

## ASYMPTOMATIC BACTERIURIA AS A PREDICTOR OF PRE-ECLAMPSIA: A CASE-CONTROLLED STUDY

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### ABSTRACT

**Background:** Pre-eclampsia, an important cause of maternal and perinatal morbidity and mortality world-wide has been linked to subclinical infections, with maternal infection and inflammation postulated in its aetio-pathogenesis including asymptomatic bacteriuria which is common in pregnancy. The Objective of the study is to determine the relationship of asymptomatic bacteriuria as a risk factor for pre-eclampsia.

**Methodology:** A hospital-based case-control study among 28 pre-eclamptic pregnant women (cases) and 56 healthy pregnant women (controls) at gestational age of at least 28 weeks at the University College Hospital, Ibadan, between January 2019 and August 2019. Controls were matched with cases in age, parity and gestational age. Asymptomatic bacteriuria was determined with mid-stream urine analysis for microscopy and culture and data collected using an interviewer administered questionnaire with other details from medical records extracts. Chi-square, and multivariate regression analysis were used to assess statistical significance, odds ratio and adjusted odds ratio respectively, with P-value <0.05 and 95% confidence interval (CI).

**Results:** There was a significant association between asymptomatic bacteriuria and pre-eclampsia. The rate of asymptomatic bacteriuria was about three times higher in women with pre-eclampsia compared to those without pre-eclampsia and 1.23 times higher after adjusting for confounders (OR: 2.9, AOR:1.23). There was no significant relationship between sterile pyuria and pre-eclampsia (p-value: 0.92)

**Conclusion:** This study supports the proposition that asymptomatic bacteriuria is a risk factor for pre-eclampsia. It has not however shown whether the association is causal or casual. Further studies will be needed to explain this.

### INTRODUCTION

Pre-eclampsia is a pregnancy-specific disorder characterized by hypertension, significant proteinuria, with or without edema.<sup>1</sup> It is a progressive multi-systemic disease occurring between 20 weeks gestation to 6 weeks post-partum with potentially grave maternal and perinatal complications. Pre-eclampsia may progress to eclampsia or may be result in an array of complications such as pulmonary edema, cerebral hemorrhage, hepatic failure, renal failure, preterm delivery and perinatal and maternal mortality. Sadly, it remains a disease of theories despite the plethora of global research works, as the specific etiology is still elusive.

Pre-eclampsia is an important cause of maternal and perinatal morbidity and mortality globally, affecting 2-10% of pregnancies.<sup>2</sup> Preeclampsia and eclampsia account for up to 63,000 maternal deaths annually worldwide.<sup>3</sup> Its greatest burden is in the developing nations, and the prevalence varies across different zones. In Nigeria, it has a wide variation as low as

0.03 per 100 deliveries in Calabar to as high as 9 per 100 deliveries in Birin Kudu.<sup>4,5</sup>

Different maternal infections have been linked with the development of pre-eclampsia. However, chronic subclinical infection causes endothelial dysfunction by decreasing nitric oxide which is a crucial event in the development of pre-eclampsia.<sup>6</sup> Asymptomatic bacteriuria is a subclinical urinary tract infection that is common in pregnancy. It is defined as the presence of at least 10<sup>5</sup> colony forming units of a single bacterium per milliliter of two consecutive clean catch urine specimens or a single catheter specimen in absence of urinary symptoms<sup>7</sup>.

Screening for asymptomatic bacteriuria and prophylactic treatment in pregnancy is important to prevent adverse foeto-maternal outcomes.<sup>8</sup> World-wide, its incidence in pregnancy is 2-10%.<sup>9</sup> Studies conducted in Nigeria revealed an incidence of 28.8% in Ibadan and 86.6% in Benin.<sup>10,11</sup> It usually develops more in

the third trimester and is much commoner in multiparous women.

Prior research works have shown dissenting conclusions about the association between asymptomatic bacteriuria and pre-eclampsia. Considering the higher prevalence of asymptomatic bacteriuria in pregnancy and the proposed central role of infection in the pathogenesis of pre-eclampsia, it is worthwhile conducting this study. This is because prophylactic treatment of asymptomatic bacteriuria can be a simple and cheap way of preventing pre-eclampsia.

## METHODOLOGY

This was a case-control study conducted at the University College Hospital (UCH), Ibadan, between January 2019 and August 2019. Sample size was calculated using the formula for comparing proportions with 95% confidence interval and 15% attrition rate. Purposive sampling technique was used to select twenty-eight women who were at least 28 weeks pregnant already diagnosed with pre-eclampsia (cases) and were matched in age, parity and gestation age with 56 healthy pregnant women (control).

The inclusion criteria were pregnant patient with singleton gestation of at least 28 weeks, who consented. Pregnant women with previous history of pre-eclampsia, and systemic illnesses like - chronic hypertension, diabetes mellitus, chronic kidney disease and sickle-cell disease were excluded. Also excluded from the study were those with history of fever in the last one month, dysuria, urgency or other symptoms of urinary tract infection, the use of antibiotics, and smoking.

The World Health Organization (WHO) categorization of age was used: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 (in years). Gestational age was the number of completed weeks from the last menstrual period. Parity was the number of births after at least 28 weeks of gestation. Women who have registered for antenatal care and have had their investigations reviewed are described as booked and those who have not registered are unbooked. Blood pressure and urinalysis of participants were assessed at recruitment. Thereafter, mid-stream urine microscopy, culture and sensitivity was done. Controls had their blood pressure and urinalysis checked at delivery to confirm they remained without pre-eclampsia, or otherwise excluded.

Trained research assistants (nurses) did blood pressure measurements with Accoson mercury (manual) sphygmomanometer and dip stick urinalysis in a sterile manner. Participants were trained on how to collect

clean-catch mid-stream urine samples for urine microscopy, culture and sensitivity.

Pre-eclampsia was defined as systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg, on two occasions at least 4 hours apart in a previously normotensive patient, and a urine dipstick protein of at least 1+ after 20 weeks gestational age. Asymptomatic Bacteriuria was defined as the growth of at least  $10^5$  colony-forming units per ml of a bacterium in the urine sample.

Data was collected using interviewer-administered questionnaire and then entered into the Statistical Package for Social Sciences (SPSS) version 25. Analysis was performed using descriptive and inferential statistics. T-test was used for continuous variables (expressed as means and standard deviations) and Chi-square test was used for categorical variables. Also, bivariate and multivariate regression analysis were performed with the level of statistical significance set at P-value <0.05.

Ethical approval was obtained from the University of Ibadan/University College Hospital, Ibadan Ethics Review Committee with assigned approval number; UI/EC/0386.

## RESULT

### Socio-demographic characteristics

The mean age of participants with preeclampsia;  $32.9 \pm 5.00$  years was almost the same as the mean age of controls;  $29.9 \pm 5.05$  years. Majority were between 35 and 39 years old in both cases (35.7%) and controls (37.0%) groups. Very few were between 20 and 24 years old; 2(7.1%) versus 4(7.4%) respectively. (Table 1)

Majority of the participants were married; 26(92.9%) of preeclampsia group and 52(96.3%) of controls. Among the 28 cases, 14(50%) of them were employed while the remaining were unemployed. Among the controls, more than half (70.4%) of the participants were employed while the other 16(29.6%) were unemployed. However, this difference is not statistically significant.

In both groups, a substantial proportion of participants; preeclampsia, 16(57.1%) versus controls, 46 (85.2%) had a tertiary level of education. A similar proportion of the participants were of Yoruba ethnic group 23 (82.1%) and 45 (83.3%) of the cases and controls respectively.

**Table 1:** Socio-demographic characteristics of participants

Variables	Preeclampsia N (%)	Control N (%)	Total N (%)	p-value
<b>Ages in category (complete years)</b>				
20 - 24	2 (7.1)	4 (7.4)	6 (7.3)	0.72
25 - 29	6 (21.4)	12 (22.2)	18 (22.0)	
30 - 34	7 (25.0)	13 (24.1)	20 (24.4)	
35 - 39	10 (35.7)	20 (37.0)	30 (36.5)	
40 – 44	3 (10.7)	5 (9.3)	8 (9.8)	
Mean age $\pm$ SD	32.9 $\pm$ 5.00	29.9 $\pm$ 5.05		
<b>Marital status</b>				
Single	2 (7.1)	2 (3.7)	4(5.0)	0.49
Married	26 (92.9)	52 (96.3)	78(95.0)	
<b>Occupation</b>				
Professional	0 (0)	6 (11.1)	6 (7.3)	0.12
Skilled	6 (21.4)	13 (24.1)	19 (23.2)	
Semiskilled	0 (0)	4 (7.4)	4 (4.9)	
Unskilled	8 (28.6)	15 (27.8)	23 (28.0)	
Unemployed	14 (50.0)	16 (29.6)	30 (36.6)	
<b>Highest level of education</b>				
Primary	1 (3.6)	0 (0)	1 (1.2)	0.01
Secondary	11 (39.3)	8 (14.8)	19 (23.2)	
Tertiary	16 (57.1)	46 (85.2)	62 (75.6)	
<b>Tribe</b>				
Igbo	3 (10.7)	3 (5.6)	6 (7.3)	0.41
Yoruba	23 (82.1)	45 (83.3)	68 (82.9)	
Hausa	1 (3.6)	2 (3.7)	3 (3.7)	
Others	1 (3.6)	4 (7.4)	5 (6.1)	

**Obstetric history of participants with pre-eclampsia and without pre-eclampsia**

There is no statistically significant difference in the categories of gestational age and parity between the cases and controls. Twelve (42.9%) of cases had previous abortions as against 15(27.8%) in controls.

However, this was not statistically significant. Half of the cases were unbooked while only 5(9.3%) of those in the control group were unbooked in the index pregnancy making booking status the only statistically significant difference in obstetric characteristics between the two groups. ( $p < 0.001$ ). (Table 2)

**Table 2:** Comparison of obstetric history between the groups using . . . (t-test or chi-square or whatever test is used)

Variable	Study group		Total N (%)	P-value
	Cases (N=28) (Preclampsia)	Control (N=54)		
<b>Gestational Age (weeks)</b>				
28-33	9 (32.1)	17 (31.5)	26 (31.7)	0.93
34-36	12 (42.9)	23 (42.6)	35 (42.7)	
$\geq$ 37	7 (25.0)	14 (25.9)	21 (25.6)	
<b>Parity</b>				
Primipara	8 (28.6)	16 (29.6)	24 (29.3)	0.92
Multipara	20 (71.4)	38 (70.4)	58 (70.7)	
<b>Booking Status</b>				
Booked	14 (50.0)	49 (90.7)	63 (76.8)	<0.001
Unbooked	14 (50.0)	5 (9.3)	19 (23.2)	
<b>Previous abortion</b>				
Yes	12 (42.9)	15 (27.8)	27 (32.9)	0.17
No	16 (57.1)	39 (72.2)	55 (67.1)	

**Table 3:** Association between asymptomatic bacteriuria/sterile pyuria and preeclampsia

Exposure		Preeclampsia N= 28 (%)	Controls N = 54 (%)	p-value	OR (95% CI)
<b>Asymptomatic bacteriuria</b>	Yes	12 (42.9)	11 (20.4)	0.03	2.93 (1.08 – 7.97)
	No	16 (57.1)	43 (79.6)		
<b>Sterile bacteriuria</b>	Yes	8 (28.6)	16 (29.6)	0.92	-
	No	20 (71.4)	38 (70.4)		

### Association between asymptomatic bacteriuria/sterile pyuria and preeclampsia

A higher proportion, 12(42.9%) of preeclampsia patients was found with asymptomatic bacteriuria as compared to controls, 11(20.4%) ( $p=0.03$  OR = 2.93, CI = 1.08 – 7.97). This suggests that asymptomatic bacteriuria is almost 3 times more common in women with preeclampsia than in women without asymptomatic bacteriuria.

The proportion of cases who had sterile pyuria, 8(28.6%) was very comparable to the proportion of controls, 16(29.6%) who had sterile pyuria and there was no statistically significant difference between sterile pyuria and preeclampsia ( $p=0.92$ ). (Table 3)

The relationship between asymptomatic bacteriuria and pre-eclampsia among the study participants while adjusting for age, marital status, and parity. The adjusted odds ratio was 1.23. [AOR = 1.23 (95% CI = 1.12 – 3.14)]. This suggests asymptomatic bacteriuria has a weak positive association with pre-eclampsia. However, the relationship with sterile pyuria was not statistically significant.

### DISCUSSION

The index study sought to clarify if asymptomatic bacteriuria is a risk factor for pre-eclampsia. Participants were similar in the matched attributes across both groups thereby controlling for confounders. There was a higher age distribution when compared to similar studies by Rezavand *et al.*<sup>15</sup> and Bourghei *et al.*<sup>12</sup>. However, this could be attributable to the higher level of tertiary education among the study participants.

A higher proportion of the unbooked patients had pre-eclampsia and this was statistically significant and similar to the findings of increased risk of eclampsia as reported by Yakassai *et al.*<sup>15</sup> The proportion of women with pre-eclampsia that had asymptomatic bacteriuria were much higher than those without pre-eclampsia. This agrees with findings from different studies in different countries<sup>13,16,17</sup>. However, those with sterile pyuria were similar across both groups, contradicting the result of Rezevand *et al.*<sup>13</sup> The

difference in the laboratory methods and self-reporting of antibiotics use may be responsible.

We recommend a multi-centre and larger sample size study so as to detect the real effect of asymptomatic bacteriuria and sterile pyuria on pre-eclampsia while controlling for the booking status.

### CONCLUSION

This study supports the proposition that asymptomatic bacteriuria has a positive association with pre-eclampsia. However, it remains debatable whether this association is causal or casual. Considering the prevalence of asymptomatic bacteriuria in pregnancy and its sequelae we advocate for screening and prophylactic treatment which might be a simple and cheap way of preventing pre-eclampsia and its complications.

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