Original Research Article

Clinical Status of Pregnancy-induced Hypertension and Pre-eclampsia among Sudanese Women

Short Title

(Status of Gestational Hypertensive Disorders in Sudan)

1

Abstract

Objective: The present study has been conducted with the aim of determining the clinical status of gestational hypertensive disorders in Sudan.

Methods: An analytical case-control, comparative and descriptive cross-sectional, hospital-based study was conducted at Omdurman Maternity Hospital (OMH). It included 228 cases of gestational hypertensive disorders. Data were collected through interviews, questionnaire, and , admission records and analyzed statistically.

Results: The clinical status of pregnancy-induced hypertension and pre-eclampsia among Sudanese women has been estimated. Spontaneous pregnancies were 94.6% of the cases. Multigravida were 50.4% of pregnant Sudanese women presenting at OMH, 20.7% of them had a history of gestational hypertensive disorders and 18.1% had a history of miscarriage. Among the patients admitted with gestational hypertensive disorders 75% developed preeclampsia, 91% has shown non-syndromic complications and 52.2% were asymptomatic.

Conclusion: Maternal age between 18-40 years, nulliparous primigravida or multigravida with long latency period and history of miscarriage are the commonest risk factors of

hypertension complication during pregnancy, including preeclampsia, in Sudan. Significantly lower serum calcium and/or higher serum magnesium are associated with preeclampsia, syndromic HELLP is a rare association. Patient awareness is critical for early detection and prevention of disease progression.

Keywords: PIH, HELLP, preeclampsia, gestational electrolytes, gestational hypertension.

1. Introduction:

Pregnancy is a reproductive process in which one growing fetus, or more, develops inside the maternal uterus [1]. Normal uneventful pregnancy describes the normal physiological pattern of events in which the mother remains fit and well throughout the gestation period [2].

Physiological changes occur in a woman's body systems to varying degrees, and intensities. These include the cardiovascular, respiratory, genitourinary, and musculoskeletal systems [3].

Hypertensive disorders remain a major global health issue for women and their feti [4]. The classification of hypertensive disorders mainly depends on the time of the onset of the disorder, whether it occurs before or after 20 weeks of gestation [5]. The presence of proteinuria is the determining factor of preeclampsia [6]. Hypertensive disorders in pregnancy is directly related to maternal and fetal mortality and morbidity [7]. They are clinically defined as a change in blood pressure recorded at two different occasions; systolic blood pressure at 140 mmHg or more [8]; diastolic blood pressure at 90 mmHg or more [9]. This elevation in blood pressure is mainly responsible for the adverse

maternal and fetal outcomes [7]. However, with the appropriate prenatal care and observation of women for signs of preeclampsia, instant delivery can resolve this disorder and reduce the number and the extent of poor outcomes [10]. Therefore, these adverse outcomes of serious materno-fetal morbidity and mortality are avoidable [11].

The pregnancy-induced hypertension (PIH) and preeclampsia both cause an increase in the blood pressure which occurs after 20 weeks of gestation. In preeclampsia there is a systemic involvement and proteinuria which can result in visual, renal, and even liver problems [12]. Preeclampsia is more serious than gestational hypertension or pregnancy induced hypertension and is responsible for maternal and prenatal mortality [13]. Gestational hypertension has no systemic features as seen in preeclampsia [14], however, it also needs appropriate management during pregnancy and labor [15].

Chronic hypertension is hypertension diagnosed before 20 weeks of gestation or before pregnancy [16]. Chronic hypertensive subjects have a higher risk of developing superimposed preeclampsia during pregnancy [17]. Women with superimposed preeclampsia have similar neonatal outcomes but more maternal complications than women with preeclampsia [18].

The clinical manifestations of preeclampsia vary from patient to patient and may be symptomatic or asymptomatic [19]. The most characteristic symptoms are headache [20], and fever with or without visual disturbance [21]. Additional symptoms can be right upper quadrant pain, due to liver ischemia, and lower abdominal pain if placental abruption, occurs [22]. Convulsion can occur when preeclampsia is complicated and develops to eclampsia when vascular dysfunction affects vasculature of the brain [23].

Another complication of preeclampsia is syndromic HELLP which stands for hemolysis, elevated liver enzymes, and low platelet count [23].

Maternal urine examination for the protein spots (using urinary dip stick for protein) confirms the diagnosis with the elevation in measurement of both systolic and diastolic blood pressure [24][25]. Monitoring of women with pre-eclampsia includes the assessment of hematological parameters, hemoglobin and platelets, to detect exacerbation of the disease into the more serious eclampsia or HELLP syndrome [26]. Biochemical tests of hepatic and renal function assess the complexity of the case [27], disease progressions and early diagnosis of deterioration in the maternal clinical situation [28].

The status of gestational hypertensive disorders in Sudan is not reported. The present study has been conducted with the aim of determining the clinical status of gestational hypertensive disorders in Sudan.

2. Methods:

2.1. Ethical considerations

The study proposal was approved by the Department Pharmacology, Faculty of Pharmacy, Omdurman Islamic University, Sudan. The ethical clearance for the research project has been issued by the Ethics Committee of the Ministry of Health, Khartoum State, Sudan.

A final permission, prior to starting the study, has been obtained from the Head Consultant of Research Authorities and Ethical Committee at Omdurman Maternity Hospital.

2.2. Study design and study area

Analytical, case-control, comparative study and descriptive, cross-sectional, hospital-based study were conducted at Omdurman Maternity Hospital.

2.3. Sample size estimation

The sample size was calculated using (Raosoft Software) computer program at confident level (95%) for cross sectional study. Unmatched case control sample size calculator, for case control study, were used and the number of patients with preeclampsia in OMH during 2015 was obtained from the hospital Statistics Record.

2.4. Study- patients` criteria

2.4.1. Inclusion criteria

All clinically diagnosed cases of eclampsia, preeclampsia, HELLP, and post-partum condition of eclampsia, preeclampsia and HELLP.

2.4.2. Exclusion criteria

All pregnant women clinically diagnosed with nephritic syndrome or any deterioration in renal function, pregnant women with chronic hypertension and on antihypertensive therapy before gestation and all pregnant women with diabetes mellitus or autoimmune diseases.

2.5. Study duration

The study was conducted during the period from June 2016 to October 2017.

2.6. Data collection techniques and design

Data were collected by approaching patients with personal interviews, telephone interviews, and face to face self-administrated questionnaires. Clinical records of the

direct observation of the Senior Attendant Registrar at the time of admission were also collected. Data Collection Forms were designed pertinent to the objectives of the study.

2.7. Sources of other data

A. The patients` clinical history taken by Senior Attendant Registrar at patient admission to hospital.
B. Direct registrar interview.
C. Patients` interview.
D. Laboratory results.

2.8. Statistical methods

2.8.1. Preparation of data for statistical analysis

Raw data collection tools were retained and kept as original data records. Study logs were established and contained date of data receipt, investigation type, and data serial number. Data were entered to IBM SPSS software program base. Data cleaning was conducted including logic check, correction, and clarification.

2.8.2. Statistical analysis

Data were analyzed by means of Chi-square Test (Not used for statistical analysis) student t-test, One-way Analysis of Variants and Chen's D to compare the mean differences for various results. Differences were considered to be significant at $P \leq 0.05$.

3. Results:

3.1. Demographic characteristics of the study population

The majority of the participants were middle-aged in both groups (98.6 and 86.4%); non-employed (97.3 and 92.5%); with active lifestyle (91.9 and 89%); primary school educational level (36.5 and 28.1%); and residents to Kordofan (24.3 and 21.5). These results are shown in Table 1.

Table1: Demographic characteristics of the study population

Patterns	**Controls** (n=74)	**Patients** (n= 228)	**P-value**
	Frequency/ percentage		
1. Age			
< 18	1(1.4)	13(7.5)	**0.96**
18 – 40	73(98.6)	197(86.4)	
>40 Year	0(0.0)	8(3.5)	
2. Occupation			
House keeper	72(97.3)	211(92.5)	**0.73**
employees	2(2.7)	10(4.4)	
3. Lifestyle			
Sedentary	6(8.1)	18(7.9)	**0.41**
active	68(91.9)	203(89)	
4. Educational Level			
Illiterate	11(14.9)	39(17.1)	**0.33**
Primary school	27(36.5)	64(28.1)	
Secondary school	19(25.7)	62(27.2)	
University graduate	16(21.6)	52(22.8)	
Postgraduate certificate	1(1.4)	2(0.9)	

5. Residence			
Khartoum	13(17.6)	17(7.5)	**0.17**
Al-gazira	10(13.5)	32(14)	
Northren	6(8.1)	15(6.6)	
River Nile	8(10.8)	7(3.1)	
Blue Nile	2(2.7)	1(0.4)	
White Nile	7(9.5)	22(9.6)	
Kurdofan	18(24.3)	49(21.5)	
Al-qadarif	2(2.7)	2(0.9)	
Kassala	0(0.0)	6(2.6)	
Durfour	6(8.1)	11(4.8)	
Republic	2(2.7)	11(4.8)	
6. Father's job			
Private worker	69(93.2)	194(85.1)	**0.98**
Governmental	4(5.4)	16(7)	
Education	1(1.4)	3(1.3)	

3.2. Fertilization

In 94.6 % of the study population pregnancy was spontaneous, see Fig. 1.

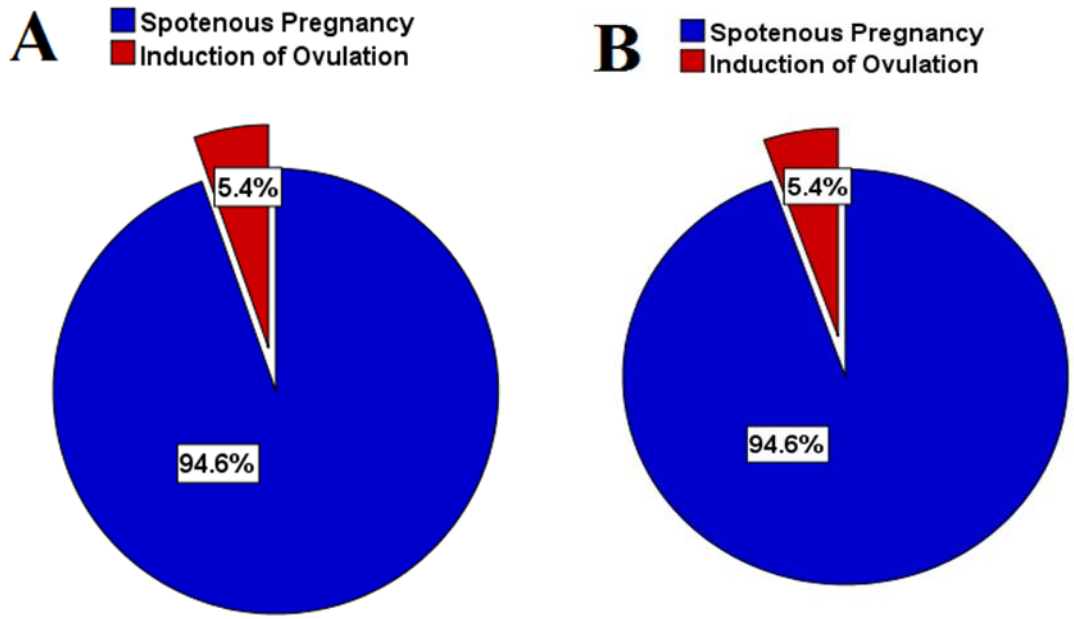

Fig. 1: The frequency distribution percentage of pregnancy status among the pregnant Sudanese women attending OMH. Data presented for patients, group (**A**), and controls, group (**B**).

3.3. The gravidity of current pregnancy

Almost half of the participants were primigravida. This is depicted in Fig. 2.

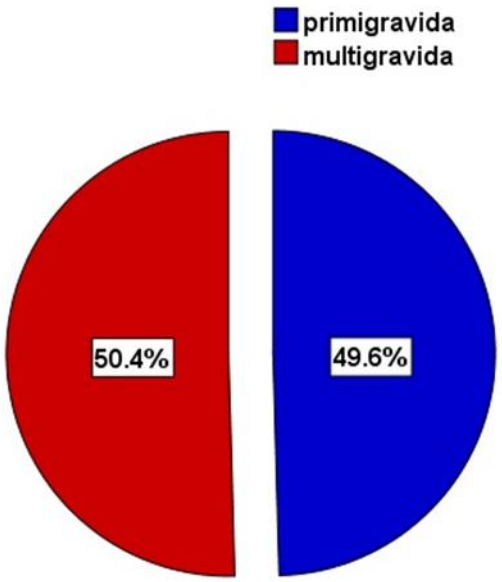

Fig. 2: The frequency distribution percentage of primigravida among pregnant Sudanese women presenting at Outpatient Clinic at Omdurman Maternity Hospital.

3.4. Maternal obstetrics history in multigravida pregnant patients

Among multigravida patients, history of eclampsia, preeclampsia, and gestational hypertension mounted up to (20%); history of miscarriage was (18.1%); history of multiple pregnancy was (1.6%); incidence of hypothyroidism was (1.1%); age range 18-40 was (1.6%), see Fig.3

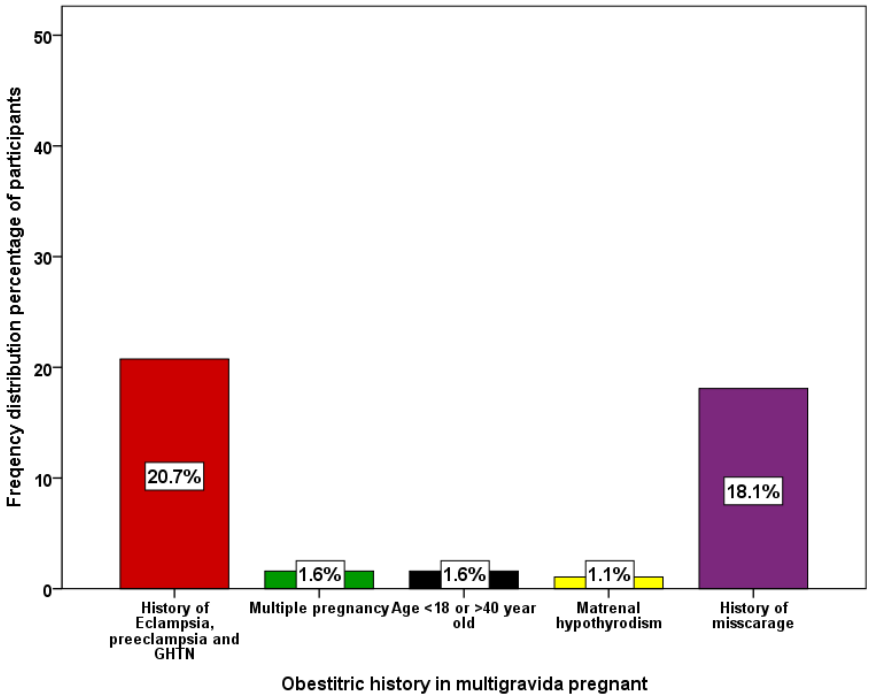

Fig. 3: The frequency distribution percentage of pregnant Sudanese women at Outpatient Clinic at OMH according to obstetrical history.

3.5. Eclamptic diseases classes

Based-on disease features, the types of gestational hypertension complications are shown in Fig. 4.

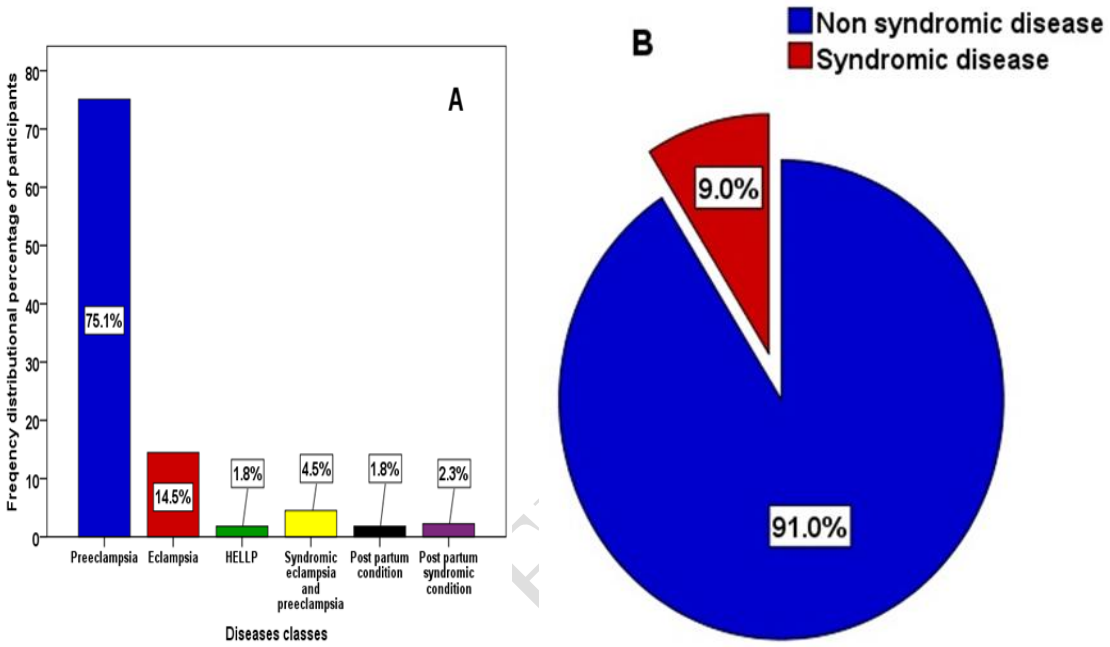

Fig. 4: The frequency distribution percentage of patients at Outpatient Clinic at OMH according to the type of gestational hypertension complication based-on disease features (**A**), and appearance of HELLP syndrome (**B**).

3.6. Clinical features and the types of symptoms

Regarding the presenting symptoms, (47.8%) were asymptomatic. Symptomatic cases had symptoms' types presented in Fig. 5

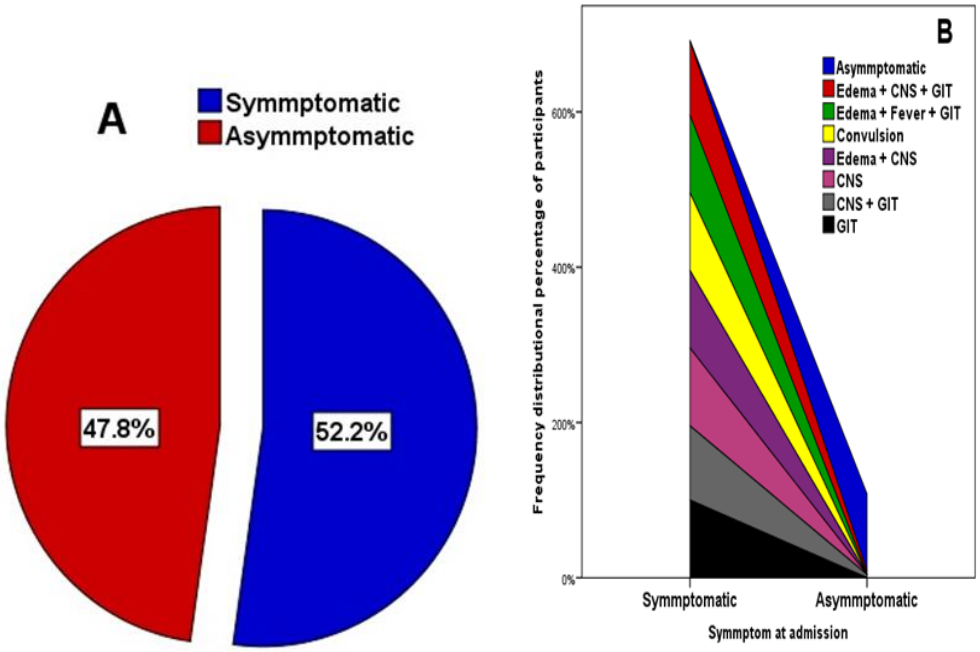

Fig. 5: The frequency distribution percentage of presenting symptoms among patients, (**A**), and type of symptoms, (**B**), at Outpatient Clinic at Omdurman Maternity Hospital.

3.7. Clinical laboratory results

The mean serum calcium was decreased for normotensive pregnant women. The serum magnesium was increased among preeclamptic pregnant women comparable to the control group as shown in table 2.

Table 2: Determinations of electrolytes including mean serum calcium and magnesium in patients of preeclampsia, and controls. The value of [Chen's D Calcium = 2.41], and [Chen's D Magnesium =1.48].

Electrolytes [g/dl]	**control** [n=74] [Mean ± SD]	**patient** [n=228]	**p-value**
Serum calcium	9.30 ± 0.56	7.97 ± 0.74	> 0.0001
Serum magnesium	1.86 ± 0.13	2.56 ± 0.96	> 0.0001

*; $P \leq 0.05$, **; $P \leq 0.01$, ***; $P \leq 0.001$

Chen's D; small ≤ 0.20; medium ≤ 0.50; large ≤ 0.80

4. Discussion:

Clinical status of pregnancy-induced hypertension and pre-eclampsia among Sudanese women has been estimated by the present study. Spontaneous pregnancies were 94.6% while induced pregnancies were 5.4% of the cases. Multigravida were 50.4% while primigravida consituted 49.65 of pregnant Sudanese women presenting at OMH. Of the former 20.7% had history of gestational hypertensive disorders and 18.1% had history of miscarriage. Among the patients admitted with gestational hypertensive disorders 75% developed preeclampsia; 14.4% developed eclampsia; 1.8% developed HELLP; 4.5, 1.8 and 2.3% developed syndromic eclampsia or preeclampsia, postpartum conditions, or postpartum syndromic conditions respectively; 9% showed syndromic complications while 91% has shown non-syndromic complications; 47.8% showed symptoms and 52.2% were asymptomatic. Symptoms included variable combinations of convulsions and/or other central nervous system symptoms, edema, and/or gastrointestinal disturbances.

The estimation of sample size using a computerized software and proper selection criteria has given valid evidence-based findings. This is shown in the normal statistic distribution of hypertensive and normotensive pregnant participants in the present investigation.

It has been determined that the majority of PIH patients (86.4%) were in age category of 18- 40 years. This is justified by the fact that this is the age with high potential for conception in females at child- bearing age.

It has, presently, been determined that a large cohorts of controls, (24.3%) and of PIH patients, (21.5%), are from the rural area of Kurdofan; that most are illiterate, (17.1%); or primary school graduates, (28.1%); and that most are from low socio-economic background, (85.1%). These estimates can be attributed to low awareness about the early warning symptoms such as tachycardia, and oliguria. This is the consistent with ElFarra et. al., [29], who concluded that patients` awareness about the early warning symptoms can identify pregnant hypertensive women at high risk and allow timely diagnostic and therapeutic interventions. Moreover, studies have shown that up to 77 % of women affected with preeclampsia lack knowledge about preeclampsia, and therefore cannot take preventive measures [30].

Referral from rural areas of Kurdofan of PIH cases and normal control signals scarsity of maternity health care services and absence of the pregnancy follow up and antenatal visits rather than genetic predisposition to the disease, this in the line with the Shaker et. al., [31], who concluded that the frequency of antenatal care visits during pregnancy has a significant effect on maternal and fetal outcomes in patients with PIH. Additionally, the maternal inflammatory marker investigation which, currently, is not supported in Kurdofan rural areas may have affected the referral decision. Wright et. al., [32], reported that early maternal inflammatory marker investigation assessed the diagnosis of disease and early interventions. Prevalence of low socio-economic status among the present patients contributes to reluctancy to approach maternity care centers to avoid antenatal visits expenses, which contributes to poor outcomes. This is consistent with Wright et. al., [33], who studied the cost- effectiveness in the management of preeclampsia complications.

The present study reveals that 20.7% of multigravida patients with PIH had previous history of preeclampsia. This can be taken as an evidence that the incidence of pregnancy-induced hypertension complications is heightened with progress of age and gravidity. This is logical although it contradicts an earlier report by Raymer et. al., [34]. It has been shown that multigravida with bad obstetrics history, (18.1%) are at increased risk for developing preeclampsia. The finding is consistent with a previous report of the risk factors associated with preeclampsia [35]. Never-the-less, the finding that a previous history of miscarriage increases the risk of present miscarriage as a complication of preeclampsia agrees with earlier observations [36].

The present finding that half of the reeclapmptic patients were primigravida, and the other half were multigravida, suggests the nature of the pathogenesis of the disease, and the response of maternal immunity to hemi-allogeneic placental cells, and that the co-expressing of maternal and paternal genomes in the same place contributes to the stimulation of maternal immunity. This is in the line with the findings of a previous report [37], that concluded that the immunological alterations were suggested to be a major etiology of placentation disease and therefore preeclampsia.

It has been estimated that the better half of patients in the current investigation, (52.2%), had a characteristic presentation of CNS or GIT symptoms and generalized edema. On the other hand, the second half (47.8% of patients) went naïve for routine follow up at antenatal care units and were referred to this specialized hospital for further care and investigations wherein the diagnosis of preeclampsia or other disease complications has been confirmed. These findings are consistent with an earlier report [38].

The present estimations of the significant differences in the serum calcium and magnesium between patients in one hand, and controls in the other, suggests that these divalent cations may play a role in the pathogenesis of preeclampsia. This is consistent with the estimations by previous investigators, [39], for serum calcium levels, and, [40], for serum magnesium levels.

5. Conclusion:

Status of pregnancy-induced hypertension and and its complications among Sudanese women is determined. Maternal age between 18-40 years, nulliparous primigravida or multigravida with long latency period, and history of miscarriage are the commonest risk factors of hypertension complication during pregnancy, including preeclampsia, in Sudan; significantly lower serum calcium and/or higher serum magnesium are associated with preeclampsia; syndromic HELLP is a rare association. Patient awareness is critical for early detection and prevention of disease progression. We recommend dissemination of antenatal healthcare facilities in rural areas of the country to contribute to early detection, and prevention of poor natal outcomes.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

References

[1] Lin LH, Maestá I, Braga A, Sun SY, Fushida K, Francisco RPV, et al. Multiple pregnancies with complete mole and coexisting normal fetus in North and South America: A retrospective multicenter cohort and literature review. Gynecol Oncol 2017;145:88–95.

[2] Foo FL, Collins A, McEniery CM, Bennett PR, Wilkinson IB, Lees CC. Preconception and early pregnancy maternal haemodynamic changes in healthy women in relation to pregnancy viability. Hum Reprod 2017;32:985–92.

[3] Cakmak B, Ribeiro AP, Inanir A. Postural balance and the risk of falling during pregnancy. J Matern Neonatal Med 2016;29:1623–5.

[4] Stuart JJ. Preeclampsia and Vascular Function : A Window to Future Cardiovascular Disease Risk. J Women Heal 2016;25:284–91.

[5] Gupta N, Gupta T, Asthana D. Prediction of Preeclampsia in Early Pregnancy by Estimating the Spot Urinary Albumin/Creatinine Ratio. J Obstet Gynecol India 2017;67:258–62.

[6] Sachan R1, Patel ML2, Sachan P3, Shyam R4, Verma P1 DS. Diagnostic accuracy of spot albumin creatinine ratio and its association with fetomaternal outcome in preeclampsia and eclampsia.No Title. Niger Med J 2017;58:58–62.

[7] Raio L, Bolla D, Baumann M. Hypertension in pregnancy. Curr Opin Cardiol 2015;30:411–5.

[8] Perry H, Sheehan E, Thilaganathan B, Khalil A. Home blood-pressure monitoring

in a hypertensive pregnant population. Ultrasound Obstet Gynecol 2018;51:524–30.

[9] Kintiraki E1, Papakatsika S2, Kotronis G2, Goulis DG1 KV. Pregnancy-Induced hypertension. Hormones (Athens) 2015;14:211–23.

[10] Duffy JY, Hameed AB. Cardiovascular disease screening. Semin Perinatol 2015;39:264–7.

[11] Hodgins S. Pre-eclampsia as Underlying Cause for Perinatal Deaths: Time for Action. Glob Heal Sci Pract 2015;3:525–7.

[12] Robbins MS, Farmakidis C, Dayal AK, Lipton RB. Acute headache diagnosis in pregnant women. Neurology 2015;85:1024–30.

[13] Gh BFNM. Systems Biology in Reproductive Medicine Application of metabolomics to preeclampsia diagnosis. Syst Biol Reprod Med 2018;64:1–16.

[14] Schlembach D, Homuth V, Dechend R. Treating Hypertension in Pregnancy. Curr Hypertens Rep 2015;17:1–7.

[15] Hasegawa J, Ikeda T, Sekizawa A, Tanaka H, Nakata M, Murakoshi T, et al. Maternal Death Due to Stroke Associated With Pregnancy-Induced Hypertension. Circ J 2015;79:1835–40.

[16] Luizon MR, Pereira DA, Sandrim VC. Pharmacogenomics of Hypertension and Preeclampsia : Focus on Gene – Gene Interactions 2018;9:1–6.

[17] Costa RA, Hoshida MS, Alves EA, Zugaib M, Francisco RPV. Preeclampsia and superimposed preeclampsia: The same disease? The role of angiogenic

biomarkers. Hypertens Pregnancy 2016;35:139–49.

[18] Valent AM, Defranco EA, Allison A, Salem A, Klarquist L, Gonzales K, et al. Expectant management of mild preeclampsia versus superimposed preeclampsia up to. Am J Obstet Gynecol 2015;212:1–8.

[19] Kuessel L, Zeisler H, Ristl R, Binder J, Pateisky P, Schmid M, et al. The usefulness of CYFRA 21-1 to diagnose and predict preeclampsia: A nested case-control study. BMC Pregnancy Childbirth 2016;16:1–11.

[20] Tanaka K, Matsushima M, Matsuzawa Y, Wachi Y, Izawa T, Sakai K, et al. Antepartum reversible cerebral vasoconstriction syndrome with pre-eclampsia and reversible posterior leukoencephalopathy. J Obstet Gynaecol Res 2015;41:1843–7.

[21] Shainker SA, Edlow JA, O'Brien K. Cerebrovascular emergencies in pregnancy. Best Pract Res Clin Obstet Gynaecol 2015;29:721–31.

[22] Sperling JD, Dahlke JD, Huber WJ. The Role of Headache in the Classification and Management of Hypertensive Disorders in Pregnancy. Obestetrics Gynecol 2015;126:297–302.

[23] Ditisheim A, Wuerzner G, Ponte B, Vial Y, Irion O, Burnier M, et al. Prevalence of Hypertensive Phenotypes after Preeclampsia:A Prospective Cohort Study. Hypertension 2018;71:103–9.

[24] Nielsen LH, Jensen BL, Fuglsang J, Andersen LLT, Jensen DM, Jørgensen JS, et al. Urine albumin is a superior predictor of preeclampsia compared to urine plasminogen in type I diabetes patients. J Am Soc Hypertens 2018;12:97–107.

[25] Sarno L, Maruotti GM, Saccone G, Sirico A, Mazzarelli LL, Martinelli P. Pregnancy outcome in proteinuria-onset and hypertension-onset preeclampsia. Hypertens Pregnancy 2015;34:284–90.

[26] Gutierrez-aguirre CH, García-lozano JA, Rubén O, Iglesias-benavides JL, Cantú-OG, González-llano O, et al. Comparative analysis of iron status and other hematological parameters in preeclampsia. Hematol (Ameterdam, Netherlands) 2017;22:36–40.

[27] Dacaj R, Izetbegovic S, Stojkanovic G, Dresha S. Elevated Liver Enzymes in Cases of Preeclampsia and Intrauterine Growth Restriction. Med Arch 2016;70:44–7.

[28] Vilchez G, Lagos M, Kumar K, Argoti P. Is mean platelet volume a better biomarker in pre-eclampsia? J Obstet Gynaecol Res 2017;43:982–90.

[29] ElFarra J, Bean C, Martin JN. Management of Hypertensive Crisis for the Obstetrician/Gynecologist. Obstet Gynecol Clin North Am 2016;43:623–37.he Obstetrician/Gynecologist. Obstet Gynecol Clin North Am 2016;43:623–37.

[30] Vata PK, Chauhan NM, Nallathambi A, Hussein F. Assessment of prevalence of preeclampsia from Dilla region of Ethiopia. BMC Res Notes 2015;8:4–9.

[31] Mohamed Shaker El-Sayed Azzaz A, Martï¿½nez-Maestre MA, Torrejï¿½n-Cardoso R. Antenatal care visits during pregnancy and their effect on maternal and fetal outcomes in pre-eclamptic patients. J Obstet Gynaecol Res 2016;42:1102–10.

[32] Wright E, Audette MC, Ye XY, Keating S, Hoffman B, Lye SJ, et al. Maternal

vascular malperfusion and adverse perinatal outcomes in low-risk nulliparous women. Peganacy Hypertens 2018:183–8.

[33] Wright E1, Audette MC, Ye XY, Keating S, Hoffman B, Lye SJ, Shah PS KJ. Maternal Vascular Malperfusion and Adverse Perinatal Outcomes in Low-Risk Nulliparous Women. Obestetrics Gynecol 2017;130:1112–20.

[34] Rymer-Haskel N, Schushan-Eisen I, Hass Y, Rahav R, Maayan-Metzger A, Hendler I. Characteristics and severity of preeclampsia in young and elderly gravidas with hypertensive disease. Eur J Obstet Gynecol Reprod Biol 2018;228:120–5.

[35] Shen M, Smith GN, Rodger M, White RR, Walker MC, WuWen S. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS One 2017;12:1–13.

[36] Magee LA, Pels A, Helewa M, Rey E, Von Dadelszen P, Audibert F, et al. The hypertensive disorders of pregnancy (29.3). Best Pract Res Clin Obstet Gynaecol 2015;29:643–57.

[37] Nair RR, Verma P, Singh K. Immune-endocrine crosstalk during pregnancy. Gen Comp Endocrinol 2017;242:18–23.

[38] Jodkowska A, Martynowicz H, Kaczmarek-wdowiak B, Mazur G. Thrombocytopenia in pregnancy – pathogenesis and diagnostic approach Małopłytkowość u kobiet ciężarnych – patogeneza i różnicowanie. Postep Hig i Med Dowiadczalnej 2015;69:1215–21.

[39] Sun L-J, Xu G-F, Lv M, Zhou H, Huang H-F, Luo Q. Predictive Value of Maternal Serum Biomarkers for Preeclampsia and Birth Weight: A Case–Control Study in Chinese Pregnant Women. J Women's Heal 2018;00:1–6.

[40] Čabarkapa V, Bogavac M, Jakovljević A, Pezo L, Nikolić A, Belopavlović Z, et al. Serum magnesium level in the first trimester of pregnancy as a predictor of pre-eclampsia – a pilot study. Hypertens Pregnancy 2018;00:1–10.