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Research Article

Pharmacotherapy Practices and Clinical Outcomes of Pre-Eclampsia/Eclampsia: An Observational study

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Abstract

Background: This study observes fetal, pregnancy, and maternal outcomes with different regimens of Magnesium sulphate ($MgSO_4$), used for prophylaxis and treatment of convulsions in eclampsia.

Methods: In this observational study, the current prescribing practice and management outcomes of pre-eclampsia/eclampsia were observed in three tertiary care hospitals in Lahore, Pakistan. Data were collected by using data collection form, containing information related to patient demographics, history, laboratory findings, drug administration record, and therapeutic outcomes for pregnancy, fetus, and mother.

Results: Of the 50 patients studied, most (74%) were of eclampsia. The mean age of the patients was 25.7 (+5.05) years with the majority (36%) in the age range 21–25 years. Forty-one patients received $MgSO_4$, of which most received the Pritchard regimen (n = 35), whereas only 5 patients were managed with Zuspan regimen. Liner logistic analysis revealed better fetal outcomes (OR 0.217, CI –0.283 – 1.543) and pregnancy outcomes (OR 0.186, CI –0.164 – 0.635) with Zuspan regimen as compared to Pritchard. Whereas, both regimens showed no difference in maternal outcomes (OR 0.044, CI –0.129 – 0.170).

Conclusion: Zuspan regimen proved to be better in morbidity and mortality associated with eclampsia. Additionally, national as well as institutional guidelines should be developed, implemented, properly monitored, and evaluated for management of pre-eclampsia/eclampsia. Mandatory in-service training and expertise should be provided for health professionals at all levels of the healthcare system, especially those working in gynecological setup.

Keywords: pre-eclampsia, magnesium sulphate, eclampsia, prescribing practices, management outcomes, Pakistan

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1. Introduction

Pre-eclampsia is a disorder involving many systems of the body and occurs after the 20th week of pregnancy. It is usually associated with high blood pressure (>140/90 mmHg) and proteinuria (>300 mg protein in 24 hr urine sample)[1, 2]. According to the guidelines of the Royal College of Obstetrician and Gynecology, severe pre-eclampsia is defined as:

A systolic blood pressure of >170 mmHg or diastolic blood pressure of >110 mmHg on two occasions 4–6 hours apart and a proteinuria of >1 g per day or a diastolic blood pressure of >100 mmHg on two occasions, with significant proteinuria (1+ on dipstick), with two or more signs or symptoms of imminent eclampsia which include severe headache, visual disturbance, epigastric pain or vomiting, clonus, papilloedema, liver tenderness, platelet count below 100,000/cm, abnormal liver enzymes, HELLP (Hemolysis, Elevated liver enzymes, Low Platelet) syndrome, IUGR (Intrauterine Growth Restriction) and pulmonary edema.

Whereas, eclampsia is defined as "the development of convulsions and/or unexplained coma during pregnancy or postpartum in patients with signs and symptoms of pre-eclampsia" [3].

The disorder is rare in developed countries but is one of the major causes of maternal and perinatal mortality or complication in developing countries [2, 4]. Pre-eclampsia and eclampsia, along with other hypertensive complications are responsible for almost 9% of maternal deaths in Asia [5]. Females suffering from chronic hypertension, diabetes, and obesity are comparatively at higher risk of developing the disease [6]. Furthermore, the other contributing risk factors include family history of pre-eclampsia/eclampsia, extremes of reproductive age (<20 or >40 years of age), and a previous history of pre-eclampsia/eclampsia [7], nulliparity, renal disease or thrombophilia. Pre-eclampsia, if untreated, can lead to eclampsia which is associated with convulsion and can prove fatal for both mother and fetus [8].

Management of pre-eclampsia and eclampsia includes prevention or control of convulsions, blood pressure control, and maintenance of pregnancy or delivery according to patient condition. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, hypertension in pregnancy is controlled by using labetalol, hydralazine, or nifedipine [9]. The World Health Organization (WHO) has declared magnesium sulphate as the most effective and low cost drug for the prevention and treatment of convulsions in pre-eclampsia and eclampsia [10]. Although the mechanism of action of magnesium sulphate is still unclear, it is considered that it dilates the blood vessels and thus prevent cerebral ischemia and neuronal damage [2]. Magnesium sulphate is superior to phenytoin, diazepam, nifedipine [11], and nimodipine [12] for prophylaxis of eclampsia [13]. For the management of severe pre-eclampsia and eclampsia, two regimens of magnesium sulphate are used frequently namely, Zuspan and Pritchard [14]. In Zuspan regimen, a loading dose of 4 gr is administered slowly in 5–10 mins intravenously, followed by a maintenance dose of 1–2 gr per hour intravenously with the help of infusion pump [15]. Whereas, in Pritchard regimen,

4 gr bolus dose of magnesium sulphate is administered slowly in 5–10 min via IV route followed by 5 gr intramuscular (IM) dose on each buttock (10 gr total dose) for every 4 hr subsequently [16]. In the developing countries, like Pakistan, due to the lack of proper administration facilities, for example, infusion pumps and adequate staff skills, modifications in the magnesium sulphate regimen have been observed [14, 17], which can result in poor maternal and fetal outcomes.

Management of severe pre-eclampsia and eclampsia must balance risk–benefit ratio of induced preterm delivery and maternal/fetal complications. Key issues in the management include screening of women at high risk and prevention of recurrence [18]. The objective of this study was to evaluate the prescribing practices and to document management outcomes of pre-eclampsia/eclampsia both in mother and fetus in patients admitted in the tertiary care hospitals of Lahore, Pakistan.

2. Materials and Methods

A prospective observational study involving patients with pre-eclampsia and eclampsia using a data collection form was conducted between 2013, March 1st and May 31st in the three tertiary care hospitals of Lahore, Pakistan, catering the needs of pre-eclamptic and eclamptic patients referred from different regions of the Punjab province. The main purpose of this exercise is to investigate the previous practices for the management of pre-eclampsia and eclampsia before the implementation of the new management policy updates in clinical management of pre-eclampsia and eclampsia.

Table 1: Demographic characteristics and clinical history of patients (n = 50).

Variables	n (%)
Diagnosis	
Eclampsia	37 (74%)
Pre-eclampsia	13 (26%)
Patient age (yrs)	
16–20	9 (18%)
21–25	18 (36%)
26–30	16 (30%)
31–35	6 (12%)
36–40	1 (2%)
Gestational age (wks)	
20–24	5 (10%)
25–29	8 (16%)
30–34	20 (40%)
35–39	15 (30%)
>40	2 (4%)
Gravidity	
Primigravida	26 (52%)
Multigravida	24 (48%)

Table 2: Demographic characteristics and clinical history of patients (*n* = 50).

Variables	n (%)
Parity	
Nulliparity	27 (54%)
Multiparity	23 (46%)
Extent of urine albumin	
+1	8 (16%)
+2	12 (24%)
+3	13 (26%)
+4	17 (34%)

Table 3: Therapeutic management of patient with eclampsia and pre-eclampsia (*n* = 50).

–	Total	Drug used		Regimen used		
		$MgSo_4$ alone	$MgSo_4$ + Diazepam	Zuspan (IV)	Pritchard (IV+IM)	IM Alone
Patients who received anticonvulsants (*n* = 41)						
Eclampsia	35	24	11	4	18	13
Pre-eclampsia	6	6	0	1	3	2
Patients who did not receive Mg SO_4 (*n* = 9)						
Eclampsia	2	–	–	–	–	–
Pre-eclampsia	7	–	–	–	–	–

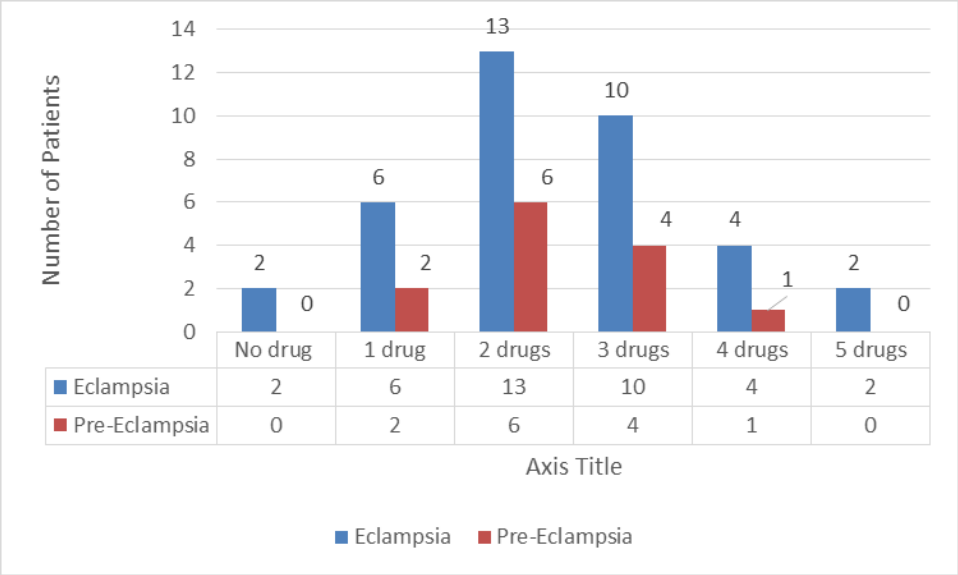

Figure 1: Number of antihypertensive drugs used by eclampsia/pre-eclampsia patients (*n* = 50).

TABLE 4: Linear association of different therapeutic interventions on fetal, maternal, and pregnancy outcomes of eclampsia/pre-eclampsia patients (n = 50), ORs, and 95% CI.

Predictors		Fetal outcomes observed				Maternal outcomes observed				Pregnancy outcome		
		Stable	Need for admission to NICU	Intra uterine death, still birth, neonatal death	OR [95% CI]	Stable	Admitted in ICU due to complications	Death	OR [95% CI]	Delivery	Termination	OR [95% CI]
Regimens for $MgSo_4$ (n = 41)[☒]	Zuspan regimen (IV)	4	1	0	0.217[–0.283 – 1.543]	5	0	0	0.044[–0.129 – 0.170]	5	0	0.186[–0.164 – 0.635]
	Pritchard regime (combination of IV+IM)	20	1	15		35	1	0		27	9	
Anti-hypertensive drugs (n = 50)[*]	0–2 drugs	19	1	9	0.177[–0.210 – 0.900]	29	0	0	0.168[–0.034 – 0.129]	22	6	0.057[–0.236 – 0.351]
	3 or more drugs	10	1	10		20	1	0		14	7	
Anti-convulsant drug(s) (n = 41)[☒]	$MgSo_4$ alone	19	2	9	0.185[–0.277 – 1.072]	30	0	0	0.259[–0.020 – 0.200]	25	5	0.200[–0.108 – 0.482]
	$MgSo_4$ + Diazepam	5	0	6		10	1	0		7	4	

[*]Significant ($P < 0.05$); [☒]Only administered to eclampsia patients.

For linear logistic regression: Magnesium sulphate regimens (ref Zuspan regimen); Anti-hypertensive drugs (ref 0-2 drugs); Anti-convulsant drugs (ref $MgSO_4$ alone).

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2.1. Patient selection criteria

A simple random sampling method was used to identify patients with pre-eclampsia/eclampsia. All patients with gestation period of 20th week and over or 10 days postpartum were included in the study. Whereas pregnant women with history of essential hypertension or gestational hypertension and that of epilepsy were excluded. A structured data collection form was used to collect data relevant to patients' demographic, medical history, current medical condition, medication chart, vitals and lab parameters.

2.2. Statistical analysis

Data were analyzed using the statistical package for social sciences software (SPSS) version® 22. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as percentages. The association of different therapeutic interventions with outcomes variables namely, fetal, maternal, and pregnancy, was analyzed through linear logistic regression. Three predicting variables included in the regression analysis were regimens of $MgSO_4$, number of antihypertensive drugs, and the nature or combination of anticonvulsant drug(s) being administered to the patients. For all the statistical tests, a *P*-value < 0.05 was considered as statistically significant.

3. Results

Upon completion of the study duration, 50 patients met the inclusion criteria, of whom 37 (74%) were diagnosed with eclampsia, 13 (26%) with pre-eclampsia, and none of the patient was presented with a previous history of hypertension. Most of the patients were referred from rural and peripheral areas in acute emergency conditions to the studied tertiary care hospitals of Lahore. The mean age of the patients was 25.7 (+5.05) years with the majority (*n* = 18 [36%]) in the age range 21–25 years. The mean gestational age was 32.3 (+4.7) weeks, while most patients were in the gestational age range of 30–34 weeks. The convulsive fits of the majority of the eclamptic patients in the study were of antepartum nature (*n* = 39 [78%]), followed by postpartum (*n* = 7 [13%]) and intrapartum (*n* = 4 [8%]). The demographic details along with the clinical history of the patients is presented in Table 1.

The majority (*n* = 30 [60%]) of patients were treated with $MgSO_4$ alone, followed by 11 (22%) who received a combination of magnesium sulphate with diazepam, details of which are presented in Table 2. Twenty-one patients (42%) of this study were prescribed with three or more antihypertensive drugs during hospitalization. Further details about antihypertensive treatment are presented in Figure **1**. The regression analysis revealed better fetal (OR 0.217, CI –0.283 – 1.543) and pregnancy outcomes (OR 0.186, CI – 0.164 – 0.635) with Zuspan regimen as compared to the Pritchard regimen of $ZnSO_4$. Whereas, both regimens showed no difference in maternal outcomes (OR 0.044, CI –0.129 – 0.170).

Magnesium sulphate use alone showed better maternal (OR 0.259, CI –0.020 – 0.200), pregnancy (OR 0.200, CI –0.108 – 0.482), and fetal outcomes (OR 0.185, CI –0.277 – 1.072) as compared to its use in combination with diazepam. Whereas fetal and maternal outcomes were comparatively better controlled with one or two anti-hypertensive, as shown in Table 3.

4. DISCUSSION

This study is perhaps among the very few regional studies conducted in the Punjab province of Pakistan that are aiming to explore the management of pre-eclampsia/eclampsia and factors that might be associated with the therapeutic outcomes. In addition, the study also aims to evaluate the prescribing practices and management outcomes among female patients of pre-eclampsia/eclampsia in three tertiary care hospitals of Lahore. To date there is sacristy of the comprehensive comparison of the outcomes among pre-eclampsia/eclampsia patients in Pakistani setting. Most of the studies that are published regionally have just assessed its prevalence and have not provided any in-detail insight to the factors that influence the outcomes of pre-eclampsia/eclampsia [19, 20]. Therefore, regardless the data is old, it has given an in-depth

In this study, nulliparity and primigravida were found in 27 (54%) and 23 (46%) patients, respectively, as pre-eclampsia is generally regarded as a disease of first pregnancy [21]. Family and previous history of pre-eclampsia/eclampsia are considered as risk factors for the disease [22], which is in line with our study results, where we observed 14% of our studied patients had family history of the diseases. WHO recommends magnesium sulfate as a safe, the most effective, and low-cost anticonvulsant treatment for pre-eclampsia and eclampsia [10]. Magnesium sulphate is a part of National Essential Drug List, Pakistan 2007 for use in eclampsia and pre-eclampsia [23]. In our study, 95% of the patients with eclampsia and 46% with pre-eclampsia received magnesium sulphate. WHO recommends full IV regimens for prevention and treatment of eclampsia [10]. NICE clinical guidelines also state the use of full IV regimen [9]. The IV regimen (Zuspan regimen) results in more stable serum levels of magnesium but demands the use of an infusion pump for safe delivery and has a greater potential for accidental overdose [24]. Only 10% patients of this study were managed with Zuspan regimen, and no fetal maternal death and pregnancy termination was observed in those cases. Whereas Prichard regimen (combined IV and IM) was the most frequently administered regimen. According to the NICE guidelines, recurrent seizures should be treated with an additional dose of 2–4 gr IV magnesium sulphate [9]. The Magpie trial found that only 0.3% of the women treated with magnesium sulfate required calcium gluconate in order to treat toxicity [25]. In our study, calcium gluconate administration was needed for only one patient. According to the NICE clinical guidelines, for the acute management of hypertension in eclampsia and pre-eclampsia, labetalol orally or intravenously, nifedipine orally, or IV hydralazine can be used. Hydralazine was most used antihypertensive in both eclampsia and pre-eclampsia in this study. Other commonly used anti-hypertensive agents in pre-eclampsia/eclampsia were isosorbide dinitrate, nifedipine, methyldopa, mannitol, and amlodipine besylate.

The management of pre-eclampsia must balance the risk–benefit ratio of induced preterm delivery and maternal/fetal complications [18]. In this study, the mode of delivery and decisions about continuation and management or termination of pregnancy were also documented. Babies of 58% women were delivered successfully and were stable after delivery. However, 4% of the newborns were admitted in neonatal intensive

care unit (NICU) immediately after birth due to various issues, and 32% intrauterine death (IUD), 2% still birth, and 4% neonatal deaths occurred. No maternal death was reported throughout our study period due to eclampsia/pre-eclampsia in women receiving $MgSO_4$, and 96% women were stable after therapy, which is in line with the findings of a previous study in which the women with eclampsia who were treated with magnesium sulfate had a lower risk of morbidity and mortality as compared to women treated with other anticonvulsants [26].

The findings of this study clearly show that the Zuspan regimen is associated with better fetal, maternal, and pregnancy outcomes, although it was employed in a very small number of cases. The choice for regime selection is mainly dependent on the facilities available and the training and expertise of the staff [14]. Although it is the most effective regimen for eclampsia management, its infrequent use could be due to inadequate training and expertise for Zuspan regimen use and lack of administration and monitoring devices. As administration of $MgSo_4$ requires intensive monitoring, doctors were reluctant to use magnesium sulphate especially in pre-eclampsia. Most of the patients were managed with the Pritchard regimen of $MgSO_4$, the possible reasons could be lack of skillful staff [14]. Additionally, specific institutional guidelines on dose, timing, and indications were not observed in the studied hospitals. Standards of care were not only non-uniform at the three tertiary care hospitals, but also within the units of the same hospital; a similar findings were observed in another study conducted in Peshawar, Pakistan [27]. Furthermore, our observations are consistent with the findings of a qualitative study suggesting a huge knowledge gap among community healthcare providers regarding the treatment of eclampsia and pre-eclampsia in Pakistan [28]. In addition, the patient load in tertiary care hospitals is greater compared to the number of healthcare professionals making use of drugs like magnesium sulphate, which requires intensive monitoring during administration.

5. Conclusion

Despite the encouraging observation that majority of the patients with pre-eclampsia and eclampsia were treated successfully with $MgSO_4$, the Zuspan regimen should be preferred over Pritchard due to its better fetal and pregnancy outcomes. The findings of this study suggest the formulation of national and institutional guidelines and appropriate training of healthcare professionals at all levels of care for the effective and timely management of pre-eclampsia and eclampsia.

5.1. Strengths and limitations of the study

The small retrospective sample size can be a limitation of this study which was unavoidable due to time constraint. However, the study included patients from all the three hospitals where patients of eclampsia and pre-eclampsia were referred and subsequently treated. Another reason for apparently small number of patients being treated in this hospital despite eclampsia being responsible for one in every ten maternal deaths could be the involvement and popularity of informal healthcare system [29, 30]. The informal healthcare system being led by traditional birth attendants and spiritual healers is being practiced by a significant proportion of population

in Pakistan due to its easy affordability and accessibility [28, 31, 32]. Furthermore, the number of patients in the studied hospitals was larger than the number of attending doctors making frequent monitoring sometimes difficult; therefore, combined IV and IM regime was mostly in practice. The IM dosing regimen, while potentially safer, requires repeated painful IM injections. Finally, this study has demonstrated a valuable insight into the risk factors and comparative therapeutic outcomes among eclampsia/pre-eclampsia patients. These factors are important for the national public authorities to consider while implementing or updating the therapy guidelines.

Declarations

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Ethical Considerations

Ethical approval was obtained from the research and ethics committees of Lady Willingdon Hospital, Lahore; Sir Ganga Ram Hospital, Lahore; and Lahore General Hospital, Lahore. Written informed consent was obtained from all participants after explaining them the nature of the study.

Competing Interests

None.

Availability of Data and Material

All Data is presented in this article; any additional information shall be available on request.

Funding

None.

Abbreviations and Symbols

HELLP: Hemolysis, elevated liver enzymes, low platelet syndrome

IUGR: Intrauterine growth restriction

NICE: National Institute for Health and Clinical Excellence

WHO: World Health Organization

IV: Intravenous

IM: Intramuscular

SD: Standard deviation

SPSS: Statistical package for social sciences software

$MgSO_4$: Magnesium sulphate

OR: Odds ratio

CI: Confidence interval

P-value: Probability value

NICU: Neonatal intensive care unit

IUD: Intrauterine death

References

[1] August, P., & Sibai, B. M. (2024). Preeclampsia: Clinical features and diagnosis. UpToDate.

[2] Duley, L. (2005). Evidence and practice: The magnesium sulphate story. Best Practice & Research. Clinical Obstetrics & Gynaecology, 19(1), 57–74. https://doi.org/10.1016/j.bpobgyn.2004.10.010

[3] Murlidhar, V., & Bolia, S. (2006). Intensive care management of severe pre-eclampsia and eclampsia. Apollo Medicine, 3(1), 102–110. https://doi.org/10.1177/0976001620060115

[4] Bilano, V. L., Ota, E., Ganchimeg, T., Mori, R., & Souza, J. P. (2014). Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: A WHO secondary analysis. PLoS One, 9(3), e91198. https://doi.org/10.1371/journal.pone.0091198

[5] Khan, K. S., Wojdyla, D., Say, L., Gülmezoglu, A. M., & Van Look, P. F. (2006). WHO analysis of causes of maternal death: A systematic review. Lancet, 367(9516), 1066–1074. https://doi.org/10.1016/S0140-6736(06)68397-9

[6] Steegers, E. A., von Dadelszen, P., Duvekot, J. J., & Pijnenborg, R. (2010). Pre-eclampsia. Lancet, 376(9741), 631–644. https://doi.org/10.1016/S0140-6736(10)60279-6

[7] Sibai, B., Dekker, G., & Kupferminc, M. (2005). Pre-eclampsia. Lancet, 365(9461), 785–799. https://doi.org/10.1016/S0140-6736(05)17987-2

[8] Rathore, R., Butt, N. F., Iqbal, A., & Khan, M. Z. U. (2010). Complications and outcome of patients of pre-eclampsia and eclampsia presenting to medical wards of Mayo Hospital Lahore. Annals of King Edward Medical University, 16(1), 17.

[9] National Collaborating Centre for Women's and Children's Health (UK). (2010). Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. London: RCOG Press.

[10] WHO. (2011). WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia: Summary of recommendations. https://iris.who.int/bitstream/handle/10665/119627/WHO_RHR_14.17_eng.pdf

[11] Magee, L. A., Miremadi, S., Li, J., Cheng, C., Ensom, M. H., Carleton, B., Côté, A. M., & von Dadelszen, P. (2005). Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. American Journal of Obstetrics and Gynecology, 193(1), 153–163. https://doi.org/10.1016/j.ajog.2004.11.059

[12] Belfort, M. A., Anthony, J., Saade, G. R., Allen, J. C., Jr., & the Nimodipine Study Group. (2003). A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. The New England Journal of Medicine, 348(4), 304–311. https://doi.org/10.1056/NEJMoa021180

[13] Euser, A. G., & Cipolla, M. J. (2009). Magnesium sulfate for the treatment of eclampsia: A brief review. Stroke, 40(4), 1169–1175. https://doi.org/10.1161/STROKEAHA.108.527788

[14] Tukur, J. (2009). The use of magnesium sulphate for the treatment of severe pre-eclampsia and eclampsia. Annals of African Medicine, 8(2), 76–80. https://doi.org/10.4103/1596-3519.56232

[15] Zuspan, F. P. (1978). Problems encountered in the treatment of pregnancy-induced hypertension. A point of view. American Journal of Obstetrics and Gynecology, 131(6), 591–597. https://doi.org/10.1016/0002-9378(78)90816-5

[16] Pritchard, J. A., Cunningham, F. G., & Pritchard, S. A. (1984). The Parkland Memorial Hospital protocol for treatment of eclampsia: Evaluation of 245 cases. American Journal of Obstetrics and Gynecology, 148(7), 951–963. https://doi.org/10.1016/0002-9378(84)90538-6

[17] Begum, R., Begum, A., Johanson, R., Ali, M. N., & Akhter, S. (2001). A low dose ("Dhaka") magnesium sulphate regime for eclampsia. Acta Obstetricia et Gynecologica Scandinavica, 80(11), 998–1002. https://doi.org/10.1034/j.1600-0412.2001.801105.x

[18] Uzan, J., Carbonnel, M., Piconne, O., Asmar, R., & Ayoubi, J. M. (2011). Pre-eclampsia: Pathophysiology, diagnosis, and management. Vascular Health and Risk Management, 7(7), 467–474.

[19] Malhan, A., Hyder, M.., Baloch, S., Zahegul, Roshan, S., Dembra, G., & Arshad, M. (2023). Frequency of preeclampsia in pregnant women presenting in a tertiary hospital: Frequency

of preeclampsia in pregnant women. Pakistan Journal of Health Sciences, 4(04), 30–33. https://doi.org/10.54393/pjhs.v4i04.652

[20] Soomro, S., Kumar, R., Lakhan, H., & Shaukat, F. (2019). Risk factors for pre-eclampsia and eclampsia disorders in tertiary care center in Sukkur, Pakistan. Cureus, 11(11), e6115. https://doi.org/10.7759/cureus.6115

[21] Dekker, G., & Sibai, B. (2001). Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet, 357(9251), 209–215. https://doi.org/10.1016/S0140-6736(00)03599-6

[22] Thangaratinam, S., Langenveld, J., Mol, B. W., & Khan, K. S. (2011). Prediction and primary prevention of pre-eclampsia. Best Practice & Research. Clinical Obstetrics & Gynaecology, 25(4), 419–433. https://doi.org/10.1016/j.bpobgyn.2011.02.008

[23] Drug Regulatory Authority of Pakistan. (2022). National essential medicine lists.

[24] Shoaib, T., Khan, S., Javed, I., & Bhutta, S. Z. (2009). Loading dose of magnesium sulphate versus standard regime for prophylaxis of pre-eclampsia. Journal of the College of Physicians and Surgeons—Pakistan, 19(1), 30–33.

[25] McDonald, S. D., Lutsiv, O., Dzaja, N., & Duley, L. (2012). A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use. International Journal of Gynaecology and Obstetrics, 118(2), 90–96. https://doi.org/10.1016/j.ijgo.2012.01.028

[26] Duley, L., Henderson-Smart, D. J., Walker, G. J., & Chou, D. (2010). Magnesium sulphate versus diazepam for eclampsia. Cochrane Database of Systematic Reviews, 2010, CD000127.

[27] Shaheen, B., Hassan, L., & Obaid, M. (2003). Eclampsia, a major cause of maternal and perinatal mortality: A prospective analysis at a tertiary care hospital of Peshawar. JPMA. The Journal of the Pakistan Medical Association, 53(8), 346–350.

[28] Sheikh, S., Qureshi, R. N., Khowaja, A. R., Salam, R., Vidler, M., Sawchuck, D., von Dadelszen, P., Zaidi, S., Bhutta, Z., & the CLIP Working Group. (2016). Health care provider knowledge and routine management of pre-eclampsia in Pakistan. Reproductive Health, 13(2, Suppl 2), 104. https://doi.org/10.1186/s12978-016-0215-z

[29] White Ribbon Alliance-Pakistan. (2020). Saving mother's life: addressing barriers to the use of magnesium sulphate is a project funded by the Maternal and Newborn Health Programme - Research and Advocacy Fund (RAF), and implemented by White Ribbon Alliance-Pakistan. https://fsm.org.pk/wp-content/uploads/2020/08/Policy-Brief-MGSO4.pdf

[30] National Institute of Population Studies, Islamabad, Pakistan. (2008). Pakistan demographic and health survey 2006-07. https://dhsprogram.com/pubs/pdf/FR200/FR200.pdf

[31] Shaikh, B. T., & Hatcher, J. (2005). Health seeking behaviour and health service utilization in Pakistan: Challenging the policy makers. Journal of Public Health, 27(1), 49–54. https://doi.org/10.1093/pubmed/fdh207

[32] Anwar, M., Green, J., & Norris, P. (2012). Health-seeking behaviour in Pakistan: A narrative review of the existing literature. Public health, 126(6), 507–517.