Readiness of public healthcare facilities on the management and referral of pre-eclampsia in Zanzibar

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Abstract

Background: Proper management of pre-eclampsia/eclampsia depends on the availability of well-functioning healthcare facilities. A significant number of women with pre-eclampsia in Zanzibar are referred late and most end up with eclampsia or even death. This raised a concern about whether healthcare facilities are prepared enough for the management of pre-eclampsia/eclampsia.

Objectives: To assess the readiness of public healthcare facilities for the management and referral of pre-eclampsia/eclampsia.

Methods: A descriptive cross-sectional study was conducted in Zanzibar targeting all public healthcare facilities. A sample of 54 healthcare facilities of all levels was randomly selected. Physical observation, questionnaire and review of hospital records were used for data collection. Descriptive statistics were used for analysis.

Results: National, regional and district hospitals have all the required equipment, supplies and drugs by 100% compared to primary healthcare units where a significant shortage was observed in equipment [working oxygen cylinder 1(2.1%), strips for proteinuria 25(54.3%)], drugs [diazepam 11(23.9%) and magnesium sulphate 14(30.4%)], test [urine for protein test 29(63%)], knowledgeable healthcare providers 46(38.8%) and skilled healthcare providers 47(39.8%). All primary health care units had clear criteria for referring a patient with pre-eclampsia, but only 19(41.3%) provide pre-referral treatment and only 17(36.9%) had vehicles for transporting the referred patient.

Conclusion: There is a huge shortage of resources in lower healthcare facility levels where most pregnant women have their initial contact. Necessary measures should be taken to well-equip primary healthcare units to improve their capability to proper diagnosis, manage and timely referral of patients with pre-eclampsia.

Keywords: Pre-eclampsia, facility readiness, management, referral, Zanzibar

Introduction

Pre-eclampsia is responsible for high maternal and neonatal morbidity and mortality (Kuklina *et al.*,2009). Its prevalence is high in developing countries (Belay & Wudad 2019; Wandabwa *et al.*, 2010)

Tanzania and Zanzibar (Frank *et al.*, 2020; Tufton & Patel 2011; Machano & Joho 2020) than in developed countries (Fingar *et al.*, 2006).

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The consequence of its high prevalence is reflected in the number of maternal and deaths and their neonatal related complications. In Tanzania, the maternal mortality rate is 556 per 100,000 live birth (DHS, 2016; Herklots et al., 2017) and 18.9% of these death are associated with preeclampsia/eclampsia (Makuwani et al., 2020), while the maternal mortality in Zanzibar is 155 death per 100,000 live birth (MoHASWZ, 2018) and severe pre-eclampsia contributes to 25.8% of maternal morbidity and 21.8% of maternal mortality (Herklots et al., 2017). What gives hope is that maternal deaths could be prevented if pregnant women access quality Antenatal Care Services (ANC) (Raven et al., 2011). However, the ANC quality improvement depends on the availability of skilled attendants, as well as well-functioning healthcare facilities (Ameh et al., 2012) and the availability and accessibility of these services in a nearby community.

Pregnant women attending ANC services are required to undergo several measurements and tests to allow early detection, early treatment and timely referral of hypertensive disorders of pregnancy including preeclampsia. This helps to prevent complications like eclampsia and even death. Screening of pre-eclampsia/eclampsia requires simple tools like sphygmomanometer, stethoscope and albustix for checking protein in the urine. Moreover, tests like renal function test, liver function test and evaluation of platelets counts which are mostly needed in the severe form of pre-eclampsia or eclampsia are also important (ACOG, very 2002). Pharmacological agents like methyldopa, nifedipine, hydralazine, and labetalol, are highly recommended to be available in each facility for controlling high blood pressure. All these are to be available to all levels of healthcare facilities (WHO, 2011).

According to the guideline provided by the Ministry of Health Zanzibar (Management Protocols of Obstetric and Newborn Care), all pregnant women attending ANC at any healthcare facility level have to be screened for pre-eclampsia, and those with signs of pre-eclampsia should manage according to the guideline. Moreover, all women with signs of severe pre-eclampsia seen at the primary healthcare level have to be treated with pre-referral treatment and referred immediately as per the guideline procedure to the nearest healthcare facility of secondary level, while most complicated cases have to be referred to a tertiary hospital for further management.

However, evidence showed that the majority of pregnant women in Zanzibar are referred late and most end up with eclampsia. Hence the questions come whether all levels of healthcare facilities in Zanzibar are prepared enough in terms of availability of the required equipment, medications, and adherence to referral guidelines as well as the availability of healthcare providers with knowledge and skills of management of pre-eclampsia. Therefore, this study assessed healthcare facility readiness for the management and referral of pre-eclampsia in Zanzibar.

Donabedian model for measuring the quality of care

This study was guided by model for measuring quality care by Donabedian (Fig. 1) 2008). This model has three (NHSI. approaches to the evaluation of the quality of care, which are structure, process, and outcome. The current study adopted two approaches; the structure which measured the availability of resources in the healthcare facilities like skilled and knowledgeable health care providers, availability of guidelines, tests, supplies and equipment, ambulance, and medication. The second approach adopted in this study is a process which measured the adherence to the guideline on the treatment of preeclampsia/eclampsia and in making a referral to women with signs of severe preeclampsia.



Figure 1: The Donabedian model for quality of care

Methodology

Study settings and study population

This study was conducted in Zanzibar which is united with and a part of Tanzania. The study targeted all public healthcare facilities and assessed their antenatal care units. The health delivery system in Zanzibar is organized into three levels which are the primary level, secondary and tertiary level. The primary level is the lowest level which includes Primary Health Care Unit (PHCU), Primary Health Care Unit Plus (PHCU +) and Primary Health Care Center or Cottage (PHCC). In total, there are 122 PHCU, 34 PHCU+, and 4 PHCC. The secondary level which is the middle level of health care delivery includes district hospitals and regional hospitals. There are two district hospitals and one regional hospital, and the highest level of health care delivery is the tertiary level or national hospital. There is only one referral hospital in Zanzibar which provides referral services from the district and regional hospitals.

Study design, sample size and sampling

This was a descriptive cross-sectional study designed. The sample size was calculated using a formula put forward by WHO which states that in assessing lower health facility levels if there are 100 or fewer, should study all of them. If there are more than 100 then take at least 30% (WHO, 2009). In this regard, the total number of primary healthcare facilities in Zanzibar (PHCU and PHCU+) is 156, therefore only 30% was taken which is

equal to 46 primary healthcare facilities. Moreover, the total number of health centers is 4, district hospitals are 2, the regional hospital is 1, and referral hospital is 1, thus all of them were included in the study. Therefore, the total number of healthcare facilities that were included in this study was 54. Censor method was used to select health centers, district hospitals, regional hospitals and referral hospital while systematic random sampling method was used to select 46 PHCUs.

Definition of variables in this study:

Readiness of healthcare facility: When the healthcare facility had all the required equipment, medications, tests, guidelines, clear referral pathway procedure, and skilled and knowledgeable healthcare providers for the management and referral of patients with pre-eclampsia or eclampsia.

Management of pre-eclampsia: All treatment, measurements and tests are done on an admitted pregnant woman diagnosed with pre-eclampsia (mild or severe) at the time of data collection.

Referral of pre-eclampsia: Procedures of referring a patient with a severe or complicated case of pre-eclampsia or eclampsia to the higher healthcare health facility level based on the recommended guidelines. The guideline has seven items and all of them were assessed.

Data collection methods and tools

The availability of equipment, medications and tests related to the management of preeclampsia in each healthcare facility was assessed by physical observation and noting the availability of a particular item using the pre-prepared checklist adopted from Maembe & Pembe (2015). Data on the of pre-eclampsia management were collected by reviewing patients' case files and noting the type of management given to a patient using a checklist tool which was formulated (STG, 2017). Moreover, data on the referral of severe or complicated cases of pre-eclampsia were collected by reviewing the facility records and noting the availability items (referral guideline, clear referral pathway, ambulance etc.) or conduct (providing pre-referral treatment etc.) using a checklist tool which was adopted from WHO (2013). Data on the characteristics of healthcare providers within each healthcare facility was obtained using self-administered questionnaire, and their knowledge and skills on the management of pre-eclampsia were assessed using adopted tool (Olaoye et al., 2019; Mothers & Survive 2017).

Data analysis

Data were analysed using SPSS software version 25. Descriptive statistics were used and results were presented in frequency and percentage. Cross tabulation was also performed to compare the distribution of variables in different healthcare facility levels and data are presented in two-by-two tables.

Ethical Considerations

The study obtained ethical clearance from the University of Dodoma Research Ethics Committee (UDOM-REC) and Zanzibar Health Research Institute (ZAHRI) with reference number ZAHREC/04/ST/JAN/2021/02.

Results

Distribution of equipment, drugs and tests for the management of pre-eclampsia

The results showed that, the equipment that was available in most healthcare facilities was a functioning blood pressure machine which was available in 49(90.7%) healthcare facilities, while the stripes for measuring protein in urine were available in 32(59.3%) healthcare facilities. Moreover, the drug that was most available in most healthcare facilities was methyldopa which was available in 25(46.3%) healthcare facilities, while the least available drug was hydralazine which was available in 6(11%) healthcare facilities (Table 1).

comparing the availability When of equipment, medications and tests in each healthcare facility level, the results showed that tertiary and secondary hospitals have all required equipment, drugs and the diagnostic tests except for patella hammer which was missing in district hospitals and a liver and renal function tests that were missing in regional hospitals and in one district hospital. As for the healthcare facilities of primary level, the PHCUs are the most significant with missing essential equipment, drugs and tests compared to PHCU+ and health centers (Table 1).

able 1: Distribution of Equipment, Drugs and Tests for the Management of Pre-eclampsia in Each Level c	эf
lealthcare Facility (N = 54)	

Item	Total						
	available	Avail	ability in Ea	ch Level o	of Healthcare I	Facility	
		PHCU	PHCU+	Health	District	Regional	Tertiary
		(n=24)	(n=22)	centre	hospital	hospital	hospital
				(n=4)	(n=2)	(n=1)	(n=1)
	n (%)	n(%)	n(%)	n (%)	n(%)	n (%)	n (%)
Equipment							
Guideline for P/E	40(74.1%)	11(45.8)	21(95.5)	4(100)	2(100)	1(100)	1(100)
management							
Working BP machine	49(90.7)	19(79.2)	22(100)	4(100)	2(100)	1(100)	1(100)
Working stethoscope	48(88.9)	19(79.2)	21(95.5)	4(100)	2(100)	1(100)	1(100)
Working	42(77.8)	14(58.3)	20(90.3)	4(100)	2(100)	1(100)	1(100)
Working	18(33.3)	0(0.0)	10(45.5)	4(100)	2(100)	1(100)	1(100)
Working oxygen	9(16.7)	0(0.0)	1(4.5)	4(100)	2(100)	1(100)	1(100)
cylinder							
Working patellar	3(5.6)	0(0.0)	0(0.0)	1(25%)	0(0.0)	1(100)	1(100)
nammer			·-(- · -)	(()		((, , ,)	(()
catheter	20(37.0)	0(0.0)	12(54.5)	4(100)	2(100)	1(100)	1(100)
Urinary bag	20(37.0)	0(0.0)	12(54.5)	4(100)	2(100)	1(100)	1(100)
Syringe	46(85.2)	16(66.7)	22(100)	4(100)	2(100)	1(100)	1(100)
Strips for proteinuria	32(59.3)	14(58.3)	11(50.0)	3(75.0)	2(100)	1(100)	1(100)
Cannula	37(68.5)	12(50.0)	18(81.8)	3(75.0)	2(100)	1(100)	1(100)
Drugs				(()		(()	
injection Magnesium sulphate	22(40.7)	0(0.0)	14(63.6)	4(100)	2(100)	1(100)	1(100)

Injection	19(35.2)	2(8.3)	9(40.9)	4(100)	2(100)	1(100)	1(100)
Calcium	8(14.8)	0(0.0)	2(9.1)	2(50)	2(100)	1(100)	1(100)
Injection	6(11.1)	0(0.0)	0(0.0)	2(50)	2(100)	1(100)	1(100)
Injection	22(40.7)	3(12.5)	11(50.0)	4(100)	2(100)	1(100)	1(100)
Methyldopa Nifedipine	25(46.3) 23(42.6)	7(329.2) 6(25)	12(54.5) 9(40.9)	2(50) 4(100)	2(100) 2(100)	1(100) 1(100)	1(100) 1(100)
test							
Urine for	37(68.5)	15(62.5)	14(69.9)	4(100)	2(100)	1(100)	1(100)
Renal function test	3(5.6)	0(0.0)	0(0.0)	1(25)	1(50)	0(0.0)	1(100)
Liver function test	4(7.4)	0(0.0)	0(0,0)	2(50)	1(50)	0(0.0)	1(100)

Characteristics of healthcare providers working in ANC

Results of this study showed that in all 54 healthcare facilities assessed, there is a total of 176 healthcare providers working in ANC units. The mean age of healthcare providers was 35.94 (SD±7.83) years, 100(56.8%) were female, 109(61.9%) were nurses and

101(56.7%) had never attended any on job training related to management of preeclampsia. In addition, half of them 90(51%) had inadequate knowledge of the management of pre-eclampsia and 93(52.3%) had inadequate skills in the management of pre-eclampsia (Table 2).

Variable	Number	Percentage
Age group (years)		
Under 30	37	21.0
30-39	91	51.7
40-49	34	19.3
50 and older	14	8
Sex		
Male	76	43.2
Female	100	56.8
Professional qualification		
Diploma in Nursing	96	54.5
Degree in nursing	10	5.7
Master in Nursing	3	1.7
Clinical officer	47	26.7
Assistant medical officer	2	1.1
Medical doctor	18	10.2
Working Facility level		
PHCU	47	26.7
PHCU+	71	40.3
Health centre (PHCC)	28	15.9
District hospital	14	8
Regional hospital	5	2.8
Tertiary hospital	11	6.3
On-job training on management of pre-eclampsia		
Attended training	75	46.6

Not attended training	101	57.4
Experience in ANC (years)		
Less than 5	88	50
5 years and above	88	50
Knowledge of the management of pre-eclampsia		
Adequate knowledge	86(8 to 10 score)	49.0
Inadequate knowledge	90(4 to 7 score)	51.0
Skills in the management of pre-eclampsia		
Adequate skills	83(4 to 7 score)	47.2
In adequate skills	93(1 to 3 score)	52.8

Characteristics Distribution of Healthcare Providers Working in ANC at Each Healthcare Facility Level

Results of this study showed that the proportion of healthcare providers with a diploma in nursing is higher among those working in primary healthcare levels [PHCU =33/47(70.2%), and PHCU+ = 40/71(56.3%)] compared to those working in secondary [regional 1/5(20%)] and tertiary level [3/11(27.3%)]. Moreover, the proportion of healthcare providers who have attended on-the-job training on the management of pre-

eclampsia is higher among those working in the secondary level [district=11/14(78.6%), regional=4/5(80%)and tertiary level [8/11(72%)] compared to those working in primary level [PHCU =20/47(42.6%), PHCU+=19/71(26.8%)]. The same trend has been observed for the knowledge and skills levels whereby the proportion of healthcare providers with adequate knowledge and adequate skills on the management of preeclampsia is higher among those working in secondary and tertiary levels compared to those working at the primary level (Table 3).

Table 3: The C	haracteristics Dist	ribution of Healthcare Providers per Healthcare Facility Level
Variable	Total	Number of healthcare providers in each facility level

Variable	Total	Number of healthcare providers in each facility level					
		PHCU	PHCU+	Health centre	District hospital	Regional hospital	Tertiary hospital
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Total number of HCP	176	47(26.7)	71(40.3)	28(15.9)	14(7.9)	5(2.8)	11(6.25)
The average number	3	2	3	7	7	5	11
of HCP in each							
facility in ANC							
Professional							
qualification		<i>,</i> , ,		<i>,</i> , ,	<i>·</i> · · ·	<i>(</i>)	,
Diploma in Nursing	96(54.5)	33(70.2)	40(56.3)	12(42.9)	7(50.2)	1(20.0)	3(27.3
Degree in nursing	10(5.7)	0(0.0)	1(1.4)	4(14.3)	2(14.3)	1(20.0)	2(18.2)
Master in Nursing	3(1.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3(27.3)
Clinical officer	47(26.5)	14(29.8)	26(36.6)	6(21.4)	1(7.1)	0(0.0)	0(0.0)
Assistant medical officer	2(1.1)	0(0.0)	2(2.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Medical doctor	18(10.2)	0(0.0)	2(2.8)	6(21.4)	4(28.6)	3(60.0)	3(27.3)
On-job training on							
management of pre-							
eclampsia							
Attended	75(42.6)	20(42.6)	19(26.8)	13(46.4)	11(78.6)	4(80.0)	8(72.7)
Not attended	101(57.3)	27(57.4)	52(73.2)	15(53.4)	3(21.4)	1(20.0)	3(27.3)
Knowledge of the							
management of pre-							
eciampsia	P(A P a)	(2(22))	28(22.4)	$((\circ \neg)$	Q(z=z)	5(100)	
Adequate knowledge	86(48.9)	18(38.3)	28(39.4)	17(60.7)	8(57.1)	5(100)	10(90.9)

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Inadequate knowledge Skills in the management of pre- eclampsia	90(51.1)	29(61.7)	43(60.6)	11(39.3)	6(42.9)	0(0)	1(9.1)
Adequate skills Inadequate skills	83(47.2) 93(52.8)	25(53.2) 22(46.8)	22(31.0) 49(69.0)	14(50.0) 14(50.0)	8(57.1) 6(42.9)	4(80.0) 1(20.0)	10(90.9) 1(90.9)

Referral Requirement of Pre-eclampsia in **Primary Healthcare Facilities**

Primary healthcare facilities were assessed if the referrals are conducted as per the established guideline. A total of 24 PHCU and 22 PHCU+ were assessed, and the results showed that; all facilities (PHCUs and PHCUs+) had established clear referral pathways, and clear criteria to refer patients and referred patients with referral notes, while only 4(16.7%) (PHCU) and 15(68.2%) (PHCU+) give pre-referral treatment to the referred patient and 3(12.5%) (PHC) and 14(63.6%) (PHCU+) had vehicles to transport the referred patient to the next higher healthcare facility level (Table 4).

Table 4: Distribution of	of referral requirement	ts within primary	y healthcare facilities (N=46)
•			, , , , , , , , , , , , , , , , , , , ,

Variable	Total	Level of he	alth facilities
		PHCU (n=24)	PCHU+ (n=22)
	n(%)	n (%)	n (%)
Availability of guidelines for referral	27	11(45.4)	16(72.7)
A clear referral pathway established	46	24(100)	22(100)
Clear criteria for a patient with pre-eclampsia	46		
to be referred		24(100)	22(100)
Patients with pre-eclampsia receive pre-	19		
referral treatment according to guideline		4(16.7)	15(68.2)
Referred patient with pre-eclampsia referred with referral note stating condition/ treatment	46		
given		24(100)	22(100)
Referred patient with pre-eclampsia accompanied by a healthcare provider	27	12(50)	15(68.2)
Availability of transport to refer patients with	17		
signs of pre-eclampsia	•	3(12.5)	14(63.6)

Discussion

Proper management of pre-eclampsia and eclampsia depends on the availability of competent healthcare providers as well as well-functioning healthcare facilities with supplies essential for screening, management and referrals (Ameh et al., 2012; Bhate-Deosthali et al., 2011; Goldenberg et al., 2011).

This study revealed that healthcare facilities of the higher levels (secondary and tertiary), have all the required equipment and supplies, medications and tests 100%, as well as healthcare providers with adequate knowledge and skills in high proportion. This is encouraging considering the low economic status of the country. Zanzibar needs to cherish this achievement for realizing the WHO's recommendation for the prevention and treatment of pre-eclampsia which requires improved quality of care (WHO, 2011). Similar findings have been reported in other developing countries. A study conducted in Afghanistan, for example, revealed wide accessibility of drugs and supplies at higher healthcare facility levels (Kim et al., 2013).

Hitherto, pre-eclampsia in Zanzibar remains the leading root of maternal death and account for 21.4% of maternal death (Herklots et al., 2017). The achievement of the accessibility of drugs and supplies will be cherished more when the problems related to pre-eclampsia are arrested to the minimum. But what is observed here is the lack of an effective strategy to supply drugs and equipment to lower healthcare facilities where most pregnant women first seek services. The situation in lower health facilities is not promising. Most lower health facility levels lack the basic equipment and supplies required for the effective management of pre-eclampsia. This affects the early detection and proper management of pre-eclampsia and thus leads to a third delay in receiving quality healthcare service. This finding is consistent with the finding (Maembe & Pembe, 2015) in Tanzania which reported a lack of basic supplies in about onethird of healthcare facilities.

Looking at specific items, this study revealed that blood pressure machines were widely available (90.7%), while strips for protein in urine tests were available only (59.3%). This result reflects the lower coverage of diagnostic tools for protein testing that is needed for the diagnosis of pre-eclampsia. It was reported that addressing pre-eclampsia, requires adequate equipment to measure both blood pressure and test for proteinuria at every level of the health system (Goldenberg et al., 2011). The unavailability of strips for protein tests may result in the delay of the diagnosis of preeclampsia and thus lead to a delay in managing and or referring patients to the high healthcare facility level. The percentage of availability in this study is lower compared to what was reported in Zambia (Nkamba et al., 2020) and Afghanistan (Kim et al., 2013) reported that urine for protein tests was available in 62.8% and 75% of healthcare facilities respectively. On the contrary, our findings are higher compared to the findings reported by Kyei et al., (2012) and Rawlins et al., (2018) who reported that urine test was available in 7% and 25% of health facilities respectively.

Furthermore, the finding from this study showed that there is a shortage of anticonvulsant drugs, only 40.7% of the facilities had injections of magnesium sulphate. Magnesium sulphate is a lifesaving drug and should be available in all healthcare facilities (Content & Process, 2013).

This indicates that most pregnant women diagnosed with severe pre-eclampsia delay receiving magnesium sulphate which has the role of preventing seizure, and this put them at risk of developing complications. The finding from this study differs from the findings of Jayanna et al., (2014) and Oguntunde et al., (2015) who reported that magnesium sulphate was available in more than half of all facilities in India and Nigeria respectively. Also, these findings differ from what was reported in Ethiopia and Rwanda where magnesium sulphate was available in 16% of Ethiopia and 4% of Rwanda (Rawlins et al., 2018) which is significantly lower compared with the finding in our study.

The referral system is an essential component of any health system which is particularly important in pregnancy and childbirth for providing access to essential obstetric care (Maskey, 2015). Usually, lower health facilities are not capable of managing pre-eclampsia, hence they need a timely and good referral system that facilitates referrals to a health facility that has management capabilities for obstetric and newborn emergencies (Adeline et al., (2018). The protocol for emergency obstetric and newborn care in Zanzibar requires that all healthcare facilities of lower level stabilize patients with severe pre-eclampsia by giving pre-referral treatment, and healthcare providers should escort the referred patient to the next appropriate level of care. However, the finding of this study showed that only 16.7% of PHCU and 68% of PHCU+ provide pre-referral treatment and 50% of PCHU and 68.2% of PHCU+ have healthcare providers escort the referred patients to the next appropriate level of care. This indicates that the referral process is poorly implemented, and this proves the existence of substandard care provided to the patients (Munabi-Babigumira et al., 2017). A similar finding was reported in Ghana that, even though the national protocol encourages health workers to accompany referred patients, only 5 of 10 respondents reported

frequently accompanying the client to the district hospital (Afari *et al.,* 2014).

Moreover, time is a vital component when dealing with rescuing two lives. It was reported that one of the causes of delay to receive healthcare services is the lack of transport within the healthcare facility. The finding of this study showed that only 12.5% of PCHU and 63.6% of PHCU+ had a vehicle to transport the referred patient with preeclampsia to the next healthcare facility level. The finding from this study is corresponding to what is reported in India by Jayanna et al. (Jayanna *et al.*, 2014) who reported that only 22% of facilities had ambulances for the transportation of referral patients.

Conclusion

Healthcare facilities of higher levels in Zanzibar have most of the medications, supplies, tests, and equipment as well as healthcare providers with adequate knowledge and skills necessary for the management of pre-eclampsia. However, a huge gap in the availability of the same was observed at lower healthcare facilities level. Moreover, the referral procedure is poorly implemented in most of the facilities of lower level. Therefore, in order address the problem of pre-eclampsia, more efforts should be focused on improving healthcare facilities of lower level by supplying adequate resources for the proper diagnosis, proper management and timely referral of patients with pre-eclampsia.

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Authors' contribution: SR conceived, designed, and conducted the study. SM and SA analyzed the data and wrote the manuscript. All authors read and approved the final manuscript.

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