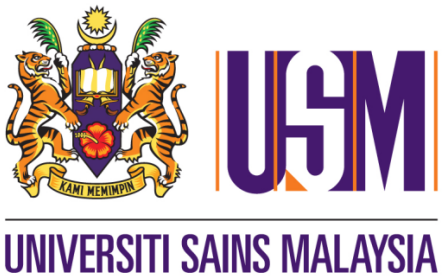
A RETROSPECTIVE STUDY ON PRE-ECLAMPSIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN

DR MAS IRFAN JAYA MAHAMOOTH

DISSERTATION SUBMITTED IN
PARTIAL FULFILMENT OF THE REQUIREMENT FOR
THE DEGREE OF MASTER OF MEDICINE
(OBSTETRICS AND GYNAECOLOGY)



UNIVERSITI SAINS MALAYSIA
2018

Acknowledgement

Bismillahirrahmannirrahim

Alhamdulillah, praise to Allah S.W.T, the Most Gracious and Most Merciful, for giving me the blessings, spirit, and strength to complete this thesis. My highest regards are dedicated to both my beloved parents Zakriya Mahamooth dan Marizan Kamarulzaman for their unconditional love and support all throughout my formative years till now . Many thanks and appreciation is directed towards the following people who helped me along this journey :

- My supervisor, Dr. Rahimah Binti Abdul Rahim who continuously spared me her time for consultation, personal guidance, encouragement and advised on various matters throughout this project.
- Head of Department, Assoc. Prof Dr. Mohd. Pazuddin Ismail, Prof. Dr Mohd Shukri Othman, Prof. Nik Mohamed Zaki Nik Mahmood, Prof. Shah Reza Johan Noor, Assoc. Prof. Dr. Adibah Ibrahim, Assoc. Prof Dr Nik Ahmad Zuky, Dr. Ahmad Amir, Dr. Nik Rafiza Nik Affendi, Dr Ahmad Akram Omar , Dr. Fauziah Jumaat , Dr Wan Rosilawati Wan Rosli, and Dr Wan Fadhlina Wan Adnan
- Lastly to everyone who were involved directly or indirectly towards this research study.

Thank You and May Allah bless you all

Table of Contents

Abstract **1**

Abstrak **3**

1.0 Introduction **5**

1.2 Literature review **6**

1.2.1 Hypertensive disorders of pregnancy **6**

1.2.2 Classification of Hypertensive disorders of Pregnancy **6**

1.3 PRE-ECLAMPSIA PATHOPHYSIOLOGY **8**

1.3.1 Abnormal placental development 8

1.3.2 Immunological factors 9

1.3.3 Genetic factors 10

1.4: MATERNAL OUTCOMES **10**

1.5 NEONATAL OUTCOME **11**

1.6 Risk Factors for developing pre-eclampsia **12**

1.7 Diagnostic tests **13**

1.7.1 Uric acid 13

1.7.2 Proteinuria 14

1.7.3 Platelet Count 14

1.7.4 Liver Enzymes 14

1.8 MANAGEMENT OF PRE-ECLAMPSIA **15**

1.9 Rational of Study **16**

2.0 Documents submitted for ethical approval **17**

2.1 Ethical Approval Letter **52**

3.0 The Manuscript **57**

3.0 Introduction **59**

3.1 Main Objective **60**

3.2 METHODOLOGY **60**

3.2.1 Study design and setting 60

3.2.2 Data Analysis and Processing: 61

3.2.4 Operational Definition **63**

4.0 RESULTS **64**

4.1 Sociodemographic Background **64**

4.2 Antenatal Background **65**

4.3 Clinical characteristics **66**

4.4 Maternal Outcome **69**

4.5 Fetal Outcomes **73**

5.0 Discussion And Conclusion **78**

6.0 Referrences 83

Appendices 88

Abstract

To determine the prevalence, sociodemographic and characteristics of patients with pre-eclampsia attending HUSM and subsequently determine the maternal and perinatal outcomes.

of these patients.

Methodology: Descriptive study, retrospective data collection for 10 years duration from 2006-2016.

Material and method: 283 cases were selected randomly and all important data such patients age, parity, BMI, medical background, gestation, clinical complaints, relevant laboratory results, mode of delivery, maternal and fetal complications were recorded and analysed.

Results: The prevalence of pre-eclampsia in HUSM for that period of study was 1.4 percent. Mean age of the patients were 30.39 years. Majority (98.2%) of patients with pre-eclampsia had antenatal booking, 59% were multigravida, while 41% were primigravida . Our patients had a mean BMI of 30 kg/m^2 and a mean haemoglobin of 10.2 g/dl . 64.7% has a raised serum uric acid level, 94% had a raised ALT level and 53% had a raised AST level. 23% of patients suffered from complications, with the most common being PPH (9.5%). A platelet level of <150 $x10^9$ was associated with a significant risk of maternal complications (95% CI 1.57, 6.52, p=0.001). Mean fetal weight was 2.53 kg, and 37% needed NICU admission. Patients with GDM had significantly higher odds of having low birth weight fetus (95% CI 2.38, 8.69, $p<0.001$) and more likely to be admitted to NICU (95% CI 0.99, 4.98, p=0.051).

Conclusion: The prevalence of pre-eclampsia in this study is much lower than those quoted in other studies, whist clinical characteristics were almost similar

Key Words: Pre-eclampsia, Maternal outcomes, fetal outcomes, sociodemographic characteristics.

Abstrak

Objektif adalah untuk menganalisis kelaziman, data sosiodemografi, ciri-ciri pesakit serta kesudahan ibu ibu serta kandungan pesakit pesakit pre-eklampsia yang datang ke HUSM

Desain :Pengumpuan data secara retrospektif dan diskriptif selama 10 tahun dari 2006 hingga 2016

Metodologi : 283 pesakit telah dipilih secara rawak dan semua butir butir mengenai umur , jumlah anak, BMI, sejarah perubatan, jangkamasa kandungan, aduan klinikal, keputusan makmal, cara bersalin serta kesudahan ibu dan anak yang dikandung direkod dan dianalisa.

Keputusan: Pre-eklampsia di HUSM mempunyai kelaziman sebanyak 1.4 peratus. Purata umur pesakit pre-eklampsia adalah 30.3 tahun. Kebanyakkan (98.2%) pesakit pre-eklampsia mempunyai pemeriksaan prenatal, 59 peratus merupakan multigravida manakala 41% merupakan primigravida. Pesakit kami mempunyai purata BMI 30.56 kg/m^2 serta purata haemoglobin 10.2 g/dl. 64.7 % mempunyai urik asid yang tinggi, 94% mempunyai ALT yang tinggi dan 53% mempunyai yang AST tinggi. Sebanyak 23% pesakit mengalami komplikasi akibat pre-eklampsia. Komplikasi paling banyak adalah pendarahan akut (9.5%). Platlet < 150 $x10^9$ g/dl berkait dengan komplikasi dikalangan ibu ibu pre-eklampsia (95% CI 1.57, 6.52, p=0.001). Purata berat bayi i pula adalah 2.53.kgs dan 37% memerlukan kemasukkan ke NICU. Kebarangkalian pesakit pre-eklampsia yang mempunyai GDM mempunyai bayi yang kurang berat

serta memerlukan kemasukan ke NICU adalah lebih tinggi berbanding berbanding dengan yang tiada.

Konklusi : Kelaziman pre-eklampsia di HUSM adah 1.4 % , lebih rendah berbanding dengan kajian-kajian lain. Walaubagaimanapun , ciri ciri klinikal pesakit hampir sama.

1.0 Introduction

Pre-eclampsia is a disorder that was first described in ancient Greek scriptures, obtaining its name from the 'Greek' word "eclampsis' which means sudden flashing. Prior to the 18th century, the term eclampsia was used to refer to the visual phenomenon experienced by the mother which accompanied the actual neurological phenomena. It was not until the 18th century would experts coin the term 'pre-eclampsia' to describe a disorder that would actually pre-empt the neurological sequalae, and make the association between hypertension and proteinuria.

Being a disorder unique to pregnancy and the postpartum period, pre-eclampsia is a disorder that affects both the mother and the unborn. Complicating at least 5-10 percent of pregnancies [1] world-wide, it is a rapidly progressing disorder and could lead to detrimental effects on the mother and fetus. With more affluent socio-economic status and increasing sedentary lifestyle, limited data has suggested an upward trend of pre-eclampsia, essentially in rapidly developing countries like Malaysia.

Despite tremendous improvements in healthcare in the recent millennia, reports of pregnant women dying from pre-eclampsia still exists. As per Noraihan et. al. [2] in Maternity Hospital Kuala Lumpur (MHKL), the prevalence of hypertensive disorder in pregnancy was 82.3 per 1000 deliveries and was one of the leading causes of maternal mortality from 1984 to 2000. This was a tremendous improvement as compared to the early 1960s where the occurrence of eclampsia was reported to be 450 per 10 000 births in MHKL [2]. With the improvement and

increased uptake of maternal child health services, the prevalence has dropped to 14–30 per 10 000 deliveries in 1993 to mid 1999.

Locally in Kelantan, the incidence of hypertensive diseases complicating pregnancy in the state was 3.8 per cent in 2012 [3]. The presence of medical retrieval teams in the state and adequate resuscitation training has contributed to considerable improvement in the management of the eclamptic mother.

1.2 Literature review

1.2.1 Hypertensive disorders of pregnancy

Defining what represents hypertension in pregnancy is complicated by the fact that blood pressure levels in pregnancy are even more dynamic than they are in non-pregnant women. There are various classifications for Hypertension in Pregnancy.

1.2.2 Classification of Hypertensive disorders of Pregnancy

The Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) 2008 and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) defines hypertension as a sustained blood pressure of ≥ 140/90 at least four hours apart [4].

1. As follows are the types of Hypertensive diseases in pregnancy :Pre-eclampsia-eclampsia: clinically diagnosed in the presence of de novo hypertension after 20 weeks of gestation, and one or more of the following:

   i. Significant proteinuria. (Albumin 2+ or more , or 24 hour urine protein of 0.3mg/24hours

   ii. Renal insufficiency

iii. Liver disease: raised transaminases

iv. Neurological problems: convulsions (eclampsia), hyperreflexia with clonus or severe headaches, persistent visual disturbances (scotoma).

v. Haematological disturbances: thrombocytopenia, coagulopathy, haemolysis.

vi. Fetal growth restriction.

2. Gestational hypertension is a clinical diagnosis defined by the new onset of hypertension in the absence of proteinuria or new signs of end-organ dysfunction.

3. Chronic hypertension is hypertension diagnosed prior to 20 weeks of gestation or presence of hypertension preconception, or de novo hypertension in late gestation that fails to re-solve postpartum. It is essential hypertension if there is no underlying cause and secondary hypertension if there is underlying cause such as renal, cardiac or endocrine disease. Chronic hypertension may present for the first time as gestational hypertension.
4. Pre-eclampsia superimposed on chronic hypertension is diagnosed in the presence of any of the following, in a woman with chronic hypertension:
    a. De novo proteinuria after 20 week gestation
    b. A sudden increase in the severity of hypertension
    c. Appearance of features of pre-eclampsia-eclampsia, and
    d. A sudden increase in proteinuria in women who have pre-existing proteinuria early in gestation

1.3 PRE-ECLAMPSIA PATHOPHYSIOLOGY

Research efforts this past decade have enable scientists and clinicians to come closer to aetiology and causality of pre-eclampsia thus improve diagnosis and even predict pre-eclampsia with the ultimate hope that this will lead to the 'holy grail' of subsequent prevention and tailored treatments for pre-eclampsia which was once called the 'greatest riddles of obstetrics and gynaecology' by Naquib Pasha Mahfouz – Father of modern obstetrics and gynaecology

The pathophysiology of pre-eclampsia is indeed complex, and to date the exact cause is still unknown, but it likely to involve the maternal-fetal-placental complex. Relative under-perfusion due to abnormal development of the placenta vasculature early in the pregnancy results in the release of antiangiogenic factors into the maternal circulation that alter maternal systemic endothelial function and lead to hypertension and other manifestations of the disease. The exact trigger for these abnormal development and the trajectory of the subsequent cascade of clinical events remains unknown and unpredictable.

1.3.1 Abnormal placental development

Defective spiral artery formation and trophoblast invasion leads to impaired placentation and placental hypo-perfusion and thus ischemia, which are thought to be the primary events leading to a state of systemic endothelial dysfunction, the pathologic precursor of pre-eclampsia.

In normal pregnancies as early as 10 week, the trophoblastic cells of the developing placenta migrate and invade both the endothelium and tunica media of

the maternal spiral arteries. As a result, these vessels undergo reformation from small muscular arterioles to large capacitance vessels of low resistance, thus ensuring greater blood flow to the placenta and thus the fetus.

However, in pre-eclampsia, the trophobastic cells migration infiltrate the decidual portion of the spiral arteries in a defective manner, and fail to invade through the myometrial segment. The spiral arteries thus do not develop into large tortuous pliable vessels for high volume, low resistance blood supply to the developing placenta and thus the fetus. Instead the vessels remain small and rigid , resulting in placental ischemia. This defective placentation has been associated with the development of pre-eclampsia.

1.3.2 Immunological factors

There is circumstantial evidence that pre-eclampsia is immune mediated, and this comes from in part the observation that prior exposure to paternal antigens appear to protect the mother against pre-eclampsia. According to Duckitt et al [5], reduced exposure to paternal antigen in nulliparous women, women with long inter-pregnancy interval, women who use barrier contraception or women who conceive via artificial reproductive methods are at increased risk of pre-eclampsia.

Immunologic abnormalities, similar to those observed in organ rejection graft versus host disease, have also been observed in pre-eclamptic women as per Gleicher et al [6]. The extravillous trophoblast (EVT) cells express an unusual combination of HLA class I antigens: HLA-C, HLA-E, and HLA-G. Natural killer (NK) cells that express a variety of receptors known to recognize class I molecules infiltrate the maternal decidua in close contact with the EVT cells [6]. Interaction between NK cells and EVT cells has been hypothesized to control placental implantation. In pre-

eclampsia, conflict between maternal and paternal genes is believed to induce abnormal placental implantation through increased NK cell activity

1.3.3 Genetic factors

Despite being generally a sporadic disease, genetic factors may have a role in susceptibility to pre-eclampsia. Cincotta et al [7] found that primigravida women with a family history of pre-eclampsia (eg, affected mother or sister) have a two- to five-fold higher risk of the disease than primigravid women with no such history. Studies of sisters, daughters, grand daughters and daughter in laws of eclamptic women and concluded have that pre-eclampsia/eclampsia was highly heritable.. The risk of pre-eclampsia is increased more than seven-fold in women who have had pre-eclampsia in a previous pregnancy.

1.4: MATERNAL OUTCOMES

Women with pre-eclampsia are at increased risk for abruptio placentae, acute renal failure, cerebral haemorrhage, disseminated intra-vascular coagulation, pulmonary oedema, circulatory collapse and oedema.

Despite having a small sample size, Stirrat et al. [8] in a retrospective cohort study of on 71 pre-eclamptic women with gestational age less than 30 weeks, found that 21% had developed HELLP syndrome, 15% had abruptio placenta, 13% had renal failure and 1.4% eclampsia.

In a much larger study , Al-Mulhim et al. [9] on the other hand reported that the commonest complication to be abruptio placenta (1.6%) followed by oliguria (7.9%), coagulopathy (6%) and renal failure (4.1%) . This is in contrast to what that has been reported in the Malaysian National Obstetrics Registry whereby eclampsia was the commonest complication at 3.26% in 2011 and 3.24% in 2012 respectively, followed by postpartum haemorrhage at 1.40% in 2011 and 0.83 % in 2012, while the incidence of abruptio placenta in 2012 was 1.08% [10].

According to Cuningham et. al. [11] despite these presentations, many women have no symptoms. Most patients are usually nulliparous and present with new-onset hypertension and proteinuria at ≥34 weeks of gestation. Approximately 10 percent of affected women develop these signs and symptoms at <34 weeks of gestation and rarely as early as 20 to 22 weeks. In approximately five percent, the signs and symptoms are first recognized postpartum (ie, postpartum pre--eclampsia), usually within 48 hours of delivery.

1.5 NEONATAL OUTCOME

Pre-eclampsia accounts for more than 40% of premature deliveries and substantially increases the risk of low birth weight, and SGA births. Ananth et al. [12] in their study found eclampsia to have substantially greater risk of delivery of very low birth weight infants (birth weight < 1,499 gm) and moderate low birth weight infants (1,500-2,499 gm) and very pre-term (Gestational age < 33 weeks) and moderately pre-term (33-36 gestational age) birth compared with women without hypertension .

A retrospective cohort study performed by Xiong et al. [13] gestation was 0.6 weeks shorter in women with severe pre-eclampsia than in normotensive women

(P<0.01). After adjustment for duration of gestation and other confounders their study showed that pre-eclampsia and severe pre-eclampsia increased the risks of intra uterine growth restriction(IUGR) and low birth weight. Babies born to mothers with pre-eclampsia are also more likely to be admitted to the NICU as compared to those who did not.

Magee et al. [14] in a multi-centre retrospective cohort study, found that 16.4% of pre-eclamptic pregnancies being complicated by low birth weight and 34.3% by pre-term birth, regardless of hypertension type.

1.6 Risk Factors for developing pre-eclampsia

Family history of hypertension, extremes of reproductive age, primigravidity, diabetes, renal disease, and hypertension prior to pregnancy are some of the predisposing factors of preeclampsia . According to Duckitt et. al. [5], women aged 40 and above are more likely to suffer from pre-eclampsia as compared to their younger counterparts. However at the sametime, women of older age are also more likely to suffer from other comorbidities that could contribute to the risk of pre-eclampsia.

Inter pregnancy interval less than six months and longer than 59 months are associated with an increased risk of adverse maternal outcome . Conde-Agudelo et al. [15] in their study found that, compared with women with inter-pregnancy interval of 18 to 23 months, women with inter-pregnancy intervals longer than 59 months had significantly increased risk of pre-eclampsia and eclampsia.

Obesity is risk for developing pre-eclampsia as per Duckiit et al [5]. The exact mechanism by which obesity is associated with an increased risk of pre-eclampsia is

not completely understood. It has been hypothesized that the increased oxidative stress due to the hyper-dynamic circulation associated with obesity and dyslipidaemia lead to pre-eclampsia .

1.7 Diagnostic tests

As there is no widely available, cheap investigative test for diagnosis of pre-eclampsia -the initial diagnosis of pre-eclampsia remains still remains clinical and the classification of severity is mainly based on the blood pressure values and both clinical and biochemical assessments. Measuring blood pressure is cumbersome in clinical setting but if raised blood pressure and proteinuria are observed at the antenatal care setting the woman should be referred for further evaluation.

1.7.1 Uric acid

Serum uric acid is used as an indicator of disease severity in established pre-eclampsia and has been reported to be better predictor for adverse perinatal outcome than blood pressure .

In a study conducted by Williams KP et al [16] found a significant elevation in serum uric acid levels over normotensive pregnant women in both women with gestational hypertension and the preeclamptic women. In this study and other similar studies however, serum uric acid levels although significantly elevated in women with gestational hypertension and pre-eclampsia, were not prognostic indicators of severity of the maternal and fetal outcome .

1.7.2 Proteinuria

Proteinuria presence of proteinuria in a pregnancy patient after 20 weeks of gestation with hypertension should alert the clinician on a diagnosis of pre-eclampsia. Dipstick proteinuria is the most common screening test for pre-eclampsia. It is easy and cheap to use. The purpose of using dipsticks is to assist in timely diagnosis of pre-eclampsia. Other methods of diagnosis include 24 hour urine protein levels and spot creatinine/protein ratio.

1.7.3 Platelet Count

As a pregnancy progresses, its physiological for the platelet levels to drop as well due to normal maternal blood volume expansion. In pre-eclampsia however, there is a more marked drop in maternal platelet levels, due to increased consumption and intravascular destruction. Microscopic endothelial injury that accompanies pre-eclampsia results in platelet consumption from the formation of fibrin microthrombi in the circulation [17]. In sync with immune mediated factors, this further potentiates the degree of thrombocytopenia in pre-eclampsic mothers.

1.7.4 Liver Enzymes

According to Dekker et al [18], elevation of serum Alanine Amino Transferase (ALT) and Aspartate Amino Transferase(AST) can be used as surrogate marker of severity of pre-eclampsia; they increase in pre-eclampsia as a result of leakage across the cell membrane .

1.8 MANAGEMENT OF PRE-ECLAMPSIA

Even though delivery is the ultimate cure for pre-eclampsia, management aimed at benefiting the mother may be detrimental to the fetus because premature birth is a significant cause of infant morbidity and mortality. Hence the management of pre-eclampsia is usually based on a step-wise protocol: Pregnant women should be screened; those at risk should be monitored once a diagnosis is made; the maternal condition should be stabilized; monitoring should be continued and delivery should be initiated at the best time for the mother and the baby . During labour, the management goals are to prevent seizures and control hypertension.

The predominant mode for controlling pre-eclampsia includes anti-hypertensive, anti-convulsions and delivery . Severe pre-eclampsia and eclampsia, are life threatening, therefore women suspected of having either condition should receive immediate and continuous care by trained health care personal

The primary objective of treatment in women with pre-eclampsia is to prevent cerebral complications such as encephalopathy and haemorrhage. . In a Cochrane review of 11 trials (1,128 women), Magee and Duley [19] observed that beta-blockers reduce the risk of severe pre-eclampsia. However, until better evidence is available, the choice of anti-hypertensive should depend on the experience and familiarity of an individual clinician with a particular drug and on what is known about the adverse maternal and fetal side effects .

The Magpie trial, a large multi-centred double blinded randomised trial carried out in 33 countries and involving nearly 10,000 pregnant women with pre-

eclampsia settled the issue for magnesium sulphate [20]. From that study it was found that women allocated magnesium sulphate had a 58% lower risk of having eclampsia as compared to placebo.

Maternal mortality was also lower among women allocated magnesium sulphate. Side effects were only minor: neither the mothers nor their babies showed any serious adverse effects from treatment . This trial showed that giving magnesium sulphate injections could save countless lives across the world if it would be given routinely to pregnant women with pre-eclampsia. Importantly, it is an inexpensive treatment, making it especially suitable for use in low-income countries .

1.9 Rational of Study

Despite the high prevalence, there is not much published data on the characteristics of these patients in Malaysia. Therefore the aim of this study is to determine the maternal and fetal outcome and associated factors in preeclamptic patients treated in a tertiary referral hospital. The results from this study will also throw some light on the predisposing circumstances of pre-eclampsia and characteristics of patients with pre-eclampsia . Recommendations can be made depending on the findings. This can help determine the future direction of the prevention and management of this dangerous condition, as it is still a significant problem in Malaysia.

2.0 Documents submitted for ethical approval

A retrospective study on Pre-eclampsia in Hospital Universiti Sains Malaysia , Kelantan

BY:

Dr Mas Irfan Jaya Mahamooth

PUM0203/14

SUPERVISOR:

DR RAHIMAH BINTI ABDUL RAHIM

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY , HUSM

A retrospective study on Pre- eclampsia in Hospital University Sains Malaysia , Kelantan

Introduction

Hypertensive disorders complicate 5–10% of pregnancies worldwide, with limited data suggesting an upward trend in incidence most likely related to increasing maternal weight and sedentary lifestyle. With few differences, all international societies define the hypertensive disorders of pregnancy as chronic hypertension, gestational hypertension and pre-eclampsia[1]. Although women with pre-eclampsia have the greatest risk of maternal and perinatal complications, what constitutes pre-eclampsia is controversial, and diagnostic distinctions are often blurred[2]. As such, it is important to view all women with a hypertensive disorder of pregnancy and their babies as being at increased risk of mortality and morbidity, and act accordingly.

Pre-eclampsia remains one of the top five causes of maternal and perinatal mortality worldwide. Our best estimate is that pre-eclampsia claims the lives of more than 70,000 women per year and more than 500,000 of their fetuses and newborns; this is equivalent to the loss of 1600 lives per day. For every woman who dies, it is estimated that another 20 suffer a life-altering morbidity[4].

Given that maternal (and perinatal) deaths and sequelae result primarily from delays in triage, transport, identification and treatment, it would seem important for the global community to turn its attention to community-based care. A community-focused approach could include community engagement and use of innovative technologies, like smartphone applications could be used to support community-based health workers.

In addition, however, care at facility must be of high quality in order for outcomes to be improved, a point that has been highlighted by the move towards encouraging more facility births and concerns about the quality of care received there. In the World Health Organization Multicountry Survey on Maternal and Newborn Health (WHOMCS) that covered 357 health facilities in 29 countries, high coverage of essential interventions was not associated with reduced maternal mortality. As such, attention must also be focused on strengthening provision of evidence-based comprehensive emergency obstetric care, conducting maternal death and near-miss morbidity surveillance and response, and performing large-scale effectiveness evaluations .

In Malaysia, from 1997-2008 the average incidence of HDP related maternal death was 13.6%. It is the 4th leading cause of maternal mortality in Malaysia [5] . In Maternity Hospital Kuala Lumpur (MHKL), hypertensive disorder is common, with a prevalence of 82.3/1000 deliveries and was one of the leading causes of maternal mortality from 1984 to 2000 , tremendous improvement as compared to the early 1960s where the occurrence of eclampsia was reported to be 450 per 10 000 births in MHKL [3]. With the improvement and increased uptake of maternal child health services, the prevalence has dropped to 14–30 per 10 000 deliveries in 1993 to mid 1999 [3].

Locally in Kelantan, the incidence of hypertensive diseases complicating pregnancy in the hospital population was 8.3 per cent (1988). Three of the 23 maternal deaths in 1988 was due to eclampsia. During that study, it was noted that the death rate in eclampsia of 4.8 per cent resulted from a combination of several factors that show wide variability. Delay in referral because of socio-cultural reasons was a problem [6]. The absence of medical retrieval teams in the state and inadequate resuscitation

while in transit contributed to considerable deterioration in the haemodynamic state of the eclamptic mother. This condition however has improved tremendously with the improvement of the Malaysian Health Services [6].

Rationale and Justification of the Study

Despite the high prevalence, there is not much published data on the outcome of these patients in Malaysia. Therefore the aim of this study is to analyze the maternal and fetal outcome and associated factors in pre-eclamptic patients treated in a tertiary referral hospital. The results from this study will also throw some light on the predisposing circumstances of pre-eclampsia and characteristics of patients with pre-eclampsia . Recommendations can be made depending on the findings. This can help determine the future direction of the prevention and management of this dangerous condition, as it is still a significant problem in Malaysia.

Literature review

For the purpose of this study, the definition below are used for this study [7]

There are various classifications for Hypertension in Pregnancy. The most recent is by the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP)

1. Pre-eclampsia-eclampsia: clinically diagnosed in the presence of de novo hypertension after gestational week 20, and one or more of the following:

i. Signicant proteinuria. (Albumin 2+ or more , or 24 hour urine protein of 0.3mg/24hours

ii. Renal insuffciency: serum creatinine ≥ 90 micromol/l or oliguria.

iii. Liver disease: raised transaminases

iv. Neurological problems: convulsions (eclampsia), hyperexia with clonus or severe headaches, persistent visual disturbances (scotoma).

v. Haematological disturbances: thrombocytopenia, coagulopathy, haemolysis.

vi. Fetal growth restriction.

Gestational hypertension is hypertension detected for the first time after 20 weeks pregnancy. The definition is changed to “transient” when pressure normalizes postpartum.

2. Chronic hypertension is hypertension diagnosed prior to gestational week 20 or presence of hypertension preconception, or de novo hypertension in late gestation that fails to resolve postpartum.

3. Pre-eclampsia superimposed on chronic hypertension is diagnosed in the presence of any of the following, in a woman with chronic hypertension:

    i. De novo proteinuria after 20 week gestation

ii. A sudden increase in the severity of hypertension

iii. Appearance of features of pre-eclampsia-eclampsia, and

iv. A sudden increase in proteinuria in women who have pre-existing proteinuria early in gestation

PRE-ECLAMPSIA: INCIDENCE, CONSEQUENCES AND RISK FACTORS

Pre-eclampsia complicates 2-8% of pregnancies [8]. Women with pre-eclampsia are at increased risk for abruptio placentae, acute renal failure, cerebral haemorrhage, disseminated intravascular coagulation, pulmonary oedema, circulatory collapse and oedema. In a retrospective cohort study of Murphy and Stirrat [9] on 71 pre-eclampticwomen with gestational age less than 30 weeks 21% had developed HELLP syndrome, 15% had abruptio placenta, 13% had renal failure and 1.4% eclampsia but maternal mortality was not observed. Al-Mulhim et al. also reported that the commonest complication to be abruptio placenta (12.6%) followed by oliguria (7.9%), coagulopathy (6%) and renal failure (4.1%) [10].

Risk Factors

Family history of hypertension, extremes of reproductive age, primi-gravidity, diabetes, renal disease, hypertension prior to pregnancy, and black race are some of the predisposing factor of pre-eclampsia [11,12,13]. Women 40 years and above are more than five times likely to die of pre-eclampsia than those between 20 and 24 years older. Some studies reflected that neither maternal age nor race had a

significant effect on the outcome of pre-eclampsia, but suggested that increased severity of disease might be an important determining factor [14,15.]

In a cohort study of 878,680 pregnancies in 700 hospitals in Latin America and Caribbean, the following risks factors were significantly associated with increased risks of pre-eclampsia: Nulliparity (RR = 6.6, 95% CI 5.6-9.8), multiple pregnancy (RR= 2.0;95%CI 0.9-6.4), history of chronic hypertension (RR=3.9; 95%CI 3.8 – 4.4), gestational diabetes mellitus (RR=3.9; 95% CI 4.6 – 6.6), maternal age > 35 years (RR=6.7; 95%CI 5.8 -7.7) and a mother not living with infant's father (RR=2.1; 95% CI 1.5 -2.6). The pattern of risk factors among nulliparous and multiparous in this study was quite similar

8 [16]. Type 1 diabetes (OR =5.58; 95%CI 2.72 - 11.43) and twin births (OR= 3.11, 95%CI 1.61 - 6.00) were also significantly associated with pre-eclampsia according to a study conducted by Ros et al. [17].

Pre-eclampsia occurs mainly in first pregnancies, suggesting that previous exposure to paternal antigen is protective [18]. Indeed a previous normal pregnancy is associated with lowered frequency of pre-eclampsia and the protective effect of multiparty is lost with change of partner [18]. The idea that paternal antigen is protective is supported by the increased risk of pre-eclampsia in those who carry a pregnancy by a new father. Data based on Norwegian population (1967-1992) confirmed the impact of paternal factor on the risk of developing pre-eclampsia. Men who fathered pre-eclamptic pregnancies were twice as likely to father a pre-eclamptic pregnancy from different women regardless of whether she had a prior pre-eclamptic pregnancy or not [18]. The protective effect of along-term sperm exposure might also provide explanation for the high frequency of pre-eclampsia in teenage pregnancy [18].

Another study of Trogstad et al. showed that a change of paternity for the second pregnancy was associated with a reduced risk of pre-eclampsia after controlling for the time since first delivery (AOR = 0.80, 95%CI: 0.72-.90), but the interaction between change in paternity and time between deliveries was significant only for women with no previous pre-eclampsia. This implies that the increase in pre-eclampsia risk ascribed to a new father may be due to insufficient control for inter-pregnancy interval [19.] Inter pregnancy interval less than six months and longer than 59 months are associated with an

increased risk of adverse maternal outcome [20]. Conde-Agudelo and Belizan in their study found that, compared with women with inter-pregnancy interval of 18 to 23 months, women with inter-pregnancy intervals longer than 59 months had significantly increased risk of pre-eclampsia (OR=1.83; 95% CI 1.72-1.94) and eclampsia (OR= 1.80; 95% CI 1.38-2.32).

Therefore health care providers should realize that the antenatal care of a multiparous patient with a new partner should be the same as in a woman presenting with her first pregnancy as far as the risk of pre-eclampsia is concerned and inter-pregnancy history needs to be taken into consideration.

Obesity is also a definite risk for developing pre-eclampsia. The exact mechanism by which obesity is associated with an increased risk of pre-eclampsia is not completely understood. Possible explanations include increased stress due to the hyper-dynamic circulation associated with obesity and dylipidemia or increased oxidative stress [18].

DIAGNOSIS