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Incidence and risk factors of pre-eclampsia in the Paropakar Maternity and Women's Hospital, Nepal: a retrospective study

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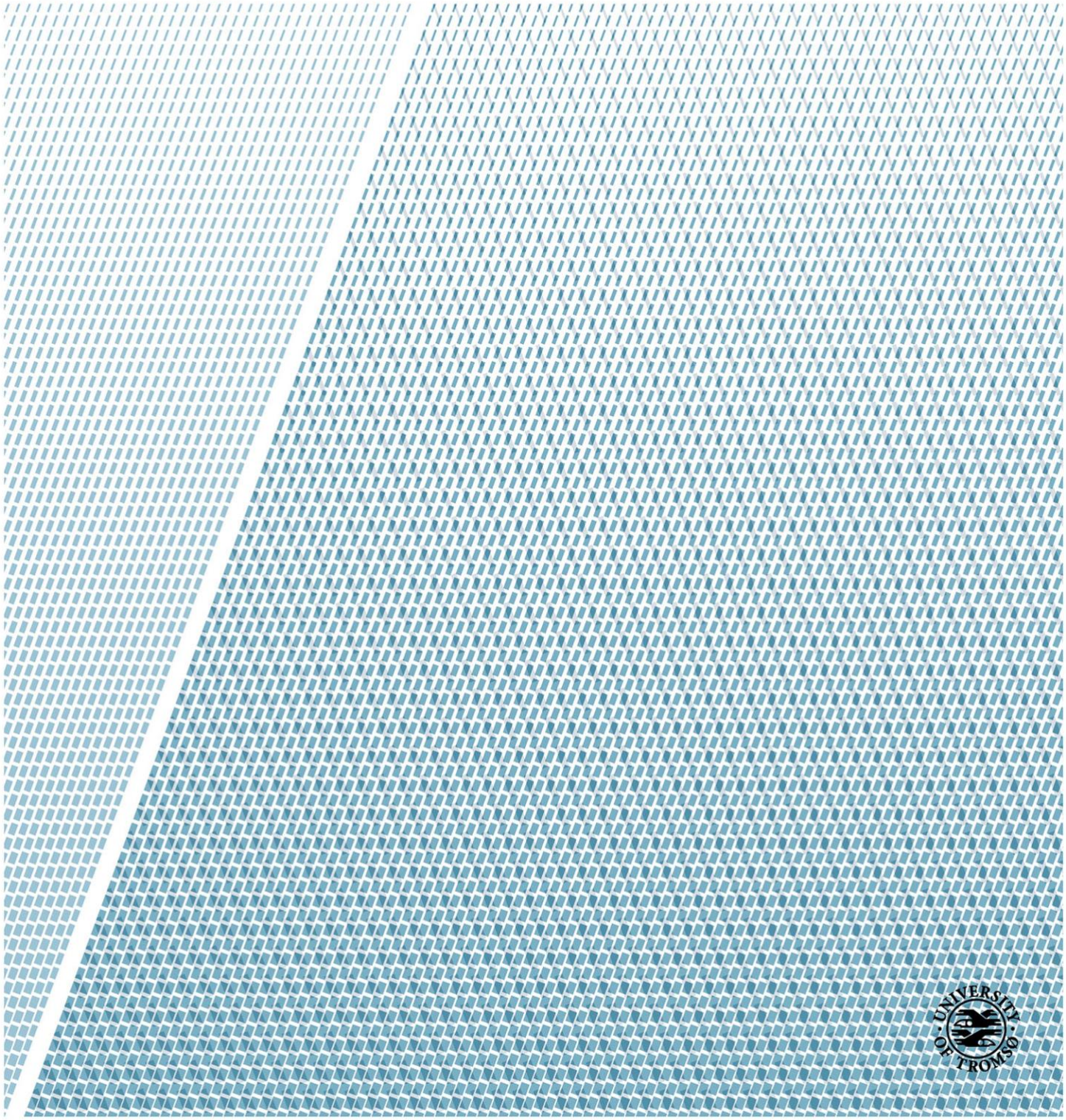

DEDICATION

This thesis is dedicated to my late lovely brother Nitesh Das who provided me encouragement and strength at every stage. He will always remain in my heart.

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PREFACE

The topic of my master's thesis is "Incidence and risk factors of pre-eclampsia in the Paropakar Maternity and Women's Hospital, Nepal: a retrospective study". I got interested in studying pre-eclampsia because of my educational background and past work experience. I went to a nursing school in Nepal for my undergraduate studies and later worked in maternal and child health department in Nepal as a registered nurse for 2 years. During that period, I witnessed many unfortunate and preventable maternal and neonatal mortality and morbidity. Pre-eclampsia is the second leading cause of maternal morbidity and mortality in Nepal. When I went through the literature search, I found that there is not much research done in pre-eclampsia in Nepal. Therefore, I decided to work in this area in order to fill this gap in the literature on incidence of pre-eclampsia in Nepal and how the risk factors for this disease are distributed there.

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ABSTRACT

Objective: To determine the incidence of pre-eclampsia and distribution of risk factors for pre-eclampsia in Paropakar Maternity and Women's Hospital, Kathmandu, Nepal.

Methods: A retrospective study was conducted that included a total of 4820 deliveries from September 17 to December 18, 2017. Data were obtained from the medical records in the hospital's Statistics Department. Associations between the risk factors and pre-eclampsia were determined using logistic regression analysis and expressed as odds ratios.

Results: The incidence rate of pre-eclampsia in the study population was 1.8%. Higher incidence of pre-eclampsia was observed for women older than 35 years (y) (OR = 3.27; CI 1.42-7.52) in comparision to mothers aged 20-24 years, primiparous women (OR = 2.12; CI 1.25-3.60), women with gestational age less than 37 weeks (OR = 3.68; CI 2.23-6.09), multiple pregnancies (OR = 8.49; CI 2.92-24.72), chronic hypertension (OR = 13.64; CI 4.45-41.81), urinary tract infection (OR = 6.89; CI 1.28-36.95) and gestational diabetes (OR = 11.79; CI 3.20-43.41). Iron and calcium supplementation appear to be protective.

Conclusion: Age of the mothers, primiparity, early gestational age, multiple pregnancies, chronic hypertension, urinary tract infection and gestational diabetes were the significant risk factors for pre-eclampsia. Iron and calcium supplementation and young aged women were somewhat protective.

LIST OF TABLES AND FIGURES

ABBREVIATIONS

AOR: Adjusted odds ratio

CI: Confidence interval

GNI: Gross National Income

HDI: Human Development Index

NHRC: Nepal Health Research Council

MDG: Millenium Development Goal

OR: Odds Ratio

PlGF: Placental growth factor

REK: Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk

WHO: World Health Organization

INTRODUCTION

1.1 Background

1.1.1 Definition Pre-eclampsia

In the American College of Obstetricians and Gynecologists' task force report (1) on hypertension in pregnancy, pre-eclampsia is defined as: an increase in systolic blood pressure to at least 140 mm of Hg and diastolic blood pressure to 90 mm of Hg or greater in two or more consecutive occasions ≥4 hours apart after 20 weeks of gestation, combined with proteinuria (a 24-hour urine collection with a total protein excretion of ≥300mg or ≥1+ on urine dipstick) and, in the absence of proteinuria, oedema (among other symptoms).

1.1.2 Epidemiology of maternal mortality and pre-eclampsia in developed and developing countries

Globally, approximately 30 3000 women die from pregnancy and childbirth-related complications annually (2, 3). Maternal mortality has declined by about 44% worldwide, but is still high (2). It declined from 385 deaths per 100 000 live births in 1990 to 216 deaths per 100, 000 in 2015 (3). Almost 99 % of maternal deaths occur in developing (low income and middle income) countries (2). According to World Health Organization (WHO), women in such countries have 33 times higher risk of dying during their lifetime from pregnancy-related complications compared to those in developed (high income) countries (4). In 2015, the maternal mortality ratio in developing countries was found to be 239 per 100 000 live births *versus* 12 per 100 000 live births in developed countries (2, 3). Low-income countries are

those with a Gross National Income (GNI) per capita of $1045 or less and middle income with GNI per capita above $1045 but less than $12 736; high income countries have a GNI above the latter (5).

Pre-eclampsia is an important cause of maternal, perinatal and neonatal morbidity and mortality; it affects about 3-5% of pregnancies (6). Its impact is higher in developing countries in which the incidence of pre-eclampsia is approximately 7 times higher than in developed countries (on average 2.8% of live births *versus* 0.4%) (7, 8). Nevertheless, the incidence for the latter varies greatly between countries. For example, the incidence of pre-eclampsia in European countries in Norway is 2.28% (9), and 4.00% in Finland (10). The study conducted in low-and middle-income countries show that the overall incidence of pre-eclampsia in African countries is 2.32%, Asian countries 3.13% and the Latin American countries 6.00% (11). Among the Asian countries, the rate of pre-eclampsia varies from 4.60% in India to Srilanka with only 1.40% (11).

1.1.3 Complications of pre-eclampsia

Both acute and long-term complications occur as the result of pre-eclampsia. Secondary deaths to pre-eclampsia are mainly due to eclampsia, uncontrolled hypertension, or systemic inflammation (12). World-wide more than 50,000 maternal deaths occur due to eclampsia (7). The latter is defined as the occurrence of seizure in a woman with preeclamptic signs and symptoms (11). Eclampsia is associated with 1.8% maternal deaths in developed nations and more than 15% in developing nations (12).

Pre-eclampsia increases the likelihood of complications such as hemorrhage and thrombocytopenia, which eventually lead to maternal and neonatal adverse

outcomes. A study in United States of America (USA) has shown that women with pre-eclampsia had 3.1% to 6.0% chance to develop hemorrhage and 0.9%-3.0% thrombocytopenia (13).

In developing countries, pre-eclampsia accounts for more than six million perinatal deaths, nearly eight million preterm births, and almost 20 million low-birthweight infants (11)**.** Bilano et al. (11) documented that pre-eclampsia accounts for almost 10% of perinatal deaths, nearly 28% of preterm births and about 35% of low-birthweight babies in Asian countries.

Furthermore, it is reported that around 20% of women develop hypertension or microalbuminuria within 7 years of a pre-eclamptic pregnancy compared to only 2% for uncomplicated pregnancies (12). Bellamy et al. (14) reported that after a pre-eclamptic pregnancy women had higher risks of hypertension (3.70%), ischemic heart diseases (2.16%), stroke (1.81%) and venous thromboembolic diseases (1.19%).

Short-term and long-term adverse outcomes related to pre-eclampsia increase the economic burden in countries and individuals due to higher health care costs. A study in the USA indicates that the total health care cost for a pre-eclamptic pregnancy was greater than of a normal pregnancy (i.e., no complications to the health of mother and fetus) (13). Similarly, preterm infants needed more intensive care and had to stay for longer periods in the hospital and thereby increased costs. In addition, infants born with gestational age <37 weeks resulted in higher costs compared to infants born at term (13). Long-term complications also increased the financial burden of medical care and supervision.

1.1.4 Pertinent Nepal context

1.1.4.1 Country profile

Nepal is a small landlocked and agricultural country with multicultural, geographical richness and diversity. It is located in the southern part of Asia wedged between India to the East and South and China to its north. It covers an area of 147 181 km. Administratively, the country is divided into 7 provinces, 77 districts, 6 metropolitan cities, 11 submetropolitan cities, 276 municipalities, and 481 rural municipalities. There are about 125 ethnic groups and 123 languages are spoken in Nepal. It is a developing country with a GNI per capita of USD 730. Political instability, deprivation, discrimination, conflicts and catastrophic events are major factors in its poor development. Despite these hindrances and decade-long conflicts, Nepal has achieved the United Nations Millennium Development Goal 4 (MDG-4) of reducing child mortality, and is likely to achieve the other 4 goals (15).

Figure 1, Map of Nepal

1.1.4.2 Health system of Nepal

The health care system of Nepal is administered by its Ministry of Health (MoH) and is responsible for all related planning and policies. It consists of the Department of Health Services that regulates the central, zonal and district hospitals, as well as the primary health care centres, health posts, sub-health posts, female community health volunteers (FCHV) and outreach clinics (see Figure 2). Health posts and sub-health posts are considered as the first place to contact for basic health services. Generally, the FCHV and the outreach clinics are responsible for all who seek healthcare in villages. The unmanaged cases at the health and sub-health posts are

referred to the district level or zonal level hospitals. The most serious cases are referred to the specialty tertiary care centre which is situated in the capital of Nepal, Kathmandu (16).

Table. 1 Demographic profile of Nepal (17):

Total Population both sexes	29, 384, 297 (July 2017 est.)
Kathmandu population (capital of Nepal)	1, 442, 271 (2018 est.)
Population growth rate	1.16% (2017 est.)
Human development index (HDI)	0.558 (2016 est.) Rank 144
Life expectancy at birth (Years)	71 years (2017 est.)
Crude birth rate	19.5 births/1000 population (2017 est.)
Total fertility rate	2.12 children born/per women
Mothers mean age at first birth	20.8 years, Median: 25-29 years (2016 est.)
Literacy rate	Male: 76.4%, Female: 53.1% (2015 est.)
GNI per capita ($USA)	$ 730 (2016 est.)
Total health expenditure	5.8% of GDP (2014 est.)

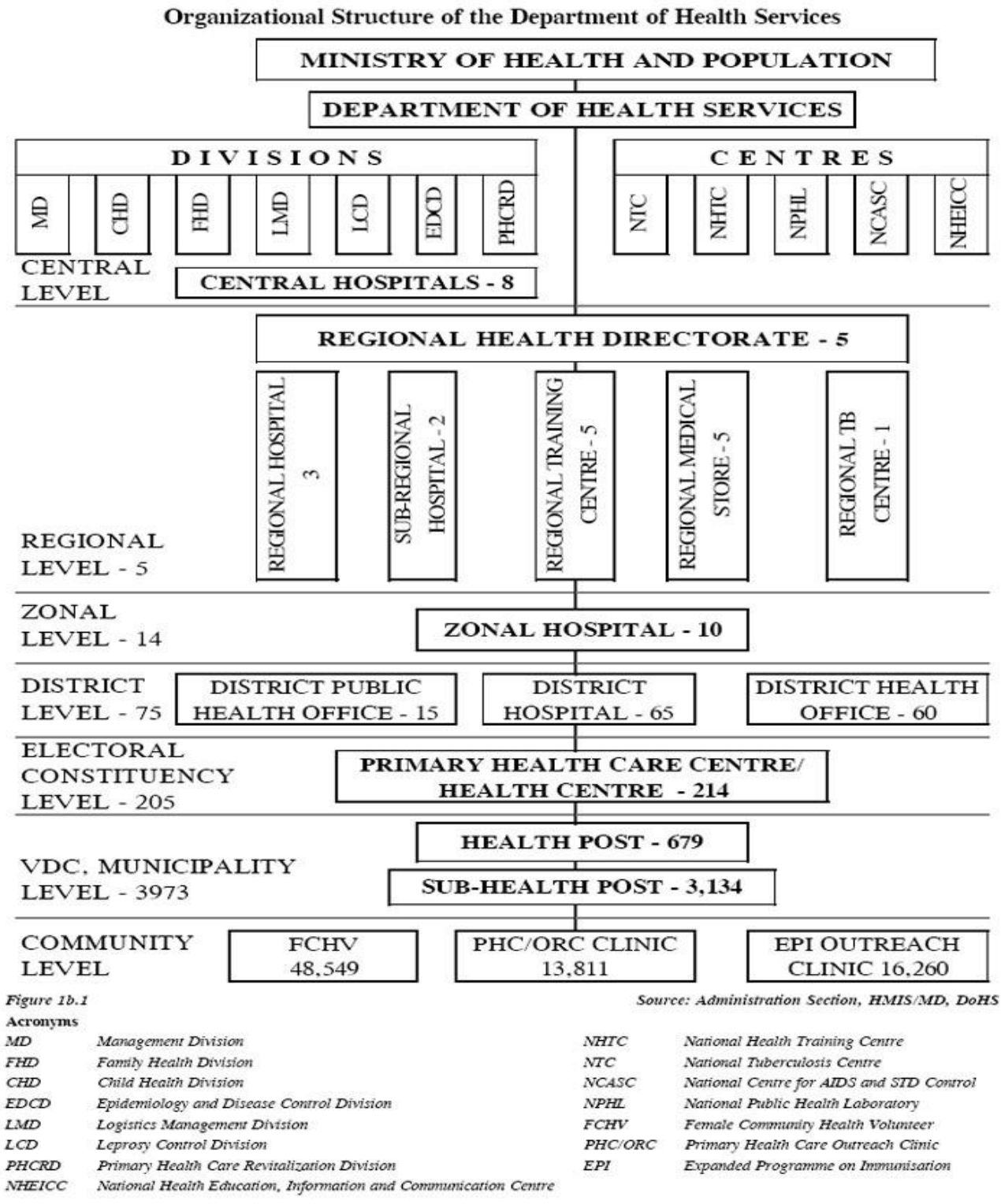

Figure 1b.1 *Source: Administration Section, HMIS/MD, DoHS*

Acronyms

MD	*Management Division*	*NHTC*	*National Health Training Centre*
FHD	*Family Health Division*	*NTC*	*National Tuberculosis Centre*
CHD	*Child Health Division*	*NCASC*	*National Centre for AIDS and STD Control*
EDCD	*Epidemiology and Disease Control Division*	*NPHL*	*National Public Health Laboratory*
LMD	*Logistics Management Division*	*FCHV*	*Female Community Health Volunteer*
LCD	*Leprosy Control Division*	*PHC/ORC*	*Primary Health Care Outreach Clinic*
PHCRD	*Primary Health Care Revitalization Division*	*EPI*	*Expanded Programme on Immunisation*
NHEICC	*National Health Education, Information and Communication Centre*		

Figure 2, Organizational Structure of the Department of Health Services of Nepal (16)

Out of pocket payment (User fees) is the largest source of funding for healthcare in Nepal followed by government expenditure. The latter derives from taxes, non-tax

revenues and external donors (mostly foreign aid) (18). A large amount of out of pocket payment is made to private health sectors both by the poor and rich in search of quality care (19). The national safe motherhood and the newborn programs were introduced to achieve good health outcomes for both mother and the newborn. The 'Aama programme' was launched to provide cash incentives for mothers who complete four or more antenatal visits. Transportation fees to reach the healthcare centres and free delivery services to promote birth preparedness encourage the institutional delivery (20), thereby improving maternal and child healthcare**.** Incentives are also provided to encourage health workers to conduct home deliveries.

1.1.4.3 Epidemiology of maternal mortality and pre-eclampsia in Nepal

Maternal mortality is on the decrease in Nepal. Maternal mortality declined from 850 per 100 000 live births in 1990 to 258 per 100 000 live births in 2015 (15). However, the ratio is still high compared to other developed and developing countries. Furthermore, the decline in maternal mortality rate is not same across the country as disparities exist between regions, rural and urban areas and different social groups (15). A study conducted in 8 districts of Nepal reported that the proportion of maternal mortality in the Rasuwa districts (17%) was two times higher than that of Sunsari and Okhaldunga (8%) (21).

Pre-eclampsia is indeed a common cause of maternal morbidity and mortality in Nepal. According to a Nepalese maternal mortality and morbidity study conducted in 2008-2009, pre-eclampsia/eclampsia is the second leading cause of this. Maternal deaths associated with pre-eclampsia/eclampsia was increased from 16% in 1998 to 21% in 2008 (21).

In 2014 Bilano et al. (11) showed that out of 8265 deliveries in Nepal, 180 (2.18%) of women developed pre-eclampsia. However, Abalos et al. (27) reported only 0.59% of pre-eclampsia incidence in Nepal out of 11239 women. This discrepancy in incidence rate may be due to unintended bias and use of different criteria in the selection of pre-eclampsia cases and/or sample size.

Pre-eclampsia has adverse effects on maternal and perinatal outcomes. It is related to more than 1% of maternal deaths in Nepal, approximately 11% perinatal death, and about 25% preterm births and 38% low birthweight (11).

1.1.5 Pathophysiology and distribution of risk factors for pre-eclampsia

The exact etiology of pre-eclampsia is not completely known. It is hypothesized that the damage and dysfunction of endothelial cells causes it. The latter may mainly be due to placental ischemia, immune maladaptation and genetic imprinting (22). Impaired trophoblastic differentiation and invasion in early pregnancy leads to abnormal placentation, which causes placental ischemia. This stimulates sustained oxidative stress and a maternal systemic inflammatory response to pregnancy and causes endothelial dysfunction (23).

There are several maternal and clinical risk factors that either alone or in combination may contribute to the high risk of pre-eclampsia (24). Genetic factors, diet, parity, gestational weight gain, maternal age, multiple pregnancies, previous history of pre-eclampsia, maternal pre-existing conditions such as diabetes, chronic hypertension, and infections are considered to play influential roles in the development of pre-eclampsia (25, 26).

Pre-eclampsia is considered as a disease of first pregnancy. A study conducted in 24 low-and- middle-income countries in three regions, namely Africa, Latin America and Asia, showed that among 6753 pre-eclampsia cases, more than 50% of women were primiparous; for non-pre-eclampsia cases (305 402) the figure was around 42 % (27). Similarly, the same study indicated that with increasing age the risk of developing pre-eclampsia increased. About 15% of pre-eclampsia deliveries were for mothers aged over 35 years, and only 8.5% of non-preeclampsia deliveries occurred in this age group (27). It has also been reported that about 10-20% of pre-eclampsia cases involve women older than 40 years (28).

Maternal diseases are also known to associated with increased pre-eclampsia risk. It has been documented that for pre-eclampsia cases the incidence of chronic hypertension and diabetes mellitus are 15-10% and 10-35% respectively (28). Moreover, a Taiwanese population study showed that about 60% of pre-eclampsia cases were primiparae mothers, 8.2% had multiple pregnancies and 8% had gestational diabetes, compared to 49.7%, 1.8% and 4.7% respectively for deliveries without pre-eclampsia. (29).

1.2 Statement of purpose

Although pre-eclampsia does not necessarily lead to maternal death, women with pre-eclampsia are at high risk of transitioning to eclampsia, which may be life threatening to both mother and fetus. Maternal, perinatal and neonatal morbidity and mortality associated with pre-eclampsia is high in Nepal compared to other developed and developing countries. To date no studies have addressed the risk factors for pre-eclampsia in Nepal.

Although there are many studies on risk factors for pre-eclampsia that have been conducted in developed countries, and few studies are conducted in developing countries. Some inconsistencies may also exist between different countries (11). Based on this, the results of the present study should be useful for other researchers in the examination of the distribution of risk factors for pre-eclampsia in Nepal. For policy and clinical purposes, it is vital to identify the most important risk factors. An understanding of the determinants of pre-eclampsia will facilitate the prioritization of interventions and thus resource allocations, and thereby to identify high-risk pregnancies (those in which the health and life of both mother and fetus are at increased risk) (11).

1.3 Objectives of the study

1.3.1 General objective

To determine the incidence of pre-eclampsia and the distribution of risk factors for pre-eclampsia in the Paropakar Maternity and Women's Hospital in Nepal.

1.3.2 Specific Objectives

To determine the incidence of pre-eclampsia in the Paropakar Maternity and Women's Hospital in Nepal and to examine the associations between pre-eclampsia and the factors listed below:

(i) Maternal age,

(ii) Parity,

(iii) Gestational age,

(iv) Multiple pregnancies,

(v) Dietary supplementations during pregnancy,

(vi) Maternal health issues including gestational diabetes, chronic hypertension, urinary tract infection and asthma,

(vii) Sub-fertility treatment.

1.4 Research Question

What are common risk factors in Nepal that lead to pre-eclampsia and their distribution?

METHODOLOGY

2.1 Study area

Our research was conducted at the Paropakar Maternity and Women's Hospital (website: http://www.pmwh.gov.np/), which was established in August 1959 and is located in the city of Thapathali, Kathmandu District of Nepal. It is popularly known as Prashuti Griha. It is the pioneer and the largest institution to provide cost-effective services. Most of the complicated and high-risk pregnancy cases are referred to this hospital from different parts of the country. Most of the instutional deliveries in the country take place at this hospital. Yearly, around 12000 babies are delivered at this hospital.

Figure 3, Paropakar Maternity and Women's Hospital.

2.2 Study period

The study period was from January to May 2018.

2.3 Study design

The study design was retrospective.

2.4 Sample size

Based on an expected prevalence of pre-eclampsia of 2.18% in Nepal (11), a sample size of 4820, a power of 80%, a significance level (p-value) of 0.05 and an exposed/non-exposed group ratio of 1:4 (30), odds ratios of ≥ 0.90 were detectable. Due to the low prevalence of diseases and time constraints the ratio 1:4 was selected.

2.5 Study population

The study cohort consisted of all pregnant women who had given birth between September 17 and December 18 of 2017. A total of 4820 women were assessed during this period.

2.6 Inclusion and exclusion criteria

All women who gave birth during the recruitment period.

2.7 Data collection

The Paropakar Maternity and Women's Hospital database of births constituted our data source. All available information about the delivering women and their newborn for the study period were entered into the study database. The latter was constructed employing Microsoft Excel to facilitate the identification of potential

risk factors for pre-eclampsia previously identified in a detailed search of the literature.

The dependent variable pre-eclampsia was entered as a binary variable, specifically women with and without pre-eclampsia were categorized as 'yes' and 'no' respectively. Those with pre-eclampsia were identified from recorded diagnoses. The latter were reviewed for specific clinical and laboratory findings and compared to the WHO criteria, including increased blood pressure (at least 140/90 mm of Hg or above on two occasions at least 4 hours apart after 20 weeks of gestation combined with proteinuria >0.3 g/24 h or ≥1 measured by a urine dipstick) (31).

The independent variables considered were: maternal age, gestational age, parity, multiple pregnancies, supplementations and maternal diseases condition such as chronic hypertension, gestational diabetes mellitus, urinary tract infection, hypothyroidism, asthma and subfertility.

Maternal age at the time of delivery was categorized as 15-19, 20-24, 25-29, 30-34, and ≥35 years. Parity was defined as the number of previous live births and stillbirths and was dichotomized into primiparity and multiparity. Gestational ages recorded at the time of delivery were classified into <37, 37-41 and >41 weeks. Supplementation included all mothers who had taken iron and calcium during pregnancy. This information was obtained from the patients' medical records. Pregnancies were designated as singletons or multiple, and the latter were grouped as twins, triplets or multi-fetal pregnancies.

Information obtained from the medical records about diseases other than pre-eclampsia included: gestational diabetes mellitus (defined as the increased blood sugar level after 20 weeks of the gestational age, and fasting glucose level

≥6.7mmol/l), as well as urinary tract infection (recorded diagnosis and White blood cells in urine sample and/or urine culture report) and hypothyroidism (recorded diagnosis and/or abnormal thyroid function test report). Respectively, the indicated variables with and without disease conditions were classified as ‘yes’ and ‘no’.

2.8 Ethical consideration

Ethical approval was obtained from the Nepal Health Research Council (NHRC) and the Norwegian Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk (REK Nord-2017/2440) (see Appendix). In addition to this, a permission letter was obtained from the director and the research committee of the Paropakar Maternity and Women’s Hospital. All registered data were anonymized prior to their use for statistical purposes and related assessments.

2.9 Statistical analysis

The information was entered into Microsoft excel and was cleaned, sorted and coded. A double data entry system was used to minimize errors. The data were analyzed using the Statistical Package for Social Science (SPSS) version 24. Descriptive statistical findings are reported as numbers and percentages in order to evaluate the distributions of dependent and independent variables. Mean, median, mode and standard deviation were also calculated.

Binary logistic regression was employed to assess the strength of the associations between dependent and independent variables. Dummy variables were created to fit the variables in the regression model to explore the interaction between outcome and predictor variables. Multi-collinearity was tested using the variance inflation factor (VIF) among the independent variables prior to their entry into the model.

Initially, the univariable logistic regression analyses were conducted to identify risk factors associations with pre-eclampsia. Variables (including potential confounders) with p-values <0.05 in this preliminary step were included in the subsequent multivariable logistic regression analysis (employing the enter method). Odds ratios and their 95% confidence intervals were calculated for the pre-eclampsia risk factors. The Hosmer-Lemeshow model goodness-of-fit test was applied.

RESULTS

3.1 Maternal age and selected pregnancy outcomes

The mean, median**,** mode (standard deviation) of maternal age were 26.4, 25.0**,** 23.0 (5.2) years in women with pre-eclampsia and 24.4, 24.0, 22.0 (4.6) in women without pre-eclampsia (Table 2). For both women with pre-eclampsia and without pre-eclampsia the mean parity was 1.6, with a mode of 1.0, while the mean gestational age for both pre-eclampsia and non-pre-eclampsia deliveries were comparable (i.e. 38.0 and 39.0 weeks respectively). Most of the deliveries in both groups occurred between weeks 37.0-41.0 of gestation. The mean birth weight of the newborn baby (2798 grams) was lower in pre-eclampsia mother compared to non-pre-eclampsia mother (2997 grams). Delivery by caesarean section was higher among the women with pre-eclampsia. About 71.8% of the pre-eclamptic mothers had a caesarean section and 26.1% among those without this impairment.

Table 2. Maternal age and selected pregnancy outcomes (N = 4820)

Pre-eclampsia		**Maternal age (years)**	**Gestational Age (weeks)**	**Parity**	**Birth weight (grams)**
Yes	*Mean*	26.4	38.0	1.6	2798
	Median	25.0	38.0	1.0	2800
	Mode	23.0	36.0	1.0	3000
	Standard deviation	5.2	16.7	0.6	740
No	*Mean*	24.4	39.0	1.6	2997
	Median	24.0	39.0	1.0	3000
	Mode	22.0	40.0	1.0	3000
	Standard deviation	4.6	12.0	0.9	474

3.2 Distributions of factors associated with pre-eclampsia

The incidence rate of pre-eclampsia in the study population was 1.8% and the distribution of factors associated with pre-eclampsia are provided in Table 3. A majority, namely 38 (44.7%), of the woman with pre-eclampsia and 2084 (44.0%) of those without pre-eclampsia were in the 20-24 year age range. Ten (11.8%) of women with pre-eclampsia were older than ≥35 years compared to 170 (3.6%) among those without pre-eclampsia. Moreover, 15 of the women (17.6%) with pre-eclamptic deliveries and 518 (10.9%) were without this disease in the 30-34 age group. Consequently, pre-eclampsia deliveries were more common for mothers with advanced age. Furthermore, 55 (64.7%) of pre-eclamptic women were primiparous compared to 2661 (56.2%) among those without. By comparison, gestational age <37 weeks was more common among pre-eclamptic deliveries (32.9%) compared to those without (9.8%) ($p = 0.000$). Also, 6% of pre-eclampsia cases had multiple pregnancies whereas only 0.3% occurred among those not so afflicted. Similarly, the proportion of diseases such as gestational diabetes (4.7% versus 0.3%), chronic hypertension (5.9% versus 0.3%) and urinary tract infection (2.4% versus 0.3%) was higher among women with pre-eclampsia compared to those without.

3.3 Univariable logistic regression analysis

When the 20-24 age group was selected as the reference population, women aged ≥35 years had an increased odds of developing pre-eclampsia (OR = 3.23; 95% CI 1.58-6.59). Similarly, the odds of developing pre-eclampsia at gestational ages <37 weeks was about 4-fold higher. Primiparous women had 1.43 times the risk of developing pre-eclampsia than multiparous mothers, but this was not statistically

significant (p = 0.12). Similarly, the odds of developing pre-eclampsia by women with multiple pregnancies, chronic hypertension, urinary tract infection, and gestational diabetes were, respectively: 10.14 (95% CI 3.82-26.87); 19.67 (95% CI 6.97-55.41); 7.58 (95% CI 1.70-33.69); and 17.93 (95% CI 5.72-56.12). Asthma and subfertility treatment did not show a significant association with the development of pre-eclampsia.

Since odds values below 1 are difficult to interpret (32), all that can be concluded is that iron and calcium supplementation during pregnancy appears to reduce the risk of pre-eclampsia.

Table 3. Distributions of factors associated with pre-eclampsia and univariable logistic regression analysis outcomes

Independent variables	**Pre-eclampsia n (%)**		**Univariable analysis**		
	Yes 85 (1.8)	**No 4735 (98.2)**	***Crude Odds Ratio***	***95% CI***	***p-value***
Age (years)					
15-19	4 (4.7)	610 (12.9)	0.36	00.128-1.01	0.053
20-24	38 (44.7)	2084 (44.0)	1	Ref.	0.000
25-29	18 (21.2)	1353 (28.6)	0.73	0.42-1.28	0.27
30-34	15 (17.6)	518 (10.9)	1.59	0.87-2.91	0.13
≥35	10 (11.8)	170 (3.6)	3.23	1.58-6.59	0.001
Parity					
Primiparity	55 (64.7)	2661 (56.2)	1.43	0.91-2.24	0.12
Multiparity	30 (35.3)	2074 (43.8)	1	Reference	-
Gestational age					
<37 weeks	28 (32.9)	466 (9.8)	4.34	2.72-6.92	0.000
37-41 weeks	54 (63.5)	3903 (82.4)	1	Reference	0.000
>41 weeks	3 (3.5)	366 (7.7)	0.59	0.18-1.90	0.38
Supplementation	75 (88.2)	*4518 (95.4)	0.08	0.04-0.16	0.000
Multiple pregnancies	5 (5.9)	29 (0.6)	10.14	3.82-26.87	0.000
Maternal Diseases					
Chronic Hypertension	5 (5.9)	15 (0.3)	19.67	6.97-55.41	0.000
Urinary tract infection	2 (2.4)	15 (0.3)	7.58	1.70-33.69	0.008
Gestational diabetes	4 (4.7)	13 (0.3)	17.93	5.72-56.12	0.000
Hypothyroidism	4 (4.7)	39 (0.8)	5.95	2.08-17.03	0.001
Sub-fertility treatment	1 (1.2)	14 (0.3)	4.01	0.52-30.88	0.182
Asthma	1 (1.2)	9 (0.2)	6.25	0.78-49.89	0.084

***Missing=169 (3.6%)**

3.4 Multivariable logistic regression analysis

Independent variables which had statistically significant association with pre-eclampsia in the univariable analysis and summarized in Table 3 were included in the multivariable analysis. The pertinent adjusted odds ratios (AORs) for these risk factors are summarized in Table 4, and the Hosmar-Lemeshow test for goodness of

fit was applied and indicated that the data adequately fit in the model (with a Chi-square value of 4.65 and a p-value of 0.59, which indicates adequate distribution among subgroups).

The statistically significant risk factors in the univariable analysis were also significant in the multivariable analysis. Most of the adjusted odds ratio were somewhat lower compared to the crude. Increased values were evident for the following: primiparity (by 48.3 %), ages 25-29 (34.3 %) and 30-34 (11.9 %), and gestational age above 41 weeks (by 22.0 %). The primiparous women now had a 2-fold higher risk of developing pre-eclampsia compared to multiparous women (AOR = 2.12; 95% CI 1.25- 3.60). Women aged above ≥35 years retained a 3.2-fold increased odds of pre-eclampsia development. The positive trend in the prevalence of pre-eclampsia with increasing age also remained after adjustment (Table 4), as did the apparent protective influence of calcium and iron intake during pregnancy. Gestational age below 37 weeks (AOR = 3.68; 95% CI 2.23-6.09), multiple pregnancy (AOR = 8.49; 95% CI 2.92-24.72) and the maternal diseases condition variables such as chronic hypertension (AOR = 13.64; 95% CI 4.45-41.81), urinary tract infection (AOR = 6.89; 95% CI 1.28-36.95) and gestational diabetes (AOR = 11.79; 95% CI 3.20-43.41) were again robustly and significantly associated with an increased risk for developing pre-eclampsia.

Table 4. Multivariable analysis of factors associated with pre-eclampsia.

Independent variables			
Age	***Adjusted Odds ratio (AOR)***	***95% CI***	***p-value***
15-19	0.25	0.08-0.74	0.01
20-24	1	Reference	0.002
25-29	0.98	0.53-1.77	0.94
30-34	1.78	0.87-3.65	0.12
≥35	3.27	1.42-7.52	0.005
Parity			
Primiparity	2.12	1.25-3.60	0.005
Multiparity	1	Reference	-
Gestational age			
<37 weeks	3.68	2.23-6.09	0.00
37-41 weeks	1	Reference	0.00
>41 weeks	0.72	0.22-2.32	0.58
Supplementation	0.062	0.03-0.14	0.00
Multiple pregnancies	8.49	2.92-24.7	0.00
Maternal Diseases			
Chronic hypertension	13.6	4.45-41.8	0.00
Urinary tract infection	6.89	1.28-37.0	0.02
Gestational diabetes	11.8	3.20-43.4	0.00

DISCUSSION

The aim of the present study was to assess the incidence of pre-eclampsia in a specified time period and to determine the distribution of risk factors for pre-eclampsia in the Paropakar Maternity and Women's Hospital, Nepal. As mentioned earlier, most of the institutional deliveries in Nepal take place at this hospital. To our knowledge, this is the first retrospective cross-sectional study using this database to determine risk factors associated with the development of pre-eclampsia. A total of 4820 deliveries were included in this study, and of these 1.8% developed pre-eclampsia. Both univariable and multivariable logistic regression analyses shows that maternal age above 35 years, gestational age below 37 weeks, multi-fetal pregnancy, chronic hypertension, urinary tract infection, and gestational diabetes were risk factors of pre-eclampsia. The multivariable analysis also indicates that the primiparity is significantly associated with an increased risk of pre-eclampsia and age 15-19 years has the protective effect. The risk factors for pre-eclampsia ascertained in this study are similar to the risk factors that have been described in other studies conducted in developing and developed countries (11, 26, 29, 33).

4.1 Incidence of pre-eclampsia

The incidence of pre-eclampsia in the present study is comparable with that reported for the Koshi Zonal Hospital Nepal; the incidence of pre-eclampsia in the present study is 1.8% and in Koshi Zonal Hospital Nepal is 1.5% (34). The findings of the current study are also comparable with findings from low-and-middle-income countries globally. Asecondary analysis of the WHO Global Survey on Maternal and Perinatal Health in 24 low-and-middle-income countries found an incidence of 2.18% (11). However, the incidence rates reported in these study are higher than that reported by the Abalos et al. (27). The latter authors suggest that

lower incidence rates likely occur when strict criteria for defining pre-eclampsia are adhered to and when under-reporting of pre-eclampsia cases occurs (27).

On other hand, the incidence of pre-eclampsia in the current study is lower than that of the neighbouring countries like India (4.0%) and China (2.8%), and higher than that reported for Sri Lanka (1.4%) (11). The variation of incidence of pre-eclampsia between the countries might be because of the different distribution of maternal risk factors, of the availability/accessibility of health services and of diagnostic capacities (11, 35). In addition, in low income countries (GNI per capita $1, 025 or less), the quality of data might be impacted by a lack of funds and therefore of manpower for routine and systematic registration of data. The latter may well cause an underestimation of the incidence of pre-eclampsia (11). A study in Nepal (21) has also shown that there is variation in the pre-eclampsia incidence within countries, likely due to variations in the distribution of risk factors in different districts. In addition, changes in the distribution of risk factors could be due to a diversity in ethnicity, cultural practices, food preparation and consumption methods, and social beliefs among the various ethnic groups. However, our study did not address these issues due to the unavailability of such data. Similarly, due to time constraints the study was conducted in only one hospital, so we are not able to differentiate the variation in incidence according to different districts.

4.2 Risk factors for pre-eclampsia

4.2.1 Maternal age

Most of the studies showed that the risk of pre-eclampsia increases with age (11, 27, 35, 36). Supporting this, our study indicates that pregnant women who were 35 years old had more than 3 times higher odds of developing pre-eclampsia compared

to 20-25 years old women. One explanation could be that when women get older there is a gradual loss of compliance of the uterine blood vessels and increased arterial stiffness (36). Furthermore, the hemodynamic adaptation during pregnancy becomes more difficult with increasing age (37). On the other hand, some studies have not found an association between maternal age and pre-eclampsia (38-40). Perhaps this is related to differences in the study design and population (39).

As reported by Al-Tairi et al. (41) women aged between 15-19 years old experienced protection against pre-eclampsia relative to the 20-24 age group. In contrast to this, the studies conducted in other developing countries like Indonesia (42) and India (43) have shown an increased risk of pre-eclampsia in younger pregnant women. This might be due to the effects of confounders, type of study design and studied population diversity.

4.2.2 Parity

Generally, pre-eclampsia is regarded as the disease of first pregnancy (44). Studies conducted in developing countries have identified that primiparity is a risk factor for this outcome (11, 29, 35, 42). Our observation that primiparous mothers had two-fold higher risk for developing pre-eclampsia than multiparous women. Because first exposure to chorionic villi (which is of fetal origin) and related maternal immunological incompetence are more likely during the first pregnancy and can increase risk of pre-eclampsia (22).

In contrast to the present findings, studies conducted in India (39, 43) report no association between parity and pre-eclampsia development. The use of the case-control study design and small sample size, as well as differences in parity distribution, may explain this discrepancy. Kumar et al. (39) also stated that parity

was not found to be associated with the occurrence of pre-eclampsia, which could reflect selection bias. For example, selection bias may occur because women from lower and middle socioeconomic status groups were only included in their study; and these groups were shown to be at lower risk compared to the high socioeconomic status groups.

4.2.3 Gestational age

Our study demonstrates that gestational age below 37 weeks is significantly associated with pre-eclampsia. Women with gestational age below 37 weeks had nearly 4 times the risk of developing pre-eclampsia compared to 37-41 weeks. This finding is in agreement with research carried out in Yemen (41). In addition, a study conducted in Pakistan (38) has also indicated that pre-eclampsia diagnosis was associated with a significantly higher proportion of women with gestational age < 37 weeks when compared to non-pre-eclampsia women (38). A high fraction of soluble fms-like tyrosine kinase-1(sFlt-1), a circulating antiangiogenic molecule of placental origin, relative to the placental growth factor (PlGF) is considered a predictive marker for early onset of pre-eclampsia (41). Because the present study fails to distinguish between early and late-onset of pre-eclampsia, it might be difficult to assess whether early gestational age is a causal factor for pre-eclampsia or of pre-term delivery. Women with pre-eclampsia have a higher probability of giving pre-term birth compared to women without pre-eclampsia (45).

4.2.4 Consumption of Supplements

A recommendation by the WHO (46) is that iron and calcium supplementations be given to women during pregnancy in Nepal because the main dietary source of calcium are grains such as maize and wheat. A significant reduction in the risk of

pre-eclampsia with the supplementation of calcium (≥1 g/day) has been reported, especially for women with low-calcium intake (6, 47). Calcium supplementation in the second half of pregnancy helps to reduce the blood pressure (47), which eventually leads to a decrease in systematic oxidative stress and thereby reduces endothelial cells damage (22, 47). Our findings concur, although it was not possible to quantify the effect for the reasons mentioned earlier (i.e., odd ratios less than 1). A limitation to the quantitation of this protective effect is the small number of women with pre-eclampsia in our study population compared to those without.

4.2.5 Multiple pregnancies

Studies conducted in India (39, 40, 43), Taiwan (29), Ethiopia (44) and 29 low-and-middleincome countries (27) have revealed that women who have given birth to twins, triplets, or multiple fetuses are more likely to develop pre-eclampsia compared to the singleton pregnancies. In agreement, our study indicates that multiple pregnancies enhanced the odds eight-fold of developing pre-eclampsia compared to the singleton pregnancies. It has been suggested that the increased risk of pre-eclampsia in development during multi-fetal pregnancies might be due to the large placental mass and increased circulating levels of soluble fms-like tyrosine kinase-1(sFlt-1); the latter leads to high soluble fms-like tyrosine kinase-1 to placental growth factor (PlGF) ratios (48) and may be taken as predictive of pre-eclampsia (41).

An Indonesian study has suggested that multiple pregnancies can be protective of pre-eclampsia occurrence (42). These authors indicated that this finding may have been due to the high proportion of multiple pregnancies in the control group (i.e.,

non-pre-eclampsia cases) (42). As the data were obtained from medical record, information bias may also have been an issue.

4.2.6 Maternal diseases

4.2.6.1 Chronic hypertension

The prevalence of chronic hypertension is high in Nepal with low awareness, prevention, and control (49), and one study found that its prevalence in reproductive age in Nepalese women is almost 8% (50). Chronic hypertension is considered an important risk factors for pre-eclampsia (26) and our estimate of a 14-fold increase concurs. Our finding is in line with studies conducted in India (39, 43), Yemen (41), Ethiopia (36), Jordan (35), Uganda (51) and the WHO Global Survey on Maternal and Perinatal Health study (11, 27). Elevated cardiac output and increased systematic vascular resistance in hypertension is suspected to lead to endothelial cell dysfunction (22).

4.2.6.2 Gestational diabetes

Our study suggests that gestational diabetes patients had nearly 12-fold higher odds of pre-eclampsia. This finding is supported by other studies conducted in developing countries (11, 38, 52). This is biologically plausible because insulin resistance and high levels of insulin cause increased sympathetic activity and abnormal tubular sodium absorption which eventually lead to endothelial cell damage and thus increased risk of pre-eclampsia (22).

4.2.6.3 Urinary tract infection

Some studies (11, 29) report that the pre-eclampsia is more common in women who have urinary tract infection, and thus our observation of a near 7-fold increase concurs. It has been

suggested that this impact may be due to the increased inflammatory response during infectious diseases (53).

4.2.6.4 Hypothyroidism

Although in the univariable analysis the risk of pre-eclampsia was increased about 6-fold in women with hypothyroidism, it was not included in the multivariable analysis. The reason being that no research has been reported about hypothyroidism as a predictor of pre-eclampsia. Additional research needs to be carried out to establish hypothyroidism as a predictor of pre-eclampsia.

4.2.6.5 Asthma and Sub-fertility treatment

Our univariable analysis suggests that asthma and sub-fertility treatment are associated with an increased risk of pre-eclampsia incidence, although statistical significance was not reached. A study conducted in India (40) observed a statistically significant association of asthma with the occurrence of pre-eclampsia; however, it had small sample size and the observed prevalence was low.

4.3 Strengths and limitations

4.3.1 Strengths

There are limited data on pre-eclampsia in Nepal. This is the first known retrospective study conducted in Nepal at the Paropakar Maternity and Women's Hospital. As maternal mortality is comparatively high in Nepal and pre-eclampsia is a well-known contributor to maternal death, it is important to identify the risk factors for pre-eclampsia to improve intensive care. This is also essential in developing and improving risk management strategies and prevention of maternal

morbidity and mortality, as well as reducing the economic burden related to pre-eclampsia.

Even though our study was retrospective in design, it could be carried out quickly and with limited costs as the data was obtained from the medical records of a statistical department of a prominent hospital. Nevertheless, the data extraction from medical record was a challenge as the relevant original data was not computerized and had to be extracted from patient journals. Pregnant women from the different parts of Nepal are referred to the Paropakar Maternity and Women's Hospital and therefore our findings might be extrapolated to the national level.

The study population of the current study involved previously diagnosed women with pre-eclampsia. According to hospital protocols, diagnosis of pre-eclampsia was made by specialists at the GYN/OBS department of the Paropakar Maternity and Women's Hospital and was based on WHO guidelines. During data collection of the study data set, the WHO criteria for Pre-eclampsia diagnosis were used to confirm the diagnoses. The latter reduced any misclassification.

Multivariable logistic regression was used to identify the factors associated with the pre-eclampsia incidence. Adjusted OR values > 0.90 (see 2.4 sample size) and confidence interval did not include 1.00. Such OR values indicate strong and significant associations between risk factors and pre-eclampsia.

4.3.2 Limitations: Despite these strengths, the study has several limitations.

4.3.2.1 Confounders

Even though the multivariable analysis was carried out, many potential confounders were not controlled for due to a lack of pertinent information. For instance, socio-

demographic data such as ethnicity, level of education, occupational status, residence area, body mass index, and smoking status which are considered as potential confounders were not assessed. The reason for this was that the pertinent data were obtained from medical records which had been generated for administrative purposes and not for research purposes, and thus were not available to us.

4.3.2.2 Bias

This study is limited to only one hospital in Nepal, which could increase the chance of selection bias. It is a government hospital and most of the people from lower or middle socioeconomic status visit this hospital. Individuals with high socio-economic status primarily go to private hospitals. Consequently, this population component may not be included in our study population. As our data were extracted from medical records, there might have been clerical errors that could have led to information bias.

Even though the diagnosis of pre-eclampsia and other maternal diseases were made by expert clinicians, there may have been instances of under-estimation or over-estimation of the diagnoses and thereby would have introduced misclassification.

4.3.2.3 Generalizability

Although this study is based on data form one referral hospital, the results may not be generalizable to the whole population. Most of the babies born in institutional setting are delivered at the study hospital, however the national average of institutional deliveries is only 55.1% (54). Approximately, 45% of deliveries take place at non-hospital settings.

Even though some of the odds ratio are high, the precision is low as indicated by the wide confidence intervals, presumably due to the relatively low prevalence of the diseases considered. This dimension reduces the generalizability of the results. Similarly, due to time constraints and financial limitations, our cohort was limited to births that took place in 3 months of 2017. In addition, the precise temporal relationship between the variables is unknown because of the cross-sectional nature of the study. This dimension reduced the ability to establish causal relationships.

CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In summary, the incidence of pre-eclampsia was 1.8% in the Paropakar Maternity and Women's Hospital of Nepal for the period September 17 to December 18 of 2017. Pre-eclampsia was found to be significantly associated with maternal age, primiparity, gestational age, multi-fetal pregnancies and maternal diseases including chronic hypertension, urinary tract infection and gestational diabetes. Increasing age was a pre-eclampsia risk factor. The result showed that women older than 35 years were at increased risk of developing pre-eclampsia compared to women with age 20-24 years. Women aged 15-19 years had the lowest apparent risk of pre-eclampsia, while those of gestational age below 37 weeks had high risks of developing this disease. The use of iron and calcium supplements during pregnancy appear to be somewhat protective, while asthma and sub-fertility treatment were not significantly associated with pre-eclampsia.

5.2 Recommendations

- As there is limited research in Nepal on the incidence of and risk factors for pre-eclampsia and since the present study was limited to one government hospital, additional research with a larger sample size and timeframe and including both private and public hospitals in different regions of Nepal is needed to establish more precisely the incidence and risk factors for pre-eclampsia.

- It is recommended that the health authorities and policy makers should use the identified modifiable and non-modifiable risk factors as a screening tool

for pre-eclampsia to predict and establish its early diagnosis in order to reduce morbidity and mortality related to this disease.

- It is recommended that effective interventions strategies be implemented that target risk factors for pre-eclampsia to improve the quality health services in the area of maternal and child health.

- Women are encouraged to consume iron and calcium containing foods during the antenatal nutritional counselling period. A detailed study on calcium and iron supplementation and dietary habits in a large group of Nepalese population is also recommended.

- An awareness programme pertaining to high risk pregnancies and related risk factors is recommended, especially among females and males of reproductive age.

- To improve the quality of data, routine and systematic registration of pertinent data is encouraged in order to increase the certainty of disease incidence.

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Appendix I

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			23.01.2018	2017/2440/REK nord
			Deres dato:	Deres referanse:
			05.12.2017	

Vår referanse må oppgis ved alle henvendelser

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Forskningsansvarlig: UiT - Norges arktiske universitet
Prosjektleder: Jon Øyvind Odland

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 04.01.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektomtale
Svangerskapsforgiftning er en alvorlig komplikasjon i slutten av svangerskapet. Mange studier er gjennomførte i alle verdensdeler, med til dels store regionale variasjoner. Som helseproblem er det fortsatt en av de uløste gåter. I Nepal er det gjort veldig lite undersøkelser og vi vet enda lite om forekomst og utfall av disse svangerskapene. helsemyndighetene har et ønske om å gjennomføre studier som kan gi mer kunnskap, spesielt i forebyggende henviskt. Vår studie skal undersøke retrospektivt journaler til alle registrerte pasienter med svangerskapsforgiftning i et år og se etter fellesnevnere og kartlegge mulige årsaksfaktorer som kan brukes i forebyggende hensikt på lokal, nasjonalt og kanskje internasjonalt nivå.

Om prosjektet
Prosjektet skal i sin helhet utføres i Katmandu. I prosjektet ønsker man å kartlegge utbredelsen av svangerskapsforgiftning. Studien skal undersøke retrospektivt journaler til alle registrerte pasienter med svangerskapsforgiftning i et år og se etter fellesnevnere og kartlegge mulige årsaksfaktorer som kan brukes i forebyggende hensikt på lokal, nasjonalt og kanskje internasjonalt nivå.

Godkjenning fra etisk komite i Nepal er vedlagt. Etisk komite i Nepal har godkjent at det behandles helseopplysninger uten innhenting av samtykke. REK har ingen innvendinger til prosjektet

Vedtak
Med hjemmel i helseforskningsloven §§ 2 og 10 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 31.07.2018, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Besøksadresse:
MH-bygget UiT Norges arktiske universitet 9037 Tromsø

Telefon: 77646140
E-post: rek-nord@asp.uit.no
Web: http://helseforskning.etikkom.no/

Appendix II

Government of Nepal

Nepal Health Research Council (NHRC)

Estd. 1991

Ref. No.: 958

06 November 2017

Ms. Seema Das
Principal Investigator, Uit The Arctic University of Norway

Subject: Approval of research proposal entitled **Incidence and risk factors of pre-eclampsia in first and subsequent pregnancies: a cross-sectional study.**

Dear Ms. Das ,

It is my pleasure to inform you that the above-mentioned proposal submitted on **07 October 2017** (**Reg.no. 399/2017** please use this Reg. No. during further correspondence) has been approved by NHRC Ethical Review Board on **02 November 2017**.

As per NHRC rules and regulations, the investigator has to strictly follow the protocol stipulated in the proposal. Any change in objective(s), problem statement, research question or hypothesis, methodology, implementation procedure, data management and budget that may be necessary in course of the implementation of the research proposal can only be made so and implemented after prior approval from this council. Thus, it is compulsory to submit the detail of such changes intended or desired with justification prior to actual change in the protocol before the expiration date of this approval. Expiration date of this study is **17 May 2018.**

If the researcher requires transfer of the bio samples to other countries, the investigator should apply to the NHRC for the permission. The researchers will not be allowed to ship any raw/crude human biomaterial outside the country; only extracted and amplified samples can be taken to labs outside of Nepal for further study, as per the protocol submitted and approved by the NHRC. The remaining samples of the lab should be destroyed as per standard operating procedure, the process documented, and the NHRC informed.

Further, the researchers are directed to strictly abide by the National Ethical Guidelines published by NHRC during the implementation of their research proposal **and submit progress report in between and full or summary report upon completion.**

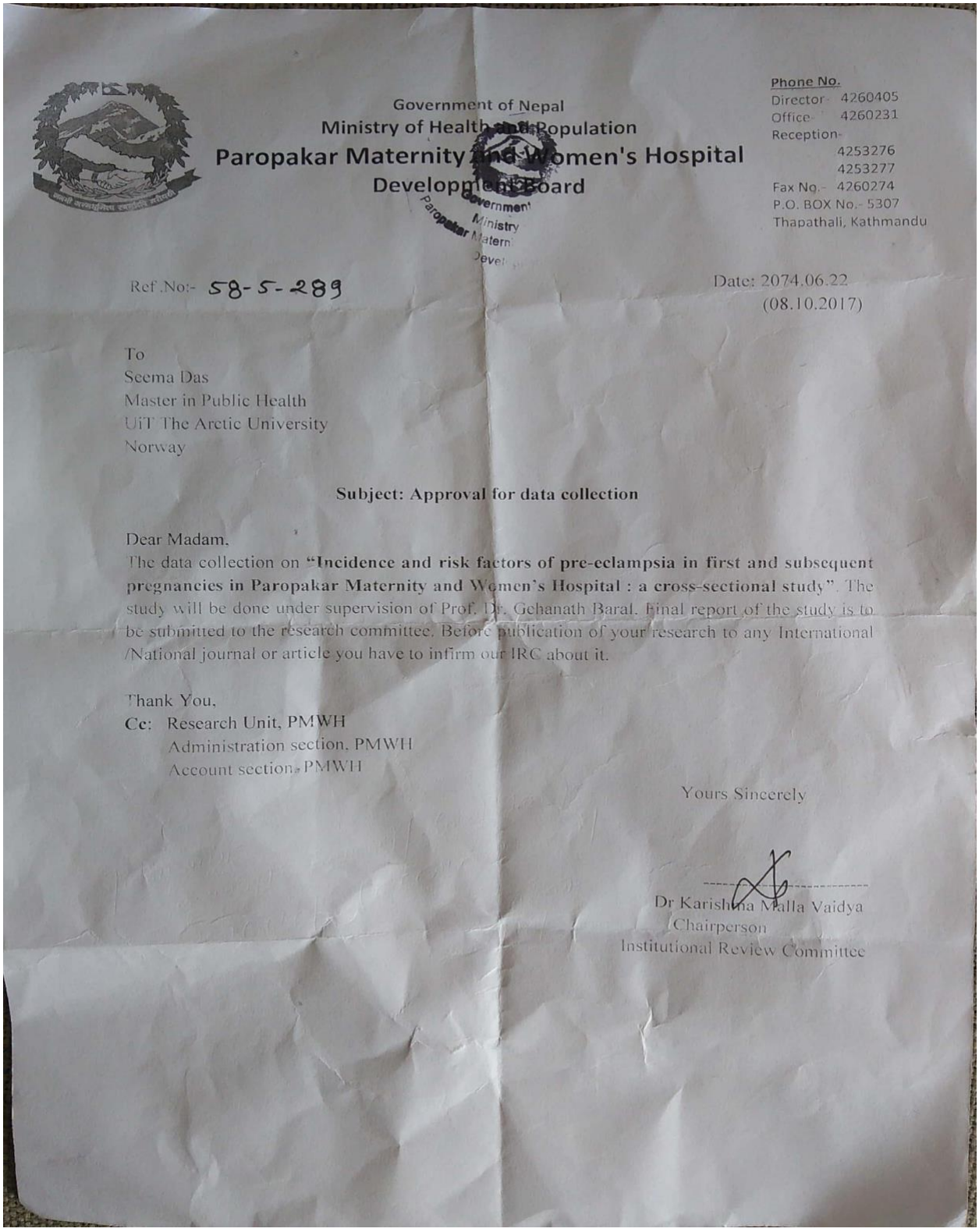
As per your research proposal, the total research amount is **NRs 40000.00** and accordingly the processing fee amount to **NRS 10000.00.** It is acknowledged that the above-mentioned processing fee has been received at NHRC.

If you have any queries, please feel free to contact the Ethical Review M & E section of NHRC.

Thanking you.

Prof. Dr. Anjani Kumar Jha
Executive Chairman

Appendix III



Government of Nepal
Ministry of Health and Population
Paropakar Maternity and Women's Hospital
Development Board

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P.O. BOX No.- 5307
Thapathali, Kathmandu

Ref.No:- 58-5-289

Date: 2074.06.22
(08.10.2017)

To
Seema Das
Master in Public Health
UiT The Arctic University
Norway

Subject: Approval for data collection

Dear Madam,
The data collection on **"Incidence and risk factors of pre-eclampsia in first and subsequent pregnancies in Paropakar Maternity and Women's Hospital : a cross-sectional study"**. The study will be done under supervision of Prof. Dr. Gehanath Baral. final report of the study is to be submitted to the research committee. Before publication of your research to any International /National journal or article you have to infirm our IRC about it.

Thank You,
Cc: Research Unit, PMWH
Administration section, PMWH
Account section, PMWH

Yours Sincerely

Dr Karishma Malla Vaidya
Chairperson
Institutional Review Committee