). This difference was more pronounced in the third trimester (72.84 $\pm$ 2.07) when compared to the second (68.92 $\pm$ 2.52) and the first trimester (65.96 $\pm$ 1.75). The body mass index (BMI) of the control group was significantly lower than pregnant women in the first trimester (26.93 $\pm$ 0.61, $P < 0.05$), the second trimester (26.42 + 0.90, $P < 0.05$) and the third trimester (30.07 + 0.89, $P < 0.05$). While there was no significant difference in the systolic blood pressure of the pregnant women and control, the diastolic

blood pressure was significantly higher in the first trimester (109.76 ± 0.91) when compared to the control (104 ± 1.0, $P < 0.05$). This significant difference was not observed in the second and third trimester. We observed negative correlation between systolic blood pressure and cortisol level. No such correlation was observed with other parameters. Furthermore, we observed positive correlation between BMI and progesterone (Table I).

Table I: Demographic characteristics and blood pressure of pregnant and control groups

Parameters	Control	1st Trimester	2nd Trimester	3rd Trimester	F-value	*P*-value
Age (Years)	27..36±0.53	28.56 ± 0.73	29..36 ± 0.83	28..96±0.66	1.53	P>0.05
Weight (kg)	59..36±1.20	65..96 ± 1.75*	68..92 ± 2.52*	72.84±2.07*	8.56	P<0.05
Height (m)	1.52±6.20E-02	1.56±1.51E-02	1.55±7.46E-02	1.56±1.21E-02	2.43	P>0.05
BMI kg/m^2	25..55±0.50	26..93 ± 0.61*	28.42±0.90*	30.07±0.89*	6.92	P<0.05
Systolic blood presure (mmHg)	66.80±1.11	61.80 ± 1..38	62.00±1.11	65.00±1.58	0.20	P>0.05
Diastolic blood presure (mmHg)	104.00±1.00	109.76 ± 0.91*	106.80 ± 1.25	105.20±1.92	2.49	P<0.05

Values express as mean± SEM. Significant differences among the three groups were analysed by ANOVA and LSD test, superscripts (*) depict significant differences between cases and controls, analyzed by Student t- test at $P<0.05$

Table 2: Comparison of hormonal levels in pregnant and control groups

Parameters	Control	1st Trimester	2nd Trimester	3rd Trimester	F-value	*P*-value
Cortisol ng/ml	93.84±9.24	393.48±18.95*	607.80±46.10*	228.64±21.52*	64.71	P<0.05
Prolactin ng/ml	4.30±0.14	4.29±0.49	11..94±1.50*	12.43±1.63*	16.10	P<0.05
Progesterone ng/ml	10.76±1.40	44..93±4.38*	69.09±1.19*	76.73±3.00*	111.39	P<0.05

Values express as mean± SEM. Significant differences among the three groups were analysed by ANOVA and LSD test, superscripts (*) depict significant differences between cases and controls, analyzed by Student t- test at $P<0.05$

Table 3: Comparison of electrolytes, urea and creatinine levels in pregnant and control groups

Parameters	Control	1st Trimester	2nd Trimester	3rd Trimester	F-value	*P*-value
Sodium mmol/L	141.94±0.83	143.40 ± 1.27	144.56 ± 0.79	142.28±1.17	1.30	P>0.05
Potassium mmol/L	3.34±9.36E.02	2.93 ± 98E.02*	2.97± 297E.02*	3.24±0.10*	7.21	P<0.05
Chloride mmol/L	104.28±0.90	106.80±1.12*	108.20±0.78*	104.52±0.95	3.91	P<0.05
HCO_3 mmol/L	25.02±0.38	23..94 ± 0.30*	23..94±0.24*	24.80±0.29*	3.46	P<0.05
Urea mg/dl	12..92±1.00	14..96±1.26	13..52±1.19	12.44±0.92	0.98	P>0.05
Creatinine mg/dl	0.54±1.92E-02	0.56±2.0E-0.2	0.520±2.20E-2	0.50±2.20E-02	1.78	P>0.05

Values express as mean± SEM. Significant differences among the three groups were analysed by ANOVA and LSD test, superscripts (*) depict significant differences between cases and controls, analyzed by Student t- test at $P<0.05$

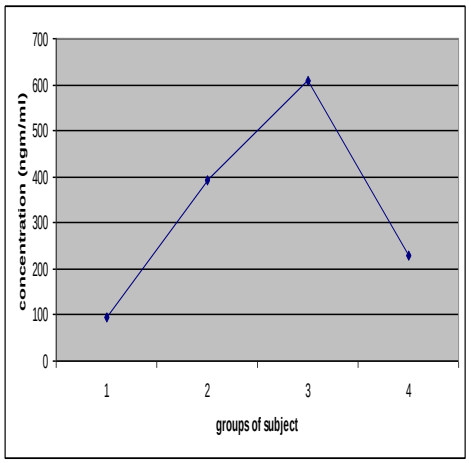
Table 4: Fasting plasma glucose, total cholesterol and total protein in pregnant and control groups

Parameters	Control	1st Trimester	2nd Trimester	3rd Trimester	F-value	*P*-value
Fasting Plasma Glucose mg/dl	88.20±2.28	70.04±0.46*	73.88±0.86*	77.04±1.15*	32.51	P<0.05
Cholesterol mg/dl	137.60±7.74	199.64±4.36*	236.08±6.19*	205.92±9.00*	34.41	P<0.05
Protein g/dl	76.04±1.24	70. 32±0.69*	72.52±0.97*	73.36±1.09*	6.92	P<0.05

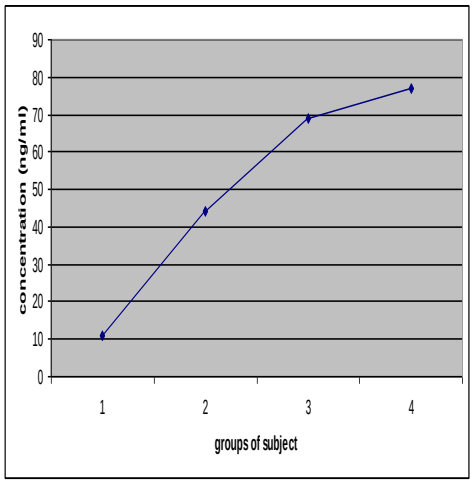
Values express as mean± SEM. Significant differences among the three groups were analysed by ANOVA and LSD test, superscripts (*) depict significant differences between cases and controls, analyzed by Student t- test at *P*<0.05

Hormonal levels

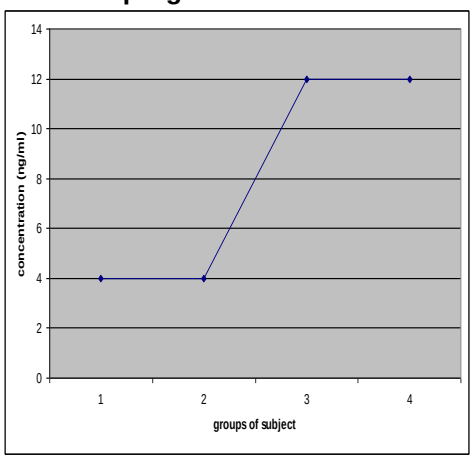
The mean values of cortisol, progesterone and prolactin observed in the pregnant group were significantly higher than in the control group ($P < 0.05$) (Table 2 and Figure 1). Cortisol reaches its peak in the second trimester (687.80 ± 46.10, $P < 0.05$) and reduced significantly in the third trimester. There was a progressive significant increase in the serum progesterone level in pregnant women at all stages of the pregnancy when compared with control group. This increase reached its peak in the third trimester (76.73 ± 3.00, $P < 0.05$). On the other hand, prolactin was not significantly different in the first trimester when compared with the control group ($P > 0.05$) but was significantly higher in the second and third trimester when compared with the control group ($P < 0.05$). The plasma concentration of cortisol correlated positively with progesterone (r = 0.435 and prolactin r = 0.232, $P < 0.05$).



a. Serum cortisol



b. Serum progesterone



c. Serum prolactin

Figure 1: Distribution of serum cortisol, progesterone, prolactin in pregnant and control groups. Key: 1 = Controls, 2= 1st Trimester, 3=2nd Trimester, 4= 3rd Trimester

Electrolytes and other biochemical parameters

Electrolyte concentrations (Table 3 and Figure 2) were significantly different in pregnant women except for sodium concentration when compared to the control group. Sodium level was not significantly higher in all the stages of pregnancy (P> 0.05) when compared with control group and showed no association with increase level of cortisol when correlated in all the stages of pregnancy. Meanwhile, chloride level was significantly increased in the first and second stages of pregnancy but no significant difference in the third stage when compared with the control group. Likewise, potassium and bicarbonate were significantly reduced in the first and second stage of pregnancy when compared with control group (P < 0.05) but showed no significant difference in
the third stage. Moreover, we observed positive correlation between chloride and cortisol but a negative correlation between cortisol, potassium and bicarbonate levels. On the other hand, the changes in the mean concentration of plasma urea and creatinine were not significantly different when compared with that of the control group. The progressive increase of cortisol during pregnancy had no association with urea and creatinine concentration in different stages of pregnancy (P > 0.05).

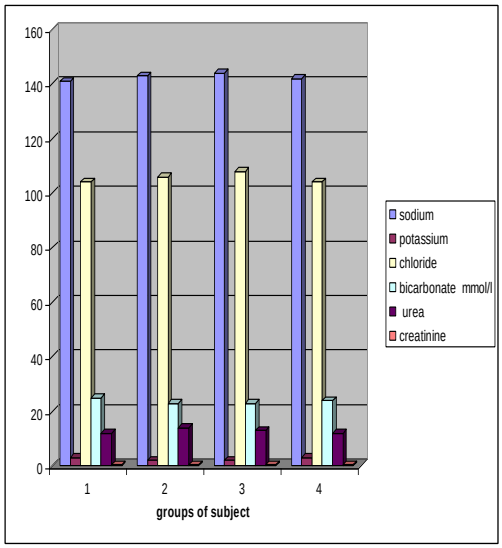


Figure 2: Pattern of electrolytes, urea and creatinine in pregnant and control groups Key: 1 = Controls, 2= 1st Trimester, 3=2nd Trimester, 4= 3rd Trimester

Plasma glucose, plasma cholesterol and plasma protein concentration

Fasting plasma glucose, plasma cholesterol and plasma protein concentration were all significantly different in all the stages of pregnancy when compared with the control group (P < 0.05) (Table 4 and Figure 3). The plasma glucose and protein were significantly reduced and cholesterol was significantly increased in all the stages of pregnancy when compared with the control group (P < 0.05). When the different parameters were correlated with cortisol, we observed negative correlation between glucose and cortisol. There was also, positive correlation between cholesterol and cortisol but there was no association between protein and cortisol in the different pregnant groups.

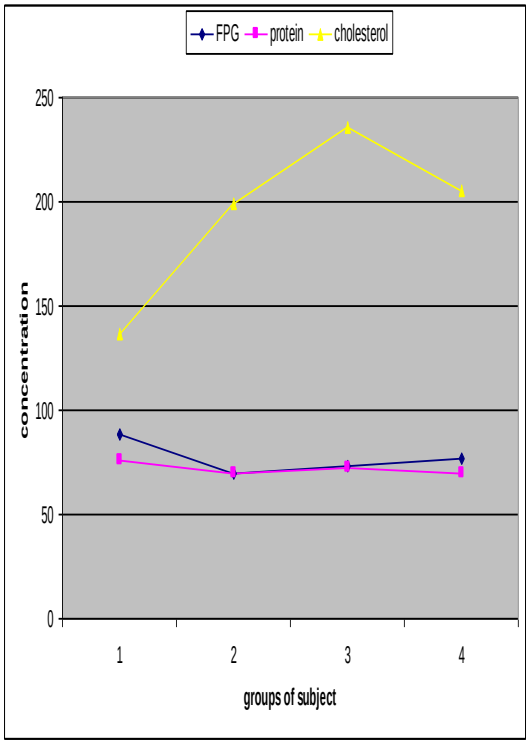


Figure 3: Distribution of plasma glucose, protein and cholesterol in pregnant and control groups. Key: 1 = Controls, 2= 1st Trimester, 3=2nd Trimester, 4= 3rd Trimester

DISCUSSION

In the present study, the associations of cortisol with reproductive hormones and other biochemical parameters were examined in three stages of pregnancy. We observed progressive weight gain from the first

trimester to term when compared with the control group. This is in accord with the observations of others that body weight increased progressively throughout pregnancy and was still higher after delivery than in the first trimester.[22,23] Consequently, our study agrees with common consensus that body mass index (BMI) increased significantly in the third trimester when compared with first, second and control groups.[24-26] Hypervolaemia has been postulated to contribute significantly to increase in body weight during pregnancy.[27] We observed a progressive significant increase in the total serum cholesterol in the pregnant women when compared to controls. Furthermore our finding shows that the higher the cortisol level the higher the total serum cholesterol. It is therefore possible that increase in cortisol and its concurrent increase in cholesterol concentration may have contributed to the increased body weight and body mass index.

Although, we observed progressive reduction in the systolic pressure among the pregnant women, this difference was not significant when compared to control group. This agrees with the report of Cleare[28] who reported that systolic pressure during pregnancy was not different from non-pregnant women. However, in contract to our findings, Holden[29] claimed that diastolic pressure in the second trimester was significantly lower than in first and third trimester. In our study, the diastolic pressure values in the first trimester increased significantly and came down to a level that was not significantly different from the controls in the second and third trimester. This pattern agrees with the observation of Andres *et al.*[30] This probably indicates a response to both physiological and emotional stress in the first trimester which was well adjusted to in the second and third trimester. Also, one may not be able to rule out the possibility of different challenges and responses to pregnancy in different ethnical setting.

Changes in hormonal level during pregnancy have long been established, especially reproductive hormones. However, there are conflicting reports on the changes at each stages of pregnancy. While hormones like progesterone is known to increase progressively throughout pregnancy, changes in prolactin and cortisol varies. The distribution of serum progesterone in our study agrees with previous reports.[31-33] Since progesterone helps to maintain integrity of pregnancy, the serum values increase as the pregnancy progresses. What is novel in our study is the positive correlation observed in the values of cortisol and progesterone in all the stages of pregnancy, this is in contrast with the observation of Keenan *et al,*[34] who reported negative association between cortisol and progesterone. Our result implies that serum progesterone increases as cortisol increases. This increase reaches its peak in the second semester. This is in agreement with the study of Nepomnaschy *et al.*[35] These investigators demonstrated that cortisol increases during the first three weeks after conception is maternal because embryos cannot produce glucocorticoids during that period.[35] They further explained that no conditions have been reported in which an impending loss could trigger an increase in maternal cortisol during the first three weeks after conception.[35] It is known that cortisol production increases in response to psychosocial and physiological challenges and could be an indication that pregnancy is at risk. On the other hand low progesterone concentrations adversely affect the development of the uterus and maintenance of pregnancy. It is then possible that rise in progesterone concentration as observed in our study, is in part compensating for the earlier increased cortisol concentration. This probably explains the positive correlation between cortisol and progesterone observed in our study. Furthermore, increase cortisol during pregnancies have been reported to be associated with spontaneous abortion and unsuccessful pregnancies are known to present a larger proportion of cortisol peaks than successful ones.[36] This further supports our hypothesis that concurrent progressive increase in the level of both progesterone (pregnancy maintenance hormone) and cortisol (stress hormone), may be a necessary compensating mechanism. In agreement with our findings, cortisol, one of the primary biomarkers of physiological stress[37] was recently demonstrated to rise progressively during pregnancy, peaking during the third trimester (mean 3-fold rise compared with controls).[38] These authors did not only associate pregnancy with significant increases in plasma free cortisol and 24-h

urinary free cortisol, but suggested that the rise in total plasma cortisol contributed to up-regulation of the maternal hypothalamic-pituitary-adrenal axis.[38]

Prolactin concentration in this study revealed no changes in the first trimester when compared to control group but increased progressively in second and third stages of pregnancy. Apart from the preparation of mammalian gland for postpartum secretion of milk for feeding the neonate, the increase in prolactin appears to be additional coping strategy for emotional challenges. McLean *et al* and Sobrinho[39,40] reported that cortisol surges were related to shock and were associated with prolactin, this observation agreed with our findings. Sobrinho[40] reports further that prolactin and cortisol is measurable markers of two different and alternative, coping strategies to psychological stress. This probably explains the positive correlation observed in the serum cortisol and prolactin levels in our study.

Morgan *et al*.[41] reported that electrolytes increased from as early as the third day after conception with an accompanying increase in renal ionic excretion and that a net retention of sodium, chloride and potassium did not occur until the final week of pregnancy when the urinary output of these ions is reduced. Richard and Emerson.[12] also reported that sodium and total osmolality were reduced during the last week of pregnancy despite the salt retention, suggesting increased fetal usage. In contrast, we observed no changes in sodium but significant increase in chloride concentration in first and second trimester compared to controls. Consequently, this was accompanied by significant reduction in potassium and bicarbonate concentration in the two stages of pregnancy. These changes were normalized by the last stage of pregnancy with the values comparable to non-pregnant controls. This implies that electrolyte imbalance characterized the first two trimesters of pregnancy with tendency toward alkalinity. This imbalance was corrected in the third trimester.

Ashwood[22] had earlier reported that pregnancy increases the glomerular filtration rate (GFR) and consequently increases the clearance of urea and creatinine. However, Tiezts[42] commented that urea and creatinine concentration increased slightly during the last four weeks (4wks) of pregnancy. Our study revealed no significant differences in urea and creatinine in all stages of pregnancy when compared to the control group. We also report no association between cortisol and urea and creatinine.

It has been shown that during early pregnancy, insulin, sensitivity increase slightly in all subgroups of pregnant women to about 14% and by late pregnancy, insulin sensitivity was reduced appropriately to 65% versus pregravid.[43] Insulin is not only important in the metabolism of glucose but also in the metabolism of fat and protein.[14,43] It is therefore not surprising that glucose, protein and cholesterol level were significantly altered in pregnancy. While glucose and protein level declined, cholesterol level increased when compared to control group. Catalano *et al.*[44] had earlier reported that subgroups of pregnant women had similar relative changes in sensitivity regardless of whether they had gestational diabetes or not. Wldinger *et al.*[45] reported that serum protein level shifted with a striking drop in albumin which could probably indicate increasing protein demand by the growing child. This may further contribute to significant reduction in protein levels in our pregnant subjects.

The increased cholesterol level reported among the pregnant women in this study agrees with that of others.[46] These authors reported 40% increase in serum cholesterol in pregnant women. It is not surprising to observe an inverse relationship between cortisol and plasma glucose level since cortisol hormone is a stress hormone, expected to be accompany by increase metabolism with consequence usage of glucose. However, it is interesting to find a positive correlation between cortisol and total cholesterol. This could be postulated to be due to reduced insulin sensitivity in pregnancy which may favour lipogenesis coupled with cortisol drive of increase glucose metabolism, which may further increase lipogenesis.

CONCLUSION

Pregnancy induces physiologic changes which coupled with emotional stress and challenges, contribute to changes in hormonal and biochemical status of pregnant women, especially, electrolytes imbalance and depletion of macronutrients (glucose and protein). The associated increase in serum cortisol is a possible indicator of emotional stress and physiological challenges in pregnancy and possible risk signal. The concurrent increase in progesterone and prolactin are compensating mechanism in response to these challenges, particularly, an increase in progesterone concentration compensating for the earlier increase in cortisol concentration. While homeostatic mechanism corrected the electrolytes imbalance, most of the biochemical and hormonal changes which are more pronounced at the first and second trimester extends to last weeks of pregnancy. This study shows that cortisol may be playing a central role in the biochemical changes that were earlier reported in pregnancy and those that are peculiar to this study. It may therefore be of clinical relevance to monitor the serum cortisol levels and some of the associated variables, especially progesterone in pregnancy and particularly, in threatening cases.

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