Tropical Medicine and International Health doi:10.1111/j.1365-3156.2011.02926.x

VOLUME 17 NO 4 PP 480–487 APRIL 2012

Risk factors for pre-eclampsia in Mulago Hospital, Kampala, Uganda

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Abstract

OBJECTIVE Pre-eclampsia contributes significantly to maternal, foetal and neonatal morbidity and mortality. The risk factors for pre-eclampsia have not been well documented in Uganda. In this paper, we describe the risk factors for pre-eclampsia in women attending antenatal clinics at Mulago Hospital, Kampala.

METHODS This casecontrol study was conducted from 1st May 2008 to 1st May 2009. 207 women with pre-eclampsia were the cases, and 352 women with normal pregnancy were the controls. The women were 15–39 years old, and their gestational ages were 20 weeks or more. They were interviewed about their socio-demographic characteristics, past medical history and, their past and present obstetric performances.

RESULTS The risk factors were low plasma vitamin C (OR 3.19, 95% CI: 1.54–6.61), low education level (OR 1.67, 95% CI: 1.12–2.48), chronic hypertension (OR 2.29, 95% CI 1.12–4.66), family history of hypertension (OR 2.25, 95% CI: 1.53–3.31) and primiparity (OR 2.76, 95% CI: 1.84–4.15) and para≥5 (3.71, 95% CI:1.84–7.45).

CONCLUSION The risk factors identified are similar to what has been found elsewhere. Health workers need to identify women at risk of pre-eclampsia and manage them appropriately so as to prevent the maternal and neonatal morbidity and mortality associated with this condition.

keywords risk factors, pre-eclampsia, Uganda

Introduction

Pre-eclampsia complicates 5–8% of all pregnancies although the incidence may be higher in poor regions (Duley 1992). It is among the leading causes of maternal, foetal and neonatal morbidity and mortality worldwide especially, in poor settings (Khan *et al.* 2006). In Mulago Hospital in Uganda in 2000, it contributed 17.6% to maternal morbidity and 21.4% to maternal mortality (Kaye *et al.* 2003).

The aetiology of pre-eclampsia is not well understood. Immune maladaptation, placental ischaemia, genetic predisposition and vascular-mediated factors lead to its development (Hubel 1999; Roberts & Gammill 2005). Risk factors for pre-eclampsia have mainly been reported from high-resource settings. Advanced maternal age is associated with pre-eclampsia (Bianco *et al.* 1996; Hartikainen *et al.* 1998). This is similar in low-resource settings (Conde-Agudelo & Belizan 2000; Lee *et al.* 2000). However, this has not been confirmed by other researchers (Mahomed *et al.* 1998; Anorlu *et al.* 2005). Low socioeconomic status is associated with the risk of developing pre-eclampsia (Haelterman *et al.* 2003; Silva *et al.* 2008). This is similar to what was found in Mexico (Ceron-Mireles *et al.* 2001) and in South Africa (Dlamini 1997), but differed from what was found by others (Gonzalez *et al.* 2000; Lawlor *et al.* 2005), perhaps because of differences in the definition of socioeconomic status.

Primigravidae are at increased risk of pre-eclampsia (Hartikainen *et al.* 1998; Stamilio *et al.* 2000; Duckitt & Harrington 2005), similarly to settings with a high total fertility rate (Conde-Agudelo & Belizan 2000; Lee *et al.* 2000; Anorlu *et al.* 2005). The reason may be exposure to chorionic villi for the first time (Dekker & Sibai 1998). Multiparous women who are impregnated by another spouse have an increased risk (Trupin *et al.* 1996) because

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of loss of protective effect of the first pregnancy. Prime paternity has been suggested (Tubbergen *et al.* 1999) and refuted (Anorlu *et al.* 2005) as a possible cause. Pre-eclampsia occurs commonly in mothers with multiple pregnancies (Ros *et al.* 1998; Maxwell *et al.* 2001), also in low-resource settings (Conde-Agudelo & Belizan 2000; Lee *et al.* 2000; Anorlu *et al.* 2005), because of a large placental mass (Roberts & Gammill 2005) and its increased demand for blood with resultant hypoperfusion and oxidative stress (Redman & Sargent 2005). Women with a history of pre-eclampsia have an increased risk of developing pre-eclampsia in a subsequent pregnancy (Makkonen *et al.* 2000; Dukler *et al.* 2001). Anorlu *et al.* (2005) found a twelvefold risk in women who had pre-eclampsia in a previous pregnancy.

Other risk factors are pre-existing hypertension (Sibai *et al.* 1998; Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005); diabetes mellitus (Ros *et al.* 1998; Conde-Agudelo & Belizan 2000); chronic renal diseases (Lee *et al.* 2000; Roberts & Gammill 2005; Vikse *et al.* 2008); a family history of hypertension (Qiu *et al.* 2003; Sanchez *et al.* 2003; Roes *et al.* 2005; Leeners *et al.* 2006); and obesity (Sibai *et al.* 1997; Mahomed *et al.* 1998; Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005; Leeners *et al.* 2006), although this was not confirmed by Knuist *et al.* (1998). The association of obesity with the risk of pre-eclampsia may be due to the increased availability of free fatty acids and insulin resistance. These alterations in lipid profile may contribute to oxidative stress.

Smoking reduces the risk of pre-eclampsia (Sibai *et al.* 1998; Conde-Agudelo & Belizan 2000), and although the risk falls with the intensity of smoking, perinatal outcomes are not good. Knuist *et al.* (1998) did not find smoking as a risk factor but did not study the effect of passive smoking. Oxidative stress plays a role in the aetiology of pre-eclampsia (Hubel 1999): women with pre-eclampsia have more oxidative stress (Bowen *et al.* 1998) and less plasma vitamin C (Bowen *et al.* 1998; Kharb 2000; Zhang *et al.* 2002) than women with normal pregnancy.

Few studies have been reported in poor resource settings about risk factors for pre-eclampsia. The major objective of this study was to determine the risk factors for pre-eclampsia in Mulago Hospital. This may help in the surveillance of mothers at risk and reduce the maternal morbidity and mortality associated with this condition.

Materials and methods

Study design

This casecontrol study was conducted at Mulago Hospital from 1st May 2008 to 1st May 2009.

Setting

This was in Mulago Hospital antenatal clinics and labour wards. Mulago Hospital is a National Referral Hospital for Uganda, a Teaching Hospital for Makerere University College of Health Sciences and a District Hospital for Kampala City Council. Women with complications in pregnancy, including pre-eclampsia, in Kampala are referred to Mulago Hospital for management. In Uganda, the total fertility rate is 6.7 per woman and about 90% of the women attend antenatal clinic once during pregnancy (Uganda Bureau of Statistics (UBOS) and Macro International Inc (2007). Mulago Hospital delivers 22,000 women annually and about 50 000 women attend antenatal clinic in 1 year.

Study population

The study population was women attending Mulago Hospital antenatal clinics and the labour wards. The women included in the study were aged 15–39 years, lived 15 km or less from hospital, and their gestational ages were 20 weeks or more. Women were excluded if they had serious medical conditions such as cardiac or sickle cell disease, if they had eclampsia or HELLP syndrome, or if they were unable to give dietary information as this study was also evaluating the role of vitamin C as a possible cause of pre-eclampsia.

Sample size calculation

The sample size was calculated using a formula from OpenEpi software package (Dean *et al.* 2009). We assumed the proportion of women in the lowest quartile of plasma vitamin C distribution to be 53% as was found in study by Zhang *et al.* (2002). With a proportion of 53% at 95% confidence interval and power of 80%, we were able to detect an odds ratio of two with a sample 207 cases and 352 controls.

Definition of cases and controls

Pre-eclampsia was defined as described in the International Society for the Study of Hypertension in pregnancy (Davey & Macgillivray 1988). Under this classification, hypertension is defined as a single blood pressure reading of ≥160/110 mmHg or two blood pressure measurements of ≥140/90 mmHg taken 4 h or more apart. The blood pressure was taken with a mercury sphygmomanometer with a woman in a sitting position after 30 min of rest. Significant proteinuria was taken as ≥1 + protein in urine on two random samples of urine taken 4 h or more apart. This was confirmed by a 24 h urine collection of 300 mg of

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protein or more. Urine was collected in women with hypertension for random urine protein estimation and 24 h urine protein determination. Pre-eclampsia was taken as hypertension which developed for the first time in a woman who was 20 weeks of pregnancy or more and had significant proteinuria or, in a woman with known hypertension before pregnancy or at booking and developed significant proteinuria after 20 weeks of pregnancy.

The controls were pregnant women with a normal blood pressure after 20 weeks of gestation with a singleton baby, with no medical diseases such as sickle cell, cardiac or renal disease.

Selection of cases and controls

The cases, who were women with pre-eclampsia as described previously, were selected daily using computer-generated random numbers from the antenatal clinic and the labour ward until the sample size was attained. About six women with pre-eclampsia are admitted to the hospital everyday. After selection of a case, two pregnant women with normal blood pressure as described above were selected the same day from the antenatal clinic using computer-generated random numbers as controls and matched to the cases by age. The women were selected by research assistants who were trained midwives.

Data collection

At recruitment, the women were interviewed about their socio-demographic characteristics, socio and family history and, their past and present obstetric performances. In the socio-demographic characteristics, information was obtained about the age of the mother in completed years, the marital status, and the level of education and information of the mothers' socioeconomic status. Information about socioeconomic status included the type of house the woman stayed in like the floor material, the wall material and the roof material. Information was obtained on household properties like use of electricity, ownership of a fridge, television, radio, bicycle, motorcycle, vehicle, source of water and the type of toilet facility. Each of these factors was given a score which was used as a proxy measure of the women's socioeconomic status as described in the Uganda Demographic and Health Survey (2007).

In the medical factors, information was obtained about history of diabetes mellitus, renal diseases, chronic hypertension and hypertension in the family. In the obstetric factors, information was obtained about the previous pregnancies and their outcomes, the complications during the previous pregnancies and the date of the last normal menstrual period. The information was obtained by interviews and abstraction from the medical charts. Maternal anthropometric measurements of mid-arm circumference were taken during the antenatal period by a well-trained observer. This was used as a measure of the women's pre-pregnancy obesity as was performed in a study in Zimbabwe (Mahomed *et al.* 1998) because women in developing counties like Uganda are unlikely to recall their pre-pregnancy weight. Blood samples were taken for haematological assays, renal and liver function tests, HIV tests and vitamin C assays. The blood samples were taken off before the onset of labour. The mean gestational age at which blood was withdrawn in the cases was 34.24 (SD 4.87) and in the controls was 32.04 (SD 0.48).

Ethical considerations

Ethical approval was obtained from the Mulago Hospital Ethics Committee, the Makerere University School of Medicine Ethics Committee and the National Council for Science and Technology in Uganda. All participants gave a written informed consent.

Data analysis

Data collected were checked, coded and entered using Epi Data 3.1 software with assistance of a statistician. Data were cleaned and transferred to STATA 10 for analysis. The frequency distributions in the maternal socio-demographic, medical and obstetric histories were compared between cases and controls. Categorical variables (e.g. level of education, marital status, socioeconomic status, smoking, alcohol intake and HIV status) between cases and controls were compared using Chi-squared test. Continuous variables (e.g. plasma vitamin C, age of women in completed years and distance from hospital) were categorized and were compared between cases and controls as above.

Bivariate analysis was performed to establish an association between the maternal socio-demographic, medical and obstetric histories and the risk of pre-eclampsia. Variables like age, vitamin C levels and distance from hospital were categorized, and the crude odds ratios with the corresponding 95% confidence intervals were computed.

To determine the factors which were significantly associated with the risk of pre-eclampsia, multivariable analysis was performed using logistic regression methods. Factors had a P value of 0.1 or less at bivariate analysis like plasma vitamin C level, marital status, distance from hospital, alcohol intake, mid-upper arm circumference, history of hypertension, family history of hypertension, and parity and, factors which were known a priori to be

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associated with pre-eclampsia, e.g., educational level, socioeconomics status, smoking, HIV status and history of diabetes, were entered in a first logistic regression model and adjusted. The factors which were not significant at this level were removed using backward elimination until a stable model was obtained. Age was not included in the model because it had been matched. The results are presented as adjusted odds ratios with the corresponding 95% confidence intervals.

Results

The background factors of the respondents are shown in Table 1. The minimum age of the women with pre-eclampsia was 15 years and the maximum age was 39 years with a mean of 24.07 (SD 5.15). The minimum age of the controls was 16 years, and the maximum age was 36 years with the mean of 23.7 (SD 4.34). Women with pre-eclampsia were more likely to be single, to live further away from the hospital, to consume alcohol and to have a deficient vitamin C status than women with normal pregnancy.

The medical and obstetric factors in women with pre-eclampsia and women with normal pregnancy are shown in Table 2. Women who had chronic hypertension, who had a family history of hypertension, were primigravidae and who were gravid five or more were more likely to develop pre-eclampsia.

Table 1 The background factors of women with pre-eclampsia and women with normal pregnancy

Characteristic	Pre-eclampsia *n* (%)	Normal pregnancy *n* (%)	Crude Odds Ratio	*P*-value
Plasma Vitamin C*				
≤1.1 × 10^3 μg/l	39 (18.8)	34 (9.7)	2.34 (1.32–4.19)	0.043
1.1–2.0 × 10^3 μg/l	117 (56.5)	214 (60.8)	1.12 (0.74–1.67)	
>2.0 × 10^3 μg/l	51 (24.8)	104 (29.5)	1	
Age				
≤19	44 (21.3)	68 (19.3)	1.27 (0.78–2.02)	0.33
20–24	80 (38.7)	157 (44.6)	1	
25–29	46 (22.2)	81 (23.0)	1.11 (0.71–1.71)	
≥30	37 (17.9)	46 (13.1)	1.58 (0.94–2.62)	
Education level				
Primary or none	83 (40.1)	119 (33.8)	1.31 (0.91–1.86)	0.135
Secondary or above	124 (59.9)	233 (66.2)	1	
Marital status*				
Single	44 (21.3)	49 (13.9)	1.67 (1.06–2.62)	0.025
Married	163 (78.7)	303 (86.1)	1	
Distance from Mulago*				
5 km or less	97 (46.9)	215 (61.1)	1	0.001
More than 5 km	110 (53.1)	137 (39.9)	1.78 (1.26–2.52)	
Socioeconomic status				
Low	69 (33.3)	100 (28.4)	1.08 (0.71–1.66)	0.18
Middle income	65 (31.4)	137 (38.9)	0.74 (0.49–1.13)	
High	73 (35.3)	115 (32.7)	1	
Smoking status				
Yes	03 (1.2)	03 (0.9)	1	0.6
No	204 (98.8)	349 (99.1)	0.59 (0.12–2.93)	
Alcohol intake*				
Yes	31 (15.0)	32 (9.1)	1.8 (1.03–2.97)	0.08
No	176 (85.0)	320 (90.9)	1	
MUAC (cm)*				
≤23	05 (2.56)	12 (3.5)	1	<0.001
24–25	10 (5.13)	35 (10.2)	0.66 (0.19–2.41)	
26–27	08 (4.10)	67 (19.6)	0.29 (0.08–1.02)	
≥28	172 (88.2)	228 (66.7)	1.81 (0.63–5.2)	
HIV status				
Positive	18 (8.7)	33 (9.4)	0.92 (0.48–1.74)	0.8
Negative	189 (91.3)	319 (90.6)	1	

MUAC, mid-upper arm circumference.
*$P < 0.1$

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Table 2 Medical and obstetric factors in women with pre-eclampsia and women with normal pregnancy

Characteristic	Cases *n* (%)	Controls *n* (%)	Crude Odds Ratio	*P*-value
History of diabetes				
Yes	5 (2.4)	4 (1.1)	2.15 (0.5–9.65)	0.2
No	202 (97.6)	348 (98.9)	1	
History of hypertension*				
Yes	22 (10.6)	17 (4.8)	2.3 (1.2–4.5)	0.009
No	185 (89.4)	335 (95.2)	1	
Family history hypertension*				
Yes	101 (48.8)	106 (30.1)	2.2 (1.6–3.2)	<0.001
No	106 (51.2)	246 (69.9)	1	
Parity*				
Primigravidae	112 (54.1)	148 (42.1)	2.1 (1.4–3.0)	<0.001
Gravida 2–4	68 (32.9)	186 (52.8)	1	
Gravida 5+	27 (13.0)	18 (05.1)	4.1 (2.1–7.9)	

*$P < 0.1$.

Factors that were independently associated with the risk of pre-eclampsia are shown in Table 3. Women who had low plasma vitamin C were 3.2 times as likely to develop pre-eclampsia as women with normal or high vitamin C levels. Women who had primary level of education or no education at all were 1.7 times more likely to develop pre-eclampsia compared to women who had secondary level of education or higher. Women who had chronic hypertension were 2.3 times more likely to develop pre-eclampsia compared to women who did not have chronic hypertension. Similarly, women who had a family history of hypertension were 2.2 times more likely to develop pre-eclampsia as women who did not. Lastly, primigravidae were three times more likely to develop pre-eclampsia than women who were gravida 2–4, whereas women who were gravid five or more were four times more likely to develop pre-eclampsia than women who were gravida 2–4.

Table 3 The factors independently associated with pre-eclampsia

Characteristic	Adjusted Odds Ratio
Vitamin C (μg/l)	
$\leq 1.1 \times 10^3$	3.19 (1.54–6.61)
0.11×10^3	1.23 (0.80–1.88)
$>2.0 \times 10^3$	1
Education status	
Primary or none	1.67 (1.12–2.48)
Secondary or above	1
Distance to Mulago	
5 km or less	1
More than 5 km	2.03 (1.39–2.96)
Alcohol consumption	
Yes	1.65 (0.93–2.94)
No	1
History of hypertension	
Yes	2.29 (1.12–4.66)
No	1
Hypertension in family	
Yes	2.25 (1.53–3.31)
No	1
Parity	
Primegravidae	2.76 (1.84–4.15)
Gravida 2–4	1
Gravida 5+	3.71 (1.84–7.45)

Discussion

In this paper, we examined the risk factors for pre-eclampsia in Uganda and found that the predictors for pre-eclampsia were similar to what has been described in other low-resource and high-resource countries. Women who had primary level of education or no education at all were two times likely to develop pre-eclampsia as women who had secondary or higher level of education. Other researchers in low-resource settings (Mahomed *et al.* 1998; Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005) have not found this association between the level of education and risk of developing pre-eclampsia. However, researchers from high-resource countries (Hartikainen *et al.* 1998; Ceron-Mireles *et al.* 2001) agree with this finding while others do not (Sibai *et al.* 1995). Though, education level was used as a measure of the socioeconomic status. Other studies (Haelterman *et al.* 2003; Silva *et al.* 2008), but not ours, found low socioeconomic status associated with pre-eclampsia. The association of low socioeconomic status and pre-eclampsia is unclear but could be due to poor nutrition and stressful life conditions which may lead to over reactivation of the sympathetic nervous system (Leeners *et al.* 2007).

Primiparity was associated with a triple risk of developing pre-eclampsia after controlling for confounders. This is similar what has been found in other studies in

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both low- (Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005) and high-resource countries (Hartikainen *et al.* 1998; Stamilio *et al.* 2000). This is because of exposure to chorionic villi for the first time, which is foetal in origin and may be due to immunological incompetence seen in first pregnancy (Dekker & Sibai 1998). Pre-eclampsia is a disease of the first pregnancy. Even an abortion in a previous pregnancy has been found to be protective (Sibai *et al.* 1995). Women who were gravida five or more were four times more likely to develop pre-eclampsia compared to women who were gravida 2–4. This is similar to what was found in Jordan (Abu-Heija & Chalabi 1997), but differed from what was found in Nigeria (Anorlu *et al.* 2005) and Latin America (Conde-Agudelo & Belizan 2000). Women who were gravida five or more were probably older and more likely to develop essential hypertension and pre-eclampsia.

Women who had chronic hypertension were 2.3 times more likely to develop pre-eclampsia after controlling for confounders. This was similar to what was found by other researchers in low- (Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005) and high-resources settings (Sibai *et al.* 1998; Sibai 2002), perhaps because of insulin resistance. It activates the sympathetic nervous system. It may also activate the tubular sodium re-absorption and aggravate the cytokine-mediated oxidative stress (Dekker & Sibai 1998). Pre-eclampsia develops early in women with chronic hypertension and is severe, and the women are at increased risk of adverse maternal and perinatal outcomes (Sibai *et al.* 1998). Similarly, women with a family history of hypertension were 2.2 times more likely to develop pre-eclampsia after controlling for confounders. This is similar to what has been found in other studies in low-resource settings (Conde-Agudelo & Belizan 2000; Anorlu *et al.* 2005) and is in agreement with what was found in high-resource countries (Qiu *et al.* 2003; Roes *et al.* 2005).

Obesity was not found to be a risk factor for pre-eclampsia in this study. However, others (Mahomed *et al.* 1998; Conde-Agudelo & Belizan 2000; Lee *et al.* 2000) in low-resource settings have found an increased risk with obesity as well as other researchers in high-resource countries (Hartikainen *et al.* 1998; Ros *et al.* 1998).The association of obesity with pre-eclampsia may be due to hyperlipidaemia with abundance of low-density lipoproteins which may predispose the women to oxidative stress and endothelial cell dysfunction (Hubel 1999).

Women who had low plasma vitamin C level were 2.9 times more likely to develop pre-eclampsia. Poston & Raijmakers (2004) show that oxidative stress plays a role in the aetiology of pre-eclampsia. Vitamin C is the first line in defence against oxidative stress and is consumed in the process. It also recycles reduced vitamin E and glutathione which are other antioxidants and this consumes it further. While initial studies of supplementation with vitamin C and E showed a reduction in oxidative stress and pre-eclampsia (Chappell *et al.* 1999, 2002), subsequent studies have failed to do so (Rumbold *et al.* 2006; Villar *et al.* 2009). This could have been because the populations selected were from high-resource settings with good nutritional status or were a heterogeneous group with different risks and there could have been some benefit in some groups. Women who lived more than 5 km from Mulago hospital were two times more likely to develop pre-eclampsia than women who lived close by. It is probable that women with pre-eclampsia were more likely to be referred to Mulago hospital and hence came from health centres which were further from hospital than women with normal pregnancy.

Alcohol consumption during pregnancy was not associated with pre-eclampsia in this study. Other investigators (Salihu *et al.* 2011) have found a protective effect of prenatal alcohol consumption with pre-eclampsia, although the other pregnancy outcomes were not good. The explanation of this protective effect on alcohol consumption is not clear but could be due to recall bias in the comparison group or deliberate under reporting.

Limitations

This study was conducted in a referral hospital, and the women seen at this hospital may not be representative of the ones seen in the community and this could bring in a selection bias; hence, there was a restriction of distance. Women with eclampsia and HELLP syndrome were excluded and this could have affected the representativeness of the cases.

Conclusion

The risk factors identified are the known risk factors and similar to what has been found elsewhere. Health workers need to identify women at risk of developing pre-eclampsia and counsel them. Pregnant women at risk should be monitored and managed appropriately to prevent the maternal and neonatal morbidity and mortality associated with this condition.

Acknowledgements

We thank the African Population and Health Centre (APHRC), Mulago Hospital management and Makerere University for the support.

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