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Original Article

Some Biochemical Changes In Proteinuric Pregnant Women: Exploring Effective Management Of Proteinuria In Pregnancy

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ABSTRACT

Background: Pregnancy involves many physiological and biochemical changes that impact fetal growth and maternal safety, sometimes leading to serious complications. Proteinuria is a complication of pregnancy, particularly in women with hypertension or diabetes, and is associated with increased risk of preeclampsia, a pregnancy-related hypertensive disorder that can lead to maternal and fetal morbidity and mortality. Aim: This study was taken to evaluate some biochemical changes that occur in pregnant women with proteinuria, and determine if avoidance of these changes can effectively arrest or treat proteinuria in pregnancy. Methods: This was a cross-sectional study involving 60 pregnant women (aged 18 to 45 years) with proteinuria attending the antenatal clinic of ESUT Teaching Hospital, Parklane, Enugu State, Nigeria. Another 57 age-matched apparently healthy pregnant women attending the same clinic were recruited as controls. Antioxidant trace elements (zinc and selenium) were estimated by atomic absorption spectrophotometry, lipids and lipoproteins were estimated by enzymatic methods, while serum electrolytes were determined using ion-selective electrodes. Results: Mean serum electrolyte levels showed no significant differences between the two groups ($p > 0.05$). Also, there were non-significant changes in lipid and lipoproteinlevels in pregnant women with proteinuria when compared with the controls, except for triglycerides,which showed a significant increase ($p=0.05$). However, pregnant women with proteinuria have significantly ($p=0.002$ each) lower levels of zinc and selenium compared to controls.Sodium and total cholesterol exhibited positive correlation with proteinuria severity ($r = 0.445$, $p = 0.001$), while others showed non-significant correlations with proteinuria severity. Conclusion: From the results, significant biochemical changes in pregnant women with proteinuria were changes in antioxidants, implicating oxidative stress as a major cause of proteinuria in pregnancy. Arrest of oxidative stress at the onset of pregnancy may likely prevent the occurrence of proteinuria in pregnancy. This calls for early antenatal registration and care.

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Introduction

During pregnancy, there are series of normal and abnormal physiological and biochemical changes that either help in the proper maintenance of the fetal growth and maternal safety or cause maternal morbidity and fetal distress. The latter can further lead to maternal and fetal mortality if not properly taken care of or managed. Proteinuria in pregnancy is one of such problems resulting from abnormal biochemical changes, and it refers to the presence of protein in urine.

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Generally, proteinuria may indicate renal impairment, but in the case of pregnancy, it is linked to preeclampsia and gestational hypertension, also called pregnancy-induced hypertension [1]. But it is not yet clear whether preeclampsia is the cause of proteinuria or the reverse, given that some pregnant women with proteinuria did not have preeclampsia, while some who developed preeclampsia had no protein in their urine.

Proteinuria is an independent risk factor for cardiovascular morbidity and mortality, with an estimated 8–10% of pregnancies worldwide being affected by hypertension during pregnancy[2], posing serious risks to the health of both the mother and the fetus. There are a number of potential causes of proteinuria during pregnancy. In normotensive pregnant women, there may be an increase in protein excretion, either due to less efficient reabsorption capacity of the kidney tubules or elevated glomerular permeability, ensuring that during the early and middle stages of pregnancy, proteinuria tendsto increase [3,4].

When proteins are filtered into the tubules, even the large ones like albumin are reabsorbed[5]. However, when the reabsorption capacity is defective or saturated, proteins will be excreted in urine, proteinuria. Furthermore, part of the physiological changes during pregnancy, likeincreases in estrogen and human chorionic gonadotropin levels,can affect kidney function and make the glomerular filtration barrier more permeable[6].Pathologically, elevated blood pressure, preeclampsia, and

damage to other organ systems, more frequently the kidneys,and the need to clear more solutes from the system, like in diabetes, may lead to an elevation of glomerular filtration rate and cause an increase in protein leakage into the urine[6,7,8].

The major risk factors for proteinuria in pregnancy include first-time pregnancy, obesity, and family history. This potentially dangerous pregnancy complication, characterized by high blood pressure and preeclampsia, begins after 20 weeks of pregnancy, and can lead to maternal and fetal morbidity and mortality [9]. The biochemical changes associated with proteinuria are characterized by imbalances in the urinary excretion of proteins, electrolytes, and other solutes, leading to respiratory difficulty, muscular weakness, and heart arrhythmias as a result of electrolyte imbalances[10].

Electrolyte imbalances have been associated with a variety of pregnancy health-related problems such as heart palpitations, breathing difficulties, and cardiac dysrhythmia[11]. Particularly, a positive correlation has been established between the severity of hyponatremia and the severity of preeclampsia[12].Other biochemical changes during pregnancy includealterations in serum levels of other macromolecules andmicronutrients, especially antioxidant micronutrients. It is expected that plasma lipid concentrations will increase during pregnancy due to estrogen stimulation and insulin resistance.

It is also expected that during the first and second trimesters of pregnancy, there should be an increase in maternal fat accumulation, associated with both hyperphagia and increased lipogenesis. Lipid metabolism plays critical roles in pregnancy, with regard to fetal development, placental function, maternal health, and preeclampsia prediction. Pregnancy increases demand for metabolic fuels for fetal growth and development and causes hormonal changes in the body that may lead to changes in lipids across different trimesters of pregnancy [13]. Lipid derangements have been linked to proteinuria in non-pregnant individuals, but the relationship between proteinuria in pregnancy and lipid derangement is not yet well established.

However, the risk of adverse pregnancy outcomes, including gestational diabetes mellitus, preeclampsia, preterm birth, and fetal growth disorders,has been linked to dyslipidemia [14,15].Antioxidants, like zinc and selenium, are essential trace elements that play critical roles in maintaining normal kidney function and antioxidant defenses [16]. Zinc is involved in the regulation of protein synthesis and degradation, while selenium is a cofactor for glutathione peroxidase [17]. Deficiencies in these elements have been linked to an increased risk of proteinuria and kidney disease [18]. Despite the importance of zinc and selenium in maintaining normal kidney function, there is a limited understanding of their role in proteinuria during pregnancy.

Recent studies have suggested that deficiencies in these elements may contribute to the development of proteinuria during pregnancy [19,20], probably due to decreased antioxidant activity in conditions burdened by oxidative stress. This study aims to evaluate some biochemical changes in pregnant women with proteinuria, with the expectation that guarding against such changes early in pregnancy may help to avoid this life-threatening condition.

Materials and Methods

Ethical clearance: Ethical clearance for this study was obtained from the Ethical Clearance Committee of Faculty of Basic Medical Sciences, College of Medicine, Enugu State University of Science and Technology. Subsequently, individual consent was sought and obtained from each participant after the purpose and procedures of the research was fully explained.

Study design: This is a cross-sectional study involvingsixty (60) pregnant women attending the antenatal clinic ofEnugu State University Teaching Hospital, Parklane, Enugu, Nigeria. They were aged 18 to 45 years and appeared to be healthy, but they had proteinuria. Controls were fifty-nine (59) age-matched pregnant women attending the same clinic who did not have proteinuria.All the subjects who participated in thestudy gave verbal consent for the research.

Inclusion Criteria: Included in the study were pregnant womenaged between 18 – 45 years whotested positive for proteinuria andhad no history of chronic disease that could affect the values of the parameters under investigation. And also, those who showeda willingness to participate in the study by givinginformed consent were included.

Exclusion Criteria: Exclusion criteria included age outside the age range of 18 to 45 years, history or presence of chronic disorders that can affect the parameters under investigation, presence of fetal abnormalities or other severe complications of pregnancy, and refusal to participate or give consent.

Sample Size: Sample size was determined using Taro Yamane's Formula,

$n = (Z^2 \times P \times (1-P)) / E^2$

Where

n = sample size

Z = 1.96 (for 95% confidence)

P = 0.25 (estimated proportion of pregnant women with proteinuria)

E = 0.11 (margin of error)

Calculation:

$n = (1.96^2 \times 0.25 \times (1-0.25)) / 0.11^2$

$n = (3.8416 \times 0.25 \times 0.75) / 0.0121$

$n = 0.7203/0.0121$

$n = 59.53$

$n = 60$

Sample collection: A total of 5.0ml of whole blood was collected from the ante-cubital vein of each participant into a plain, grease-free glass test tube. This was allowed to stand at room temperature for 10 minutes to clot and retract. It was then spun in a centrifuge at 5 rpm for five minutes. The serum was then separated into three unequal aliquots and stored frozen till needed for analysis.

Laboratory analysis: Serum electrolytes (sodium, potassium, chloride, and bicarbonate) were estimated using ST-100B Electrolyte analyzer (SensaCore Medical Instrumentation PVT Ltd, India). Operational guidelines were fully adhered to while using the equipment. The lipids and lipoproteins were determined as earlier reported [21], while zinc and selenium were estimated by atomic absorption spectrophotometry using Agilent FS240AA Atomic Absorption Spectrophotometer (Agilent Technologies, USA)as described by the American Public Health Association in 1995 [22].

Data analysis: Data obtained from this study were analyzed using the Statistical Package for Social Sciences (SPSS, version 23). Data were presented as means and standard deviations. One-way analysis of variance (ANOVA) and Spearman's rho correlation were used to determine the mean difference. P value of <0.05 wasconsidered statistically significant.

RESULTS

An earlier preliminary study was conducted to determine the prevalence of proteinuria among pregnant women attending the antenatal clinic of Enugu State University Teaching Hospital, Parklane,Enugu. Out of 180 pregnant women enrolled in the study, 44 of them, representing 24.4% had protein in their urine samples.During the actual study, 60 pregnant women with proteinuria were mobilized based on the calculation of the study population. The differences in severity of proteinuria were noted as +, ++, and +++, and presented in Table1.

Table 1: Severity of proteinuria in pregnancy in the study group

Level of proteinuria	Frequency	Percentage (%)
+	33	55.0%
++	21	35.0%
+++	6	10.0%
Total	60	100%

Table 2 shows the demographic distribution of the pregnant women with proteinuria.The majority of the subjects (35.0%) were between 26 and 30 years of age, while the least were those between 41 and 45 years of age. The highest number of the pregnant women with proteinuria (46.7%) was in their third trimester, while the lowest number (20.0%) was in their first trimester.

Table 2: Demographic distribution of pregnant women with proteinuria.

Age	Frequency	Percentage (%)
20-25 years	10	16.7%
26-30 years	21	35.0%
31-35 years	19	31.7%
36-40 years	8	13.3%
41-45 years	2	3.3%
Total	**60**	**100%**
Trimester		
First	12	20.0%
Second	20	33.3%
Third	28	46.7%
Total	**60**	**100%**

Table 3 shows all the studied parameters in pregnant women with proteinuria and those without proteinuria. The results showed that there were no statistically significant differences in the levels of electrolytes in the two groups.Likewise, there were no significant differences in lipid levels, except for triglycerides,which showed a statistically significant increase (p = 0.02) in pregnant women with proteinuria when compared with those without proteinuria. However, there were statistically significant decreases (p = 0.002 each) in the serum levels of zinc and selenium in pregnant women with proteinuria when compared with the levels from those without proteinuria.

Table 3: Means ± SD of biochemical parameters in proteinuric and non-proteinuric pregnant women

Variables	Control N=59	Tests N=60	P-value
Sodium (mmol/L)	138.98±3.21	138.75±3.53	0.750
Potassium (mmol/L)	3.96±0.42	4.01±0.38	0.582
Bicarbonate (mmol/L)	24.76±2.37	24.41±2.32	0.471
Chloride (mmol/L)	100.91±1.73	100.81±3.45	0.841
Total Chol (mmol/L)	5.66±2.46	6.04±1.01	0.92
HDL (mmol/L)	1.48±1.0	1.62±0.73	0.59
LDL (mmol/L)	3.38±2.12	3.54±1.36	0.43
VLDL (mmol/L)	0.86±0.36	0.84±0.54	0.45
Triglycerides (mmol/L)	1.88±2.4	1.95±0.85	0.02*
Zinc (µmol/L)	13.69±4.07	10.61±3.51	0.002**
Selenium (µg/L)	139.01±22.06	119.92±25.10	0.002**

***indicates levels of significance**

Table 4 shows the correlation between the studied parameters and the severity of proteinuria. There were no significant changes in the levels of all the electrolytes as the severity of proteinuria increased, except sodium,which decreased significantly. Likewise, there were no significant correlations between the lipid profile and severity of proteinuria, except for total cholesterol,which increased significantly.Furthermore, there wasa strong negative correlation between the severity of proteinuria and serum level of zinc, but not selenium.

Table 4: Correlation between the studied parameters and severity of proteinuria

Variables	Correlation coefficient(R)	P-value
Sodium	0.445	0.001**
Potassium	0.036	0.81
Chloride	0.21	0.15
Bicarbonate	0.149	0.30
Total Cholesterol	0.407	0.04*
HDL	0.139	0.26
LDL	0.118	0.45
VLDL	0.245	0.86
Triglycerides	0.246	0.87
Zinc	0.534	0.002**
Selenium	0.155	0.397

***indicates level of significance**

The prevalence of proteinuria (24.4%)in the study population highlights its common occurrence in the study area, which necessitates continued attention to its management, given its known associations with adverse pregnancy outcomes [23,24].The majority of the pregnant women (46.7%) fell within the third trimester group. This agrees with our earlier observation that pregnant women in developing countries hardly register for early antenatal care, unless there are early complications of pregnancy[25].

The results of this study reveal no statistically significant differences in serum electrolyte levels between pregnant women with and without proteinuria. These findings suggest that serum electrolyte levels are not affected by proteinuria in pregnancy in the study population.This findingis in agreement with earlier studies [26,27], indicating that mild proteinuria does not significantly alter serum electrolyte levels.However, the significant positive correlation between sodium and proteinuria severity means that as proteinuria worsens, sodium levels may increase, indicating altered renal handling of sodium in severe or prolonged cases.

Earlier studies[28,29] have linked sodium retention to renal impairment. This implies that the severity of proteinuria may adversely alter the functions of the kidney and vice versa. Sodium regulation occurs in the kidneys, and hypernatremia is usually associated with low water intake or pathological disorders that enhance fluid loss [30]. However, proteinuria is known to cause water retention or edema [31], likewise hypernatremia, though indirectly through the creation of an osmotic gradient. Therefore, an increase in serum sodium in proteinuria will augment the action of proteinuria in causing fluid retention.

The results of the lipid profile from this study agreed with those obtained from a previous study [32], except for the triglycerides. In normal pregnancy, lipids have essential roles for efficient fetal development [33,34]; hence, they are expected to increase as gestation increases. Non-significant increases in total cholesterol and the lipoproteins from this study may be associated with changes in estrogen and progesterone levels, and increased lipolysis as gestation increased. It could also be due to endothelial dysfunction, which increases vascular permeability and releases lipid into the bloodstream, or increased lipogenesis and altered lipid metabolism caused by proteinuria-induced inflammation.

However, triglycerides were found to be statistically significantly increased in women with proteinuria. It has earlier been posited that triglycerides are an independent risk factor for cardiovascular disease [35,36].Hence, though triglyceride is known torise disproportionately in comparison to other lipid fractions in normal pregnancy [33], this rise may be the link between proteinuria and pregnancy-induced hypertension (PIH).Atherogenic lipid profile at first trimester predisposes preterm delivery[34], and preterm delivery predisposes cardiovascular disease later in life [37,38]. Therefore, hypertriglyceridemia is not only a risk factor for proteinuria that can cause preeclampsia and preterm delivery, but also postpartum cardiovascular disease.

This study showed that serum levels of both zinc and selenium were statistically significantly lower in pregnant women with proteinuria compared to those without proteinuria, suggesting a deficiency of these antioxidant trace elements in pregnant women with proteinuria. These findings are consistent with earlier studies [20,39], which also noted the importance of these micronutrients in maternal and fetal health.Both zinc and selenium play crucial roles in immune function, antioxidant defense, and overall metabolic processes [40,41], and are known to decrease significantly in uncomplicated pregnancy and can decrease further as the gestational period increases [42,43].

These changes in seemingly uncomplicated pregnancies prompted the call for the assessment of these antioxidant trace elements in early pregnancy to prevent their deficiencies and attendant consequences throughout the gestational period[44]. The present study re-emphasizes the need for early assessment and smart fortification/supplementation to avoid/prevent proteinuria in pregnancy. And for proper management when it occurs, immediate diagnostic procedures should be taken to unravel the cause(s) and adequate actions taken to ameliorate the root cause.

Conclusion

This study demonstrated no statistical changes in electrolytes and lipid profiles in pregnancy with proteinuria, except for triglycerides. However, antioxidant trace elements were statistically lower in pregnant women with proteinuria, implying that proteinuria causes oxidative stress during pregnancy, which is dangerous to both maternal and fetal health. Adequate individualized monitoring and appropriate supplementation for these antioxidants during pregnancy are advocated to prevent the menace of proteinuria in pregnancy and its attendant complications.

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