ABSTRACT

A RANDOMISED CONTROLLED TRIAL OF MGSO4 THERAPY FOR 24 HOURS VERSUS EARLY CESSATION IN PATIENTS WITH SEVERE PREECLAMPSIA

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Introduction:
Magnesium sulphate has been shown to be the optimal anticonvulsant in preventing the recurrence of seizures in eclampsia and in seizure prophylaxis in preeclampsia. Traditionally, seizure prophylaxis has been administered before delivery and continued postpartum for an arbitrary time, usually 24 hours.

Objectives:
The primary objectives of this study were to evaluate the safety and effectiveness of using clinical parameters to signal cessation of postpartum magnesium sulphate therapy among patients with Severe Preeclampsia.

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Results:
There were 52 patients in the control group and 50 patients in the intervention group. The intervention group had a significantly shorter duration of therapy ($p< 0.05$). There were no differences in mean booking BMI, weight on admission, systolic blood pressure and platelet level between two groups. However there were significance differences in mean age of the patients, delivery gestational age, diastolic blood pressure and uric acid level between two groups. There was no patient in this study had eclampsia or required the reinitiation of therapy.

Conclusions:
Clinical parameters can be used effectively and safe to shorten the duration of postpartum magnesium sulphate therapy in patients with severe preeclampsia.

Associate Professor Dr Nor Aliza Abd. Ghaffar: Supervisor
Dr Zainal Abidin Hanafiah: Co-Supervisor

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BY;
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Dr Affendi Yunus

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ABBREVIATIONS

ACOG	American College of Obstetric and Gynaecology
ANC	Antenatal Care
APEX	Accelerated Programme of Excellence
ASSHP	Australasian Society for the Study of Hypertension in Pregnancy
B.I.D	*bis in die* means 2 times a day
BMI	Body Mass Index
BP	Blood Pressure
CEMD	Confidential Enquiries into Maternal Deaths
CVP	Central Venous Pressure
CTG	Cardiotocograph
df	degree of freedom
e.g	*exempli grati*, for example
et al.	*et alii*, and others
ET-1	Endothelin-1
HDP	Hypertensive Disorder of Pregnancy
HELLP	Haemolysis, Elevated liver enzymes and Low platelets
HRPZII	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
ISSHP	International Society for the Study of Hypertension in Pregnancy
KD	Klinik Desa
KK	Klinik Kesihatan
LSCS	Lower Segment Caesarean Section
MCHC	Maternal and Child Health Clinic
MGSO4	Magnesium Sulphate
MOH	Ministry of Health
NHBPEP	National High Blood Pressure Education Program
NICE	National Institute for Clinical Excellence
NICU	Neonatal Intensive Care Unit
PE	Preeclampsia
POA	Periods of Amenorrhea
PGI2	Endothelial Prostacyclin
PIGF	Platelet Growth Factor
PRN	**Pro re nata** means as needed or as the situation arises
Q.I.D	**quater in die** means 4 times a day
RCOG	Royal College of Obstetrician and Gynaecologist
SVD	Spontaneous Vertex Delivery
Th1	Helper T cells
TNF	Tumour Necrosis Factor
T.D.S	**ter in die** means 3 times a day
USM	Universiti Sains Malaysia
UK	United Kingdom
WHO	World Health Organization

ABSTRAK

KAJIAN CUBAAN RAWAK TERKAWAL PENGGUNAAN MAGNESIUM SULPHATE SELAMA 24 JAM BERBANDING PEMBERHENTIAN AWAL BAGI PESAKIT PREECLAMPSIA

Pengenalan:
Magnesium sulphate telah terbukti sebagai antikonvulsi yang optimum di dalam pencegahan sawan yang berulang bagi eclampsia dan juga bertindak sebagai pencegah sawan bagi preeclampsia. Sebelum ini, magnesium sulphate yang digunakan sebagai pencegah sawan sebelum bersalin akan terus digunakan selepas bersalin sehingga ke suatu waktu, biasanya hingga 24 jam selepas bersalin.

Objektif:
Tujuan utama penyelidikan ini adalah untuk menilai keberkesanan dan keselamatan penggunaan kriteria klinikal sebagai petanda untuk pemberhentian magnesium sulphate selepas bersalin bagi pesakit preeclampsia.

Kaedah:
Penyelidikan secara kajian rawak terkawal penggunaan magnesium sulphate selepas bersalin telah dijalankan di HRPZII, Kota Bharu dan HUSM, Kubang Kerian bermula pada December 2009 sehingga September 2010. Pesakit di dalam kumpulan kawalan menerima rawatan sehingga 24 jam selepas bersalin. Pesakit di dalam kumpulan intervensi menerima rawatan sehingga memenuhi kriteria klinikal untuk pemberhentian rawatan. Kaedah "Independent t test, Chi-square test dan Fisher exact test" digunakan untuk menganalisa data. Kebarangkalian nilai < 0.05 dikira sebagai 'significant' secara statistik.

Keputusan:
Seramai 52 orang pesakit telah menyertai kumpulan kawalan dan 50 orang telah menyertai kumpulan intervensi. Didapati kumpulan intervensi telah menerima rawatan magnesium sulphate dengan kadar yang lebih singkat ($p< 0.05$). Tiada perbezaan dari segi purata indeks jisim tubuh, berat badan, tekanan darah sistolik and paras platelet diantara pesakit kedua-dua kumpulan kajian. Walaubagaimanapun, terdapat perbezaan dari segi purata umur pesakit, gestasi semasa kelahiran , tekanan darah diastolik, dan paras uric acid diantara pesakit kedua-dua kumpulan kajian. Tiada pesakit yang menyertai kajian ini mendapat eclampsia atau memerlukan rawatan magnesium sulphate semula setelah diberhentikan sebelum ini.

Kesimpulan:
Kriteria klinikal boleh digunakan dengan berkesan dan selamat sebagai petanda untuk mengurangkan jangkamasa penggunaan magnesium sulphate selepas bersalin bagi pesakit preeclampsia.

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CHAPTER ONE: INTRODUCTION

Background of the study

Hypertensive disorders of pregnancy (HDP) are the most common medical complications of pregnancy and are important causes of maternal and perinatal morbidity and mortality worldwide. HDP accounts for 7-10% of admission to public hospital obstetrics units in the country (CEMD Malaysia, 1997-2000). The prevalence of HDP in Malaysia is 23.3 per 1000 live births. HDP is the third leading cause of maternal mortality in Malaysia – 14.2%. The immediate associations with death were eclampsia, cardiopulmonary complications, cerebral hemorrhage, severe preeclampsia and disseminated intravascular coagulopathy (DIVC) (CEMD Malaysia, 1997-2000).

Hypertensive disease complicates 5–8% of pregnancies in the United States and ranks second only to thromboembolic disease as the leading cause of maternal mortality (ACOG, 2002). The goal of treatment in preeclampsia is to prevent eclamptic seizures and their resultant morbidity whereas, in eclamptic patients, the goal is to prevent recurrent seizures. Magnesium sulphate has been shown to be the optimal anticonvulsant for this indication (Collaborative Eclampsia Trial, 1995).

Traditionally, seizure prophylaxis has been administered before delivery and continued postpartum for an arbitrary time, usually 24 hours. Some investigators have used individual patient parameters to determine the duration of postpartum seizure prophylaxis. Ascarelli et al (1998) used a combination of patient signs (blood pressure, urinary output), symptoms (headache, visual changes), and laboratory assessments (proteinuria determination by dipstick analysis) to guide postpartum magnesium sulphate duration. In 2003, Isler et al used individual patient clinical parameters to signal cessation of postpartum seizure prophylaxis for the spectrum of pregnancy related hypertensive disorders. The conclusion of their study was clinical criteria can be used successfully to shorten the duration of postpartum magnesium sulphate therapy in patients with pregnancy related disorders. Fontenot et al (2004) used the onset of diuresis in the determination of the duration of postpartum magnesium sulphate therapy among patients with severe preeclampsia. They found that the use of diuresis in the postpartum period as determinant clinical parameter for discontinuation of magnesium sulphate in patients with severe preeclampsia was associated with no untoward outcomes or need for the re-initiation of treatment (Fontenot et al, 2004).

The purpose of this study was to determine if the duration of postpartum magnesium sulphate as a seizure prophylaxis administered in patients with the spectrum of hypertensive disorders of pregnancy (including severe preeclampsia and chronic hypertension with superimposed preeclampsia) could be guided by clinical parameters.

1.2 Justification, rationale and benefits of the study

The use of magnesium sulphate for seizure prophylaxis has been shown to be efficacious in women with severe preeclampsia. The optimal duration of magnesium therapy has not been determined. Magnesium sulphate therapy is often arbitrarily given for 24 hours after delivery, depending on severity of disease. The use of magnesium sulphate therapy is not without complication. Maternal morbidity and mortality

can occur because of magnesium overdose.

Current theories regarding the pathogenesis of preeclampsia postulate the disorder commences with abnormal placental implantation. However, the clinical manifestations
of the disease result from widespread vasoconstriction. Eclampsia is believed to be caused by ischemia from cerebral under-perfusion resulting from this vasoconstriction, although some cases of eclampsia may be caused by hypertensive encephalopathy from
cerebral over-perfusion. This study suggests that an individual clinical parameter can be used as a guide to stop the postpartum magnesium sulphate therapy.

The rationale and expected benefits of the study include:
To evaluate the safety and effectiveness of using clinical parameters to signal cessation of postpartum magnesium sulphate in patients with severe preeclampsia.

To compare the outcomes of MgSO4 therapy as postpartum seizures prophylaxis following conventional 24 hours and early cessation based on clinical parameters.

To determine the optimal duration of MgSO4 therapy in pregnant women with severe preeclampsia.

No local published data available. As far as we are aware there are no local or national data using clinical parameter to signal cessation of postpartum magnesium sulphate therapy.

The conceptual framework

Pregnant women with hypertension can be broadly divided into three categories: chronic hypertension, non-proteinuric hypertension (sometimes known as pregnancy-induced hypertension) or preeclampsia. To distinguish between these categories is clinically useful as their management and likely prognosis are disparate. The key signs of preeclampsia are hypertension and proteinuria and these are used to define the disease. These are responses to end-organ damage and they are not always the most important nor fundamental aspects of the syndrome, but are used as they are easy to measure.

Although most women who get preeclampsia do not have risk factors, a significant proportion (>1 in 3) will. Taking a careful history will allow risk assessment. The
National Institute of Clinical Excellence (NICE, 2003) antenatal guidelines suggests this is an important part of clinical management and recommends that at first contact a woman's level of risk for preeclampsia should be evaluated so that a plan for her subsequent schedule of antenatal appointments can be formulated. These guidelines have indicated the following as risk factors for developing preeclampsia; nulliparity, age 40 or older, a family history of preeclampsia (e.g. preeclampsia in a mother or sister), a previous history of preeclampsia, a body mass index (BMI) at or above 35 at first contact, a multiple pregnancy or preexisting vascular disease (e.g., hypertension or Diabetes).
.

Figure 1 Conceptual framework showing possible factors influencing the disease

Background of the study area and patient recruitment

Kelantan is located at the northeast part of Peninsular Malaysia facing the South China Sea. Also well known as "Serambi Mekah", the state is divided into 10 administrative districts namely Kota Bharu, Tumpat, Pasir Mas, Bachok, Pasir Puteh, Machang, Kuala Krai, Gua Musang, Tanah Merah and Jeli.

Kota Bharu is the state capital of Kelantan. The name means 'new city' or 'new castle/fort' in Bahasa Malaysia. The total population of Kota Bharu district is 452,131 (30.8% of the total population of Kelantan) with 226,930 females and 225,201 males. Most residents work in government and private agencies, some are involved in agricultural work such as farming and fishing and the rest are doing small scale business .

Kota Bharu was established by Sultan Muhammad II of Kelantan in 1844 as Kelantan's capital. Pantai Sabak, about 10 km from Kota Bharu, was the initial landing point of the Japanese invasion forces on 8 December 1941 in their Malayan campaign when they successfully engaged the British in jungle warfare and ultimately captured Singapore. On 1 October 2005, Kota Bharu was declared Kota Bharu, The Islamic City. This title is given to the city which observes Islamic principles in every aspect of daily life. A majority of the people of Kota Bharu are Muslims.

Kubang Kerian is a town and also a parliamentary constituency of Kota

Bharu district. The Universiti Sains Malaysia (USM) branch campus is located about 10-15 minutes drive from Kota Bharu. This campus is also referred to as the USM Health Campus established in 1983. The campus houses 3 schools namely the School of Medical Sciences, the School of Dentistry and the School of Health Sciences. The 731 bed teaching hospital is located on campus. 113 beds were allocated for the obstetrics and gynecology services.
Universiti Sains Malaysia (USM) had been granted the Apex (Accelerated Programme for Excellence) status in transforming it into the first world-class university of the country recently in April 2008. It was the first of its kind in the country. USM's transformation plan, entitled Transforming Higher Education for a Sustainable Tomorrow focused, among other things, on diagnostics, medical biotechnology, waste management, pharmaceuticals, nano technology, carbon nanotube, membrane technology and vaccinology become the fundamentals of the Apex programme. The Apex status of the Universiti Sains Malaysia strives for excellence and continuing research in medical field to provide better healthcare and services.
There were 12 health centers in Kota Bharu district. The latest Klinik Kesihatan in Kok Lanas was opened in 2007. The health centers were Klinik Kesihatan (KK) Bandar, KK Kubang Kerian, KK Wakaf Che Yeh, KK Penambang, KK Badang, KK Peringat, KK Ketereh, KK Perol, KK Lundang Paku, KK Pengkalan Chepa, KK Kedai Lalat. At every health center, there was maternal and child health services conducted at maternal and child health clinics (MCHC). Basically MCHC provides services to mothers and children. The services included antenatal and postnatal check-up, immunization, and pediatrics clinic. Each MCHC covered a few community clinics (Klinik Desa), sited at various parts of the sub-district and provide similar services. There were 32 community clinics (Klinik Desa) in Kota Bharu district. The tertiary referral hospitals for the state of Kelantan were Hospital Raja Perempuan Zainab II (HRPZ II) and Hospital Universiti Sains Malaysia (HUSM).

Patients recruited for this study were mainly from the district of Kota Bharu. However, HRPZII is a referral centre for obstetric patients from Tumpat, Pasir Mas, Tanah Merah, Jeli and Machang. HUSM is a referral centre for obstetric patients mainly from Bachok, Pasir Puteh and Besut, Terengganu. Occasionally, there are also referral cases from other district of Kelantan such as Kuala Krai and Gua Musang. Therefore, in term of locality of obstetric patients included in this study, it covered a larger area than just Kota Bharu alone.

CHAPTER TWO: LITERATURE REVIEW

2.1 INTRODUCTION

Hypertension (high blood pressure) is common during pregnancy. Around 10% of women will have their blood pressure recorded as above normal at some point before delivery. Preeclampsia ('toxaemia') is defined as hypertension accompanied by proteinuria (protein in the urine) (NHBPEP, 2000). It usually occurs during the second half of pregnancy and complicates 2% to 8% of pregnancies (WHO, 1988). For women who have hypertension alone, pregnancy outcome is similar to that for women with normal blood pressure. Outcome deteriorates once proteinuria develops.

Many women with preeclampsia have no symptoms. Women with severe preeclampsia, or very high blood pressure, may feel unwell with symptoms such as headache, upper abdominal pain or visual disturbances. Preeclampsia can lead to problems in the liver, kidneys, brain, and to abnormalities of the clotting system. Rare but serious complications include eclampsia (seizures in a woman with preeclampsia), stroke, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) and disseminated intravascular coagulation. These complications are associated with an increased risk of maternal death. As preeclampsia can affect the placenta, risks for the baby are also increased. The most common problems are those related to poor intrauterine growth and premature birth. Although the outcome following preeclampsia or eclampsia is good for most women, these conditions remain major causes of maternal mortality.

Over half a million women die each year from pregnancy-related causes, and 99% of these deaths occur in the developing world (WHO, 2005). In poor countries, maternal mortality is still 100 to 200 times higher than in Europe and North America. Women in industrialized countries have an average lifetime risk (calculated as the average number of pregnancies multiplied by the risk associated with each pregnancy) of dying from pregnancy-related causes of between 1 in 4000 and 1 in 10,000, whereas women in low-income countries have a risk that is between 1 in 15 and 1 in 50. There is no other public health statistic for which the disparity between rich and poor countries is so wide. An estimated 10% to 15% of maternal deaths in developing countries are associated with preeclampsia or eclampsia (Duley, 1992; Khan et al, 2006), as are 13% to 15% of the direct obstetric deaths in the UK (Lewis, 2007) and USA (ACOG, 1996).

Perinatal mortality is also increased following preeclampsia (Ananth et al, 1995; Roberts et al, 2005). There is less information about morbidity for either mother or baby, but it is likely that this too is high. For example, preeclampsia accounts for an estimated one fifth of antenatal admissions (Rosenberg & Twaddle, 1990) and two thirds of referrals to day care assessment units (Anthony, 1992) in the UK, and a quarter of obstetric admissions to intensive care units in France (Bouvier et al, 1996). For many women, developing preeclampsia can be a difficult and unexpected experience especially if they become ill, give birth too early or if their baby dies (Duley et al, 2006).

There is also growing evidence that women who have had gestational hypertension or preeclampsia are at increased risk later in life of hypertension, stroke, and ischaemic heart disease (Bellamy et al, 2007; Wilson et al, 2003), although it remains unclear whether this reflects a common pathway or whether having preeclampsia increases this risk. For the babies, preeclampsia is an antecedent for up to 12% of those born small-for-gestational age (Kramer et al, 2000) and 19% of those born preterm (Hewitt & Newnham, 1988). Such children are at an increased risk of developmental delay and chronic ill health in childhood. The underlying cause of preeclampsia remains unclear, and the only definitive treatment is to end the pregnancy by delivering the baby. The aim of interventions for women with preeclampsia is therefore to treat the symptoms and prevent complications, and to optimize the timing of delivery for the baby.

2.2 DEFINITION

Preeclampsia is part of a spectrum of conditions known as the hypertensive disorders of pregnancy. These disorders have a continuum with normal pregnancy. During normal pregnancy there is enormous maternal physiological adaptation to accommodate the growing fetus and

placenta. For example, cardiac output increases by about 40% in the first trimester. In contrast, blood pressure remains relatively unchanged in the first trimester, falling by about 5 to 10 mmHg in the second trimester, and rising back to pre-pregnancy levels by term. Cardiac output is influenced by peripheral resistance and blood pressure. As normal pregnancy is associated with increased cardiac output and normal or slightly lowered blood pressure, peripheral resistance falls (De Swiet, 2002). Changes in kidney function also occur in normal pregnancy, with increased protein excretion especially in the third trimester. In normal pregnancy, up to 300 mg protein in 24 hours output of urine is accepted as normal.

Classification and definition of the hypertensive disorders of pregnancy have, in the past, been controversial. More recently, there has been a shift towards agreeing on and accepting standard definitions, and ensuring they are relevant for clinical practice (Brown et al, 2001). What follows is based on current consensus.

2.2.1 Definition of hypertension

Hypertension in pregnancy is usually defined as systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or both. Any rise in blood pressure should be confirmed by a second measurement, ideally at least four hours later. Because of cardiovascular changes, automated blood pressure monitors systematically underestimate blood pressure in pregnancy and preeclampsia. If used, they should be calibrated regularly against a mercury sphygmomanometer (Shennan & Waugh, 2003). The debate over which auscultatory sound to use for assessment of diastolic blood pressure, muffling (Korotkoff phase IV) or disappearance (Korotkoff phase V), has been resolved, and Korotkoff V is now recommended as more reliable (Brown et al, 2001).

2.2.2 Definition of proteinuria

Proteinuria during pregnancy is defined as 300 mg protein, or more, in 24 hours (Brown et al, 2001). In a single midstream urine sample, this usually correlates with 30 mg/dL, 1+ or more on a dipstick, or a spot urine protein/creatinine ratio of at least 30mg/mmol.

2.3 CLASSIFICATION

2.3.1 Gestational hypertension or pregnancy-induced hypertension

This is hypertension detected for the first time during the second half of pregnancy (after 20 weeks' gestation) in the absence of proteinuria. It resolves within three months of birth.

2.3.2 Preeclampsia/eclampsia

Preclampsia is defined as hypertension and proteinuria detected for the first time in the second half of pregnancy (after 20 weeks' gestation). Eclampsia is the occurrence of seizures in a woman with preeclampsia. There is no widely accepted definition of severe preeclampsia. Nevertheless, the following are widely regarded as features of severe disease: severe hypertension (blood pressure at least 160 mmHg systolic, or 110 mmHg diastolic), severe proteinuria (usually at least 3 g (range 2 g to 5 g) protein in 24 hours, or 3+ on dipstick), reduced urinary volume (less than 500ml in 24 hours), neurological disturbances such as headache, visual disturbances, and exaggerated tendon reflexes, upper abdominal pain, pulmonary oedema (fluid in the lungs), impaired liver function tests, high serum creatinine, low platelets, intrauterine growth restriction or reduced liquor volume (Brown et al, 2000; NHBPEP, 2000).

2.3.3 Chronic hypertension

This is hypertension known to be present before pregnancy, or detected before 20 weeks' gestation. It is essential hypertension if there is no underlying cause and secondary hypertension if there is an underlying cause such as renal, cardiac, or endocrine disease. 'Chronic' hypertension may present for the first time as gestational hypertension. Hence, gestational hypertension that does not resolve after birth should be reclassified as chronic hypertension.

2.3.4 Preeclampsia superimposed on chronic hypertension

Women with chronic hypertension may then develop preeclampsia. This is diagnosed where there is new onset of proteinuria, or sudden worsening of either hypertension or proteinuria, or development of other signs and symptoms of preeclampsia after 20 weeks' gestation.

2.4 AETIOLOGY OF PREECLAMPSIA

Despite a growing understanding of the pathophysiology of preeclampsia, the underlying cause of this syndrome remains unclear. Factors that appear to have a role include maternal age, parity, obesity, maternal immune response, genetic predisposition, and maternal vascular disease (such as diabetes, chronic hypertension and autoimmune disease) (Duckitt & Harrington, 2005). Diet and nutrition may also have a role. Whether an individual woman will develop this syndrome probably depends on which of these factors she has, and how they interact.

Preeclampsia is thought to occur as a result of inadequate blood supply to the placenta, related either to abnormal implantation, or to increased demand from the placenta (for example, in a multiple pregnancy). So, although preeclampsia is usually diagnosed in the second half of pregnancy, the antecedents are present much earlier. Current thinking is that inadequate blood supply to the placenta leads to the release of unknown factors or materials into the maternal circulation which activate or injure the endothelial cells, resulting in endothelial dysfunction (abnormal functioning of cells lining blood vessels) (Roberts & Lain, 2002). Endothelial dysfunction results in widespread vasoconstriction and activation of platelets and the coagulation system. Injured endothelial cells allow leakage of fluid out of the blood vessels and into surrounding tissues, causing oedema and a reduction in the circulating blood volume. There is then inadequate blood flow to many of the woman's organs, especially the kidneys, liver, and brain. It is the vasoconstriction, micro clots, and reduced circulating blood volume that result in the clinical manifestations of preeclampsia.

Any satisfactory theory concerning the etiology and pathophysiology of preeclampsia must account for the observation that hypertensive disorders due to pregnancy are very much more likely to develop in women who:
Are exposed to chorionic villi for the first time.
Are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole.
Have preexisting vascular disease.
Are genetically predisposed to hypertension developing during pregnancy.
Although chorionic villi are essential, they need not be located within the uterus. A fetus is not a requisite for preeclampsia. Regardless of precipitating etiology, the cascade of events that leads to the preeclampsia syndrome is characterized by a host of abnormalities that result in vascular endothelial damage with vasospasm, transudation of plasma, and ischemic and thrombotic sequelae. Writings describing eclampsia have been traced as far back as 2200 B.C. (Lindheimer et al, 1999). It is thus not surprising that a number of mechanisms have been

proposed to explain its cause. Many of the absurd, and especially the dangerous, thankfully have been discarded. According to Sibai (2003), currently plausible potential causes include the following:
Abnormal trophoblastic invasion of uterine vessels.
Immunological intolerance between maternal and fetoplacental tissues.
Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
Dietary deficiencies.
Genetic influences.

2.4.1 Abnormal Trophoblastic Invasion

In normal implantation, the uterine spiral arteries undergo extensive remodeling as they are invaded by endovascular trophoblasts. In preeclampsia, however, there is *incomplete trophoblastic invasion*. In this case, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. In 1994, Meekins et al described a continuum in the number of spiral arteries with endovascular trophoblasts in placentas of normal women and in those with preeclampsia. Madazli et al (2000) showed that the magnitude of defective trophoblastic invasion of the spiral arteries correlated with the severity of the hypertensive disorder.
Using electron microscopy, De Wolf and co-workers (1980) examined arteries taken from the uteroplacental implantation site. They observed that early preeclamptic changes included endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, and medial necrosis. They found that lipid accumulates first in myointimal cells and then in macrophages. Typically, the vessels affected by atherosis develop aneurysmal dilatation and are frequently found in association with spiral arterioles that have failed to undergo normal adaptation (Khong, 1991). Obstruction of the spiral arteriolar lumen by atherosis may impair placental blood flow. It is thought that these changes cause placental perfusion to be pathologically diminished, which eventually leads to the preeclampsia syndrome (Lain and Roberts, 2002; Redman and Sargent, 2003).

2.4.2 Immunological Factors

There is circumstantial evidence to support the theory that preeclampsia is immune mediated. Certainly the microscopic changes at the maternal-placental interface are suggestive of acute graft rejection (Labarrere, 1988). There are also inferential data. For example, the risk of preeclampsia is appreciably enhanced in circumstances where formation of blocking antibodies to placental antigenic sites might be impaired. This may arise in situations in which effective immunization by a previous pregnancy is lacking, as in first pregnancies; or in which the number of antigenic sites provided by the placenta is unusually great compared with the amount of antibody, as with multiple fetuses (Beer, 1978). "Immunization" from a prior abortion does not seem to occur. Strickland and associates (1986) analyzed outcomes of over 29,000 pregnancies at Parkland Hospital and reported that hypertensive disorders were decreased only slightly (22 versus 25 percent) in women who previously had miscarried (thus who were previously "immunized") and were now having their first advanced pregnancy. The immunization concept was supported by their observations that preeclampsia developed less often in multiparas who had a prior term pregnancy. Other studies have shown that multiparous women impregnated by a new consort have an increased risk of preeclampsia (Mostello et al, 2002; Trupin et al, 1996).
Dekker and Sibai (1998) have reviewed the possible role of immune maladaptation in the pathophysiology of preeclampsia. Beginning in the early second trimester, women destined to develop preeclampsia have a significantly lower proportion of helper T cells (Th1) compared with that of women who remain normotensive (Bardeguez et al, 1991). This

Th1/Th2 imbalance, with Th2 dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic compared with normotensive women (Yoneyama et al, 2002). These helper T lymphocytes secrete specific cytokines that promote implantation, and their dysfunction may favor preeclampsia (Hayashi et al, 2004; Whitecar et al, 2001).
In women with anticardiolipin antibodies, placental abnormalities and preeclampsia develop more commonly. According to Katano and colleagues (1996), antibodies associated with glycoprotein I appear most relevant. Immune complexes and anti-endothelial cell antibodies may also be involved (Taylor and Roberts, 1999).

2.4.3 The Vasculopathy and the Inflammatory Changes

In many ways, inflammatory changes are a continuation of the placental causes discussed above. In response to placental factors released by ischemic changes, or any other inciting cause, a cascade of events is set in motion (Redman and Sargent, 2003). The decidua also contains an abundance of cells that, when activated, can release noxious agents (Staff et al, 1999). These then serve as mediators to provoke endothelial cell injury.
Redman et al (1999) have proposed that the endothelial cell dysfunction associated with preeclampsia can result from a "generalized perturbation of the normal, generalized maternal intravascular inflammatory adaptation to pregnancy". In this hypothesis, preeclampsia is considered a disease due to an extreme state of activated leukocytes in the maternal circulation (Gervasi et al, 2001). Briefly, cytokines such as tumor necrosis factor (TNF) and the interleukins may contribute to the oxidative stress associated with preeclampsia. Oxidative stress is characterized by reactive oxygen species and free radicals that lead to formation of self-propagating lipid peroxides (Manten et al, 2005). These in turn generate highly toxic radicals that injure endothelial cells, modify their nitric oxide production, and interfere with prostaglandin balance.
Not all investigators have confirmed these findings. Diedrich et al (2001) did not detect any lipid hydroperoxides in 38 preeclamptic women, 10 of whom had HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). They did, however, find other evidence of oxidative stress. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in atherosis; activation of microvascular coagulation, seen in thrombocytopenia; and increased capillary permeability, seen in edema and proteinuria.
These observations on the effects of oxidative stress in preeclampsia have given rise to increased interest in the potential benefit of antioxidants to prevent preeclampsia (Chappell et al, 1999; Zhang et al, 2002). Antioxidants are a diverse family of compounds that function to prevent overproduction of and damage caused by noxious free radicals. Examples of antioxidants include vitamin E (tocopherol), vitamin C (ascorbic acid), and beta-carotene.

2.4.4 Nutritional Factors

A number of dietary deficiencies or excesses over the centuries have been blamed as the cause of eclampsia. Dietary taboos that have included meat, protein, purines, fat, dairy products, salt, and other elements have been advocated at times. Observations and theories led to studies of dietary deprivation of various sorts that many times were models of absurdity. In more recent times, sanity and a scientific approach have prevailed. For example, blood pressure in non pregnant individuals is affected by a number of dietary influences, including minerals and vitamins. Some studies have shown a relationship between dietary deficiencies and the incidence of preeclampsia. This was followed by studies of supplementation with various elements such as zinc, calcium, and magnesium to prevent preeclampsia. Other studies, such as the one by John and co-workers (2002), showed that in the general population a diet

high in fruits and vegetables that have antioxidant activity is associated with decreased blood pressure. This is related to the case-control study by Zhang et al (2002) cited above, in which the incidence of preeclampsia was doubled in women whose daily intake of ascorbic acid was less than 85 mg.

Obesity is a potent risk factor for preeclampsia. Evidence has accrued that obesity in non pregnant individuals' causes endothelial activation and a systemic inflammatory response associated with atherosclerosis (Ross, 1999). In the study of pregnant women by Wolf and colleagues (2001), C-reactive protein, an inflammatory marker, was shown to be increased in obesity, which in turn was associated with preeclampsia.

2.4.5 Genetic Factors

The predisposition to hereditary hypertension undoubtedly is linked to preeclampsia (Ness et al, 2003), and the tendency for preeclampsia/eclampsia is inherited. Chesley and Cooper (1986) studied sisters, daughters, granddaughters, and daughters-in-law of eclamptic women and concluded that preeclampsia/eclampsia is highly heritable. The single-gene model, with a frequency of 0.25, best explained their observations. Other investigators cite possibilities of polygenic inheritance (Trogstad et al, 2004). A Swedish study by Nilsson et al (2004) that included almost 1.2 million births reported a genetic component for gestational hypertension as well as preeclampsia. They reported 60-percent concordance in monozygotic female twin pairs, which was much higher than that found by Treloar and co-workers (2001).

2.5 PATHOGENESIS OF PREECLAMPSIA

2.5.1 Vasospasm

The initial concept of vasospasm was based on direct observations of small blood vessels in the nail beds, ocular fundi, and bulbar conjunctivae. It was also surmised from histological changes seen in various affected organs (Landesman et al, 1954). Vascular constriction causes resistance and subsequent hypertension. At the same time, endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially. Wang et al (2002) have also demonstrated disruption of endothelial junctional proteins. Suzuki et al (2003) demonstrated ultrastructural changes in the subendothelial region of resistance arteries in preeclamptic women. With diminished blood flow because of maldistribution, ischemia of the surrounding tissues would lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. Ironically, vasospasm may be worse in women with preeclampsia than in those with the HELLP syndrome (Fischer et al, 2000).

2.5.2 Endothelial Cell Activation

Over the past two decades, endothelial cell activation has become the centerpiece in the contemporary understanding of the pathogenesis of preeclampsia. In this scheme, unknown factors, likely from the placenta, are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. The clinical syndrome of preeclampsia is thought to result from these widespread endothelial cell changes (Hayman et al, 2000).

Intact endothelium has anticoagulant properties, and it also blunts the response of vascular smooth muscle to agonists by releasing nitric oxide. Damaged or activated endothelial cells secrete substances that promote coagulation and increase the sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, increased capillary permeability, and elevated blood concentrations of substances associated with such activation. These latter substances are transferrable, and serum from women with preeclampsia stimulates cultured endothelial cells to produce greater amounts of prostacyclin than serum from normal pregnant women.

2.5.3 Increased Pressor Responses

Normally, pregnant women develop refractoriness to infused vasopressors (Abdul-Karim & Assali, 1961). Women with early preeclampsia, however, have increased vascular reactivity to infused norepinephrine and angiotensin II (Raab et al, 1956). Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension. Normotensive nulliparas remained refractory to infused angiotensin II, but those who subsequently became hypertensive lost this refractoriness several weeks before the onset of hypertension. Women with underlying chronic hypertension have almost identical responses (Gant et al, 1977).

2.5.4 Prostaglandins

A number of prostanoids are central to the pathophysiology of the preeclampsia syndrome. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by vascular endothelial prostaglandin synthesis. For example, when compared with normal pregnancy, endothelial prostacyclin (PGI2) production is decreased in preeclampsia. This action appears to be mediated by phospholipase A2 (Taylor & Roberts, 1999). At the same time, thromboxane A2 secretion by platelets is increased, and the prostacyclin: thromboxane A2 ratio decreases. The net result favors increased sensitivity to infused angiotensin II, and ultimately, vasoconstriction. Chavarria et al (2003a) have provided evidence that these changes are apparent as early as 22 weeks in women who later develop preeclampsia.

2.5.5 Nitric Oxide

This potent vasodilator is synthesized from L-arginine by endothelial cells. Withdrawal of nitric oxide results in a clinical picture similar to preeclampsia in a pregnant animal model (Weiner et al, 1989). In other animal studies, inhibition of nitric oxide synthesis increases mean arterial pressure, decreases heart rate, and reverses the pregnancy-induced refractoriness to vasopressors. In humans, nitric oxide likely is the compound that maintains the normal low-pressure vasodilated state characteristic of fetoplacental perfusion (Weiner et al, 1992). It also is produced by fetal endothelium and is increased in response to preeclampsia, diabetes, and infection (Parra et al, 2001). Preeclampsia is associated with decreased endothelial nitric oxide synthase expression, which increases cell permeability (Wang et al, 2004). There is not decreased nitric oxide release or production prior to the onset of hypertension (Anumba et al, 1999). Its production is increased in severe preeclampsia possibly as a compensatory mechanism for the increased synthesis and release of vasoconstrictors and platelet-aggregating agents (Benedetto et al, 2000). Thus, increased serum concentrations of nitric oxide in women with preeclampsia are likely the result of hypertension, not the cause (Morris et al, 1996).

2.5.6 Endothelins

These 21-amino acid peptides are potent vasoconstrictors, and endothelin-1 (ET-1) is the primary isoform produced by human endothelium (Mastrogiannis et al, 1991). Plasma ET-1 is increased in normotensive pregnant women, but women with preeclampsia have even higher levels (Ajne et al, 2003). According to Taylor & Roberts (1999), the placenta is not the source of increased ET-1 and it likely arises from systemic endothelial activation. Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations (Sagsoz & Kucukozkan, 2003).

2.5.7 Angiogenic Factors

Several glycosylated glycoproteins are selectively mitogenic for endothelial cells and are thought to be important in mediating the preeclampsia syndrome. Two of these are *vascularendothelial growth factor (VEGF)* and *placental growth factor (PlGF)*. Their secretion increases across normal pregnancy, and they promote angiogenesis and

induce nitric oxide and vasodilatory prostaglandins, discussed above. Placental VEGF is important in vasculogenesis and control of microvascular permeability. Paradoxically, VEGF is increased in serum from women with preeclampsia but its bioavailability is decreased (Baker et al, 1995; Simmons et al, 2000).

2.6 PATHOPHYSIOLOGY

By strict definition, preeclampsia-eclampsia fits the definition of a syndrome: *A group of symptoms or pathological signs which consistently occur together, especially with an (originally) unknown cause* (Oxford English Dictionary, 1993). Although the cause of preeclampsia remains unknown, evidence for it begins to manifest early in pregnancy with covert pathophysiological changes that gain momentum across gestation. Unless delivery supervenes, these changes ultimately result in multiorgan involvement with a clinical spectrum ranging from barely noticeable to one of cataclysmic pathophysiological deterioration that can be life threatening for both mother and fetus. These adverse maternal and fetal effects develop simultaneously. As discussed, these presumably are a consequence of vasospasm, endothelial dysfunction, and ischemia. The myriad of maternal consequences of the preeclampsia syndrome are described in terms of organ systems, but they frequently overlap. It is enigmatic that there are such wide variations of involvement of these systems in individual pregnancies.

2.6.1 Cardiovascular System

Severe disturbances of normal cardiovascular function are common with preeclampsia or eclampsia. These are related to increased cardiac afterload caused by hypertension, cardiac preload, which is substantively affected by pathologically diminished hypervolemia of pregnancy or is iatrogenically increased by intravenous crystalloid or oncotic solutions, and endothelial activation with extravasation into the extracellular space, especially the lung. In addition, left ventricular mass is increased relative to normal pregnancy (Borghi et al, 2000).

The cardiovascular aberrations of hypertensive disorders of pregnancy vary depending on a number of factors. Some of these include severity of hypertension, presence of underlying chronic disease, whether preeclampsia is present, and at what point in the clinical course they are studied. For example, some of these changes precede the onset of hypertension. Bosio et al (1999) used noninvasive Doppler hemodynamic monitoring in a longitudinal study of 400 nulliparous women commencing early in pregnancy. Gestational hypertension developed in 24 women, and 20 others had preeclampsia. Compared with normotensive women, the women who developed preeclampsia had significantly elevated cardiac outputs before hypertension developed. This substantiates earlier observations of Easterling et al (1990), except that the latter group reported increased peripheral resistance during this preclinical phase. With clinical onset of preeclampsia, there was a marked reduction in cardiac output and increased peripheral resistance. By contrast, the women with gestational hypertension maintained their significantly elevated cardiac outputs with development of hypertension.

It has been known for over 75 years that *hemoconcentration* is a hallmark of eclampsia. Zeeman and colleagues (2004b) expanded the previous observations of Pritchard and co-workers (1984) that in eclamptic women the normally expected hypervolemia was severely curtailed or even absent. Women of average size should have a blood volume of nearly 5000 mL during the last several weeks of a normal pregnancy, compared with about 3500 mL when they are not pregnant. With eclampsia, however, much or all of the anticipated excess 1500 mL of blood normally present is absent. Such hemoconcentration is likely the consequence of generalized vasoconstriction and endothelial dysfunction with vascular permeability. In women with preeclampsia, and depending

on severity, hemoconcentration is usually not as marked, whereas women with gestational hypertension usually have a normal blood volume (Silver et al, 1998).
For women with severe hemoconcentration, it was once taught that an acute fall in hematocrit suggested resolution of preeclampsia. However, this usually is the consequence of blood loss, even of normal amounts, at delivery. It may also be partially the result of intense erythrocyte destruction as subsequently described.
In the absence of hemorrhage, the intravascular compartment in eclamptic women is usually not under filled. Vasospasm and endothelial leakage of plasma has contracted the space to be filled. These changes persist until a variable amount of time after delivery when the vascular endothelium repairs. Vasodilation then occurs, and as the blood volume increases, the hematocrit usually falls. Thus, women with eclampsia:
Are unduly sensitive to vigorous fluid therapy administered in an attempt to expand the contracted blood volume to normal pregnancy levels.
Are quite sensitive to even normal blood losses at delivery.

2.6.2 Blood and Coagulation

Hematological abnormalities develop in some women with preeclampsia. Among these are thrombocytopenia, which at times may become as severe as to be life threatening. In addition, the levels of some plasma clotting factors may be decreased, and erythrocytes may display bizarre shapes and undergo rapid hemolysis.
Because thrombocytopenia can be induced acutely by preeclampsia/eclampsia, the platelet count is routinely measured in hypertensive pregnant women. The frequency and intensity of maternal thrombocytopenia varies and likely is dependent on the intensity of the disease process, duration of preeclampsia, and the frequency with which platelet counts are performed. Overt thrombocytopenia, defined by a platelet count less than 100,000/µL, indicates severe disease. In most cases, delivery is indicated because the platelet count continues to decrease. After delivery, the platelet count increases progressively to reach a normal level within 3 to 5 days. Thrombocytopenia results from platelet activation, aggregation, and consumption that are accompanied by increased mean platelet volume and decreased life span (Harlow et al, 2002).
The clinical significance of thrombocytopenia, in addition to any impairment in coagulation, is that it reflects the severity of the pathological process. In general, the lower the platelets count, the higher the maternal and fetal morbidity and mortality (Leduc et al, 1992). In 1954, Pritchard and colleagues called attention to thrombocytopenia accompanied by elevated serum liver transaminase levels in women with eclampsia. Weinstein (1982) later referred to this combination of events as the *HELLP syndrome*—hemolysis (H), elevated liver enzymes (EL), and low platelets (LP)—and this moniker now is used worldwide.
Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia (Baker & Cunningham, 1999). Since the early description by Pritchard and co-workers (1954) of coagulation abnormalities in women with eclampsia, there is little evidence that these abnormalities are clinically significant (Pritchard et al, 1984). Except for thrombocytopenia, discussed above, laboratory aberrations generally are mild. Unless there is associated placental abruption, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy, and fibrin degradation products are elevated only occasionally. Barron and colleagues (1999) found routine laboratory assessment of coagulation, including prothrombin time, activated

partial thromboplastin time, and plasma fibrinogen level, to be unnecessary in the management of pregnancy-associated hypertensive disorders. The *thrombin time* is somewhat prolonged in a third of the cases of eclampsia even when elevated levels of fibrin degradation products are not identified. The reason for this elevation is not known, but it has been attributed to hepatic derangements discussed subsequently (Leduc et al, 1992).

2.6.3 Volume Homeostasis

Plasma levels of *renin, angiotensin II*, and *aldosterone* are increased during normal pregnancy. With preeclampsia, these values decrease toward the normal nonpregnant range (Weir et al, 1973). With sodium retention, hypertension, or both, renin secretion by the juxtaglomerular apparatus decreases. Renin catalyzes the conversion of angiotensinogen to angiotensin I, which is then transformed into angiotensin II by angiotensin-converting enzyme (ACE). Thus, with preeclampsia, angiotensin II levels decline, resulting in a decrease in aldosterone secretion. Despite this, women with preeclampsia avidly retain infused sodium (Brown et al, 1988b).

Vasopressin levels are normal in women with preeclampsia despite decreased plasma osmolality (Lindheimer et al, 1999). During normal pregnancy, serum concentrations of *atrial natriuretic peptide* are maintained in the nonpregnant range despite the increased plasma volume. The peptide is released on atrial wall stretching from blood volume expansion. It is vasoactive and promotes sodium and water excretion, probably by inhibiting aldosterone, renin activity, angiotensin II, and vasopressin. Secretion of atrial natriuretic peptide is increased in women with preeclampsia (Lindheimer et al, 1999). Increases in atrial natriuretic peptide following volume expansion result in comparable increases in cardiac output and decreases in peripheral vascular resistance in both normotensive and preeclamptic women (Nisell et al, 1992). This observation may in part explain observations of a fall in peripheral vascular resistance following volume expansion in preeclamptic women.

The volume of *extracellular fluid,* manifest as edema, in women with severe preeclampsia is usually expanded beyond that of normal pregnant women. The mechanism responsible for pathological fluid retention is thought to be endothelial injury. In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure, which creates a filtration imbalance, further displacing intravascular fluid into the surrounding interstitium.

Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with normal pregnant women unless there has been vigorous diuretic therapy, sodium restriction, or administration of free water with sufficient oxytocin to produce antidiuresis.

Following an eclamptic convulsion, the serum pH and *bicarbonate* concentration are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide. The intensity of acidosis relates to the amount of lactic acid produced and its metabolic rate, as well as the rate at which carbon dioxide is exhaled.

2.6.4 Uteroplacental Perfusion

Compromised uteroplacental perfusion from vasospasm is almost certainly a major culprit in the genesis of increased perinatal morbidity and mortality associated with preeclampsia. Brosens and associates (1972) reported that the mean diameter of myometrial spiral arterioles of 50 normal pregnant women was 500 µm. The same measurement in 36 women with preeclampsia was 200 µm. Attempts to assess human maternal and placental blood flow have been hampered by several obstacles, including inaccessibility of the placenta, the complexity of its venous effluent, and the unsuitability of certain investigative techniques for humans. Measurement of blood flow velocity through uterine arteries has been used to estimate resistance to uteroplacental blood flow. Vascular

resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. Earlier studies were done to assess this by measuring these ratios from uterine and umbilical arteries in preeclamptic pregnancies. The findings indicated that in some cases, but certainly not all, there was increased resistance (Ducey et al, 1987). Matijevic & Johnston (1999) used color pulsed Doppler velocimetry to measure resistance in *uterine spiral arteries*. Impedance was higher in peripheral than in central vessels. This has been termed a "ring-like" distribution. Mean resistance was higher in all women with preeclampsia compared with normotensive controls.

2.7 MANAGEMENT

2.7.1 Prophylactic therapies

The key to modern management of preeclampsia is close surveillance and timely delivery prior to serious consequences. In an ideal world preventing the manifestation of the disease would be far more preferable. Aspirin, calcium, and antioxidants have all been investigated, with some evidence of success (Ruano et al, 2005).

Low-dose aspirin reverses the imbalance between the vasoconstrictor thromboxane A2 and the vasodilator prostacyclin, which is known to occur in preeclampsia. There are 42 randomized controlled trials published in the Cochrane collaboration demonstrating a 15% relative risk reduction in preeclampsia when either aspirin or other antiplatelet agents are given. There is a similar reduction (14%) in the risk of death to the baby as well as an 8% reduction in the risk of preterm delivery (Duley et al, 2001). It is generally accepted that aspirin should be considered in high-risk women. Benefit is seen when the prevalence of preeclampsia is only 7%, and one baby death can be prevented for every 250 treated (Duley et al, 2003). The evidence demonstrates it is safe. There are ongoing investigations as to the appropriate dose and timing as well as the population to be targeted.

There are 10 trials in nearly 7000 women demonstrating the beneficial role of calcium as preeclamptic prophylaxis and overall there is a significant reduction in the incidence of preeclampsia (Atallah et al, 2002). However, this is largely related to the success in trials in women with inadequate calcium intake, and the benefit to the baby is not as clear as aspirin. The investigations into the use of fish oils containing N3 fatty acid known to inhibit platelet thromboxane A2 have not shown a significant reduction in preeclampsia. As oxidative stress is known to be fundamental to the disease process one trial demonstrated that vitamin C and E supplementation in the second trimester of pregnancy may be beneficial, demonstrating more than a 50% reduction when high-risk women were treated (Chappel et al, 1999). This involved 1000 mg vitamin C and 400 IU vitamin E, which are known to act synergistically; however, further studies which are currently ongoing need to confirm this.

2.7.2 Assessment of the mother

The threshold of hypertension and proteinuria are relatively low to diagnose preeclampsia, so the first key aspect of management involves confirming the diagnosis to ensure that iatrogenic morbidity does not ensue. Hypertension that occurs in early pregnancy, that is, before 28 weeks' gestation results in preeclampsia developing in approximately 50% of women. In contrast women who present at term with hypertension are unlikely to develop preeclampsia (approximately a 10% risk). Care in assessing both blood pressure and proteinuria can improve assessment as false positive and negative tests are commonplace.

The syndrome of preeclampsia is multisystemic, and other organ involvement must be carefully considered, including the placenta. A careful history should also include whether women have symptoms such as visual disturbance, headaches and epigastric pain. Sometimes nausea or even vomiting can be a presenting feature. However, at least 50% of women even with severe disease will be asymptomatic (Douglas & Redman, 1994). When managing women particularly remote from term, involvement of all organ systems must be carefully investigated. Platelets are consumed due to the endothelial activation. A falling count, particularly to less than 100 × 109/l may indicate a need to consider delivery. Counts above 50 are likely to support haemostasis. An increasing haematocrit or haemoglobin indicates hypovolaemia, which is characteristic of severe disease. If labour is anticipated then clotting abnormalities should be checked as preeclampsia can cause disseminated intravascular coagulation. This is important if regional anaesthesia is used, which is preferable to general anaesthesia.

Renal tubular function can be assessed by measuring uric acid, which is a marker of disease severity, although normal levels can occur in severe disease. Acute fatty liver can result in spuriously high levels of uric acid (along with high white cell count, and low glucose). Urea and creatinine are associated with late renal involvement and generally not useful as indicators of disease severity. Liver transaminases should be measured to indicate hepatocellular damage. Normal ranges of transaminases are approximately 20% lower than non-pregnant (Girling et al, 1997). Subcapsular involvement of the liver can occur, resulting in epigastric pain with normal transaminase measurements. HELLP (Haemolysis, Elevated Liver Enzymes, and Low Platelets) syndrome occurs when liver involvement is associated with haemolysis and low platelets. This is a severe variant of preeclampsia. When protein excretion exceeds 3 g in 24 h, the circulating albumin is likely to fall (nephrotic syndrome) and this increases the risk of pulmonary oedema. Lactate dehydrogenase levels will increase in the presence of haemolysis.
Antenatal corticosteroids should be given to enhance fetal lung maturity, and are not contraindicated in preeclampsia. Steroid therapy

is also known to help recovery from HELLP syndrome and has been used in the post-partum period. Antenatal corticosteroids may actually improve biochemical markers in women with preeclampsia. The treatment of blood pressure should be reserved principally for severe hypertension, that is, blood pressures over 160/110 mmHg. However, this does require urgent therapy. Treatment of moderate hypertension maybe detrimental to fetal growth (Von Dadelszen et al, 2000), and moderate blood pressure should not be aggressively treated. Once fetal lung maturity is likely to be adequate, delivery should be considered, that is, after 32 weeks' gestation. Multiorgan involvement or fetal compromise would be indications for delivery. Close inpatient supervision is otherwise required and can be considered prior to 32 weeks' gestation or when the benefit of conservative management is judged to outweigh delivery. Conservative management will reduce neonatal morbidity, without substantially increasing maternal problems. Recent evidence suggests that under 30 week's neonatal morbidity is high, and conservative management is desirable (Shear et al, 2005). However, at least one third of women still need to be delivered for fetal reasons less than 34 weeks. The inability to control hypertension, deteriorating liver or renal function, progressive fall in platelet or albumin, or neurological complications would be indications for maternal delivery at any gestation.

2.7.3 Fetal assessment

Early onset preeclampsia is particularly involved with placental insufficiency, and more than half of babies born before 34 weeks will be growth restricted (Shear et al, 2005). This also explains why abruption is more common, occurring in about1 in 20 of these early onset cases. Fetal well-being should always be carefully considered in all cases of preeclampsia, and includes a symphyseal fundal height assessment, as well as a general enquiry as to fetal movements. At early gestations an ultrasound scan must be performed to assess fetal growth, and should include determination of the amniotic fluid index and umbilical artery Doppler waveforms. A non-reactive CTG with decelerations or a fetal condition that is deteriorating warrants delivery, as it is unlikely to improve with time and may worsen with antihypertensive therapy.

2.7.4 Intrapartum care of preeclampsia

Many units have now developed a severe preeclampsia protocol. Cases which require protocol determined management are often defined as those with severe hypertension (greater than 160/110 mmHg) or hypertension with an additional complication such as headache, visual disturbance, epigastric pain, clonus (more than three beats) or a platelet count less than 100 x 109 or AST more than 50 IU units per litre.

The confidential enquiry into maternal deaths demonstrates that the two main reasons why women die are cerebral haemorrhage or adult/acute respiratory distress syndrome (CEMD UK, 2001). The two most important factors that contribute to these deaths are therefore severe hypertension and fluid intake. The control of blood pressure and fluid balance is therefore critical. In contrast to pulmonary causes of death, in recent years, deaths related to intracerebral haemorrhage have not been reduced; suggesting control of blood pressure remains suboptimal through poor monitoring and treatment.

2.7.5 Blood pressure control

Blood pressure should be measured frequently (at least every 15 min). Automated sphygmomanometers can be used to facilitate this, or alternatively intra-arterial readings can be assessed via a peripheral arterial pressure transducer. As non-invasive measurements are obtained principally by oscillometric blood pressure devices, which underestimate blood pressure in preeclampsia (Natarajan et al, 1999). Significant changes in blood pressure should be confirmed using mercury

sphygmomanometry. Some devices are now accurate, and only those specifically assessed for accuracy in preeclampsia should be purchased in the future (Golara et al, 2002). On an individual patient basis the accuracy of any device used should be established against an observer using standard sphygmomanometry, preferably with a mercury sphygmomanometer. Mean arterial
pressures (MAP) are generally used to guide management in protocols. Antihypertensive therapy should be instigated when the MAP is =125 mmHg, or urgently if >140mmHg as above this cerebral autoregulation of pressure is not reliable. Either hydrallazine or labetalol can be used as a first line treatment, although labetalol is favoured (Magee et al, 2003).

As these are important emergency measures in preventing stroke, clinicians involved in the management of severe preeclampsia should be familiar with treatment regimes. Some protocols advocate infusing a colloid to protect the uteroplacental circulation if the baby is undelivered. This should be done with caution, and careful consideration to the impact of the overall fluid management, and preferably under central venous pressure (CVP) surveillance.

2.7.6 Control of fluid balance

Strict monitoring of input and output is essential in the preeclamptic patient. A combination of the reduced intravascular volume, leaking capillaries and low albumin make women prone to pulmonary oedema. Renal failure is a rare complication of preeclampsia but should be considered when there has been inadequate transfusion or profound hypotension following post-partum bleeding, as there is reduced intravascular volume. Oliguria is relatively common, and strict monitoring should be considered rather than aggressive blind fluid replacement. Administration of intravenous fluid in the oliguric patient must be done with caution. Most protocols will limit fluid intake to approximately 1 ml/kg/h. CVP monitoring and Foley catheter insertion should be used whenever possible. Repetitive fluid challenges should be avoided in the absence of invasive monitoring. Should the CVP be high (>8mmHg) with persistent oliguria then a dopamine infusion can be considered (1 ì/kg/min.) Haemodialysis or haemofiltration maybe necessary if the creatinine or potassium rises. Close communication with a renal physician should be sought. Administration of diuretics will only temporarily improve urine output, and confounds the reduced circulating volume. Frusemide should therefore be reserved for treating pulmonary oedema. Pulmonary artery catheterization should be considered in difficult cases.

2.7.7 Anticonvulsant management

An eclamptic fit is usually self-limiting; however, anticonvulsive therapy should be given to abort it when possible. Magnesium sulphate can be used to control such a fit (up to 8 mg given by slow intravenous infusion). Diazepam 10 mg can also be used but its anticonvulsant properties are short-lived as compared to its sedative properties. In those women who have prolonged fitting a brain scan is required to rule out an intracerebral bleed. Following an eclamptic fit magnesium sulphate is the prophylaxis of choice (Collaborative Eclampsia Trial, 1995).

Magnesium sulphate has been demonstrated to reduce cerebral ischaemia by acting as membrane stabilizer and vasodilator and is superior to both diazepam and phenytoin in preventing further fits. It is also associated with a significant reduction in the need for maternal ventilation and intensive care admissions. Magnesium sulphate is given in a 4 g intravenous loading dose in an infusion of 1 g/h. Some protocols suggest 2 g/h but efficacy has been demonstrated at 1 g/h. It is renally excreted so therefore in cases of oliguria or rising urea care must be taken regarding toxicity and this is detected by absence

of patellar reflexes. Respiratory arrest and muscle paralysis along with cardiac arrest can occur and an antidote is 10 ml of 10% calcium gluconate.

Even with severe preeclampsia, eclamptic fits are rare and occur in less than 2%. The Magpie trial evaluated giving magnesium sulphate versus placebo in women with pre-eclampsia and there was a significant reduction in fits in those women receiving treatment; magnesium sulphate will roughly halve the incidence of eclampsia (Magpie Trial, 2002). The evidence also suggests that there are less maternal deaths but trials have not been large enough to show that this is significantly so. The threshold for giving magnesium sulphate to a preeclamptic woman is uncertain but generally as the risk increases the benefit favours therapy.

2.7.8 Anaesthetic management

Endotracheal intubation can cause severe hypertension and general anaesthetic should be avoided (Allen et al, 1991). Regional blockade is therefore the anaesthesia of choice; prior to insertion a coagulopathy should be excluded. Platelet levels of more than 80 × 109 are likely to ensure haemostasis and most obstetric anaesthetists would be happy to perform this procedure under such circumstances. In women who have a Caesarean section a low threshold for invasive CVP monitoring is necessary. Careful management of fluid particularly following post-partum haemorrhage is essential. Following delivery one in three eclamptic fits will occur in the post-partum period most of these within 48 h (Douglas & Redman, 1994). Although eclampsia has been reported beyond this time it is not usually associated with serious morbidity and generally anticonvulsant prophylaxis can be stopped within a 48-h period. Blood pressure should be monitored carefully for at least 4 days following delivery as the highest reading can occur at this time (Atterbury et al, 1998). Quite frequently it is necessary to give women antihypertensive therapy at home and follow-up is recommended at 6 weeks. Methyldopa generally has unwanted side effects and other common antihypertensive therapies can be used.

2.7.9 Post-natal management

At the post-natal follow-up both blood pressure and urine should be checked for underlying renal and cardiovascular abnormalities. It is now clear that women who had preeclampsia have a doubling of subsequent ischaemic heart disease probably related to underlying vascular pathology. This risk is greater the more growth restricted and premature her baby is. At the post-natal visit future pregnancies should be discussed as well as the need for screening for hypertension in later life.

MAGNESIUM SULPHATE

Historic Perspective

Magnesium sulphate use was first reported in the early 1900s for control of tetanic convulsions (Alton & Lincoln, 1925). Shortly thereafter, Lazard reported use of magnesium sulphate for control of eclamptic convulsions with associated fivefold (30% to 5.8%) reduction of maternal mortality. Magnesium sulphate therapy was heralded as an improvement on the previous therapeutic measures for eclampsia: enemas, castor oil, and phlebotomy (Lazard, 1925). Magnesium sulphate therapy was adopted for treatment of eclamptic convulsions from observational studies and anecdotal experience. As a natural extension to its use for eclamptic seizures, magnesium sulphate was adapted for prophylaxis of seizures in women with severe preeclampsia; however, there is no systematic, controlled evidence that magnesium sulphate prevents progression to eclampsia.

The modern obstetric use of magnesium sulphate therapy for preeclampsia or eclampsia is credited to Pritchard, who popularized the

intramuscular route of administration of magnesium sulphate (10 g load followed by 5 g every 4 hours) (Pritchard, 1955). Continuous intravenous infusion was recommended by Zuspan (4 g load followed by 1 g/hour) (Zuspan, 1966) and subsequently modified by Sibai (6 g load followed by 2 g/hour) (Sibai, 1990). Pritchard identified appropriate serum levels of magnesium for treatment of eclamptic convulsions as 3.5–7 meq/L, corresponding to 4.2– 8.4 mg/dL (Pritchard, 1955). Although there is decreased incidence of seizures in magnesium-treated women (Lucas et al, 1995), no study has ever correlated explicit serum levels of magnesium with elimination of seizure activity analogous to the use of minimal inhibitory concentration and selection of antimicrobial agents. The concept of appropriate magnesium levels is from the clinical experience of Pritchard that most eclamptic seizures were successfully treated when the above magnesium levels were attained (Pritchard, 1955).

Pritchard noted that higher plasma levels of magnesium were needed for arrest of convulsions rather than for seizure prophylaxis; however, the levels suggested by Pritchard for prophylaxis were similar to those used for seizure therapy. Despite this practice, the actual magnesium level needed for prophylaxis has never been established.

Pharmacology

For many years, the Zuspan regimen was used for prophylaxis and therapy of seizures. Sibai et al (1981) noted failures with this magnesium sulphate regimen, thus evaluated 178 random magnesium levels from 120 women, obtained 2–48 hours following infusion of a 4 g intravenous magnesium sulphate loading dose followed by maintenance doses of 1–3 g per hour. Only 2 of 115 women receiving maintenance infusions of 1 g per hour magnesium sulphate had magnesium levels between 4.8– 8.4 mg/dL (recommended “therapeutic” range). Only 23 (51%) of 45 women receiving maintenance infusions of 2 g per hour magnesium sulphate had serum magnesium levels in the recommended range. All women receiving a maintenance infusion of 3 g per hour magnesium sulphate had magnesium levels within the recommended range. This study (Sibai et al, 1981) altered clinical practice in the United States accordingly, changing the maintenance magnesium sulphate infusion from 1 g per hour to 2 g per hour.

Subsequently, Sibai (1990) studied the magnesium levels achieved with varied doses of intravenous magnesium sulphate and recommended a 6 g magnesium sulphate loading dose (producing serum magnesium levels between 5–9 mg/dL) followed by 2 g/hour continuous magnesium sulfate infusion with resultant magnesium levels between 4–8 mg/dL.

Mode of Action

Despite magnesium sulphate use for more than 70 years, its mechanism of action for treatment and prophylaxis of preeclampsia or eclampsia remains an enigma. For many years, the standard dose of magnesium sulphate was 4 g intravenous loading dose followed by a maintenance infusion of 1 g/hour in many obstetric units. As discussed earlier, this dose was subsequently found to produce levels below 4.8 mg/dL in the majority of women treated (Sibai et al, 1981). Despite recognition of these insufficient levels and an increased in the maintenance dose of magnesium sulphate therapy from 1 to 2 g/hour, the incidence of eclampsia has not changed over the past 30 years (Sibai et al, 1981). This raises the questions: Does magnesium sulphate therapy prevent progression to eclampsia? or Is there a subset of preeclamptic women who are destined to develop eclampsia despite prophylactic therapy? Ideally, clinical or laboratory markers could be perfected to identify impending eclampsia in women with severe preeclampsia. Roberts (1995) suggested that the ideal management of women with preeclampsia would be selective seizure prophylaxis for those women deemed to be at greatest

risk of seizures. Does the efficacy of magnesium sulphate for seizure prophylaxis or therapy vary according to the degree of cerebral vasoconstriction in these women? Are there subgroups of women with preeclampsia who will benefit from cerebral vasodilatation while for other women such therapy would be detrimental? Future studies should evaluate this disease progression and assess specific risk factors or markers that would mandate or contraindicate magnesium sulphate seizure prophylaxis.

Current evidence adds conflicting data about the mode or site of action of magnesium sulphate. Sibai et al (1984) performed electroencephalograms on 36 eclamptic and 14 preeclamptic magnesium treated women. Twenty seven of the eclamptic women and seven of the preeclamptic women had abnormal electroencephalograms despite therapeutic magnesium levels (4.5–11 mg/dL). Two women with eclampsia had clinical seizure activity during their postpartum electroencephalograms despite magnesium levels of 9.6 and 11 mg/dL. It was concluded that if magnesium suppresses seizure activity, the mechanism is distinct from modification of the electroencephalogram, refuting a direct action of magnesium sulphate on eclamptic seizures.

Adverse Effects and Safety

The use of magnesium sulphate is associated with a high rate of minor side effects, such as feeling warm, flushed, nausea or vomiting, muscle weakness, dizziness, and irritation at the site of injections. The reported rates of these effects in randomized trials ranged from 15% to 67% (Magpie Trial, 2002; Belfort et al, 2003; Witlin et al, 1997). These side effects were the most common reason for the woman's request to stop treatment early in the Magpie Trial. In addition, the use of magnesium sulphate is associated with major side effects such as respiratory depression and postpartum haemorrhage (2.4% vs 1.0%, P= 0.03) (Belfort et al, 2003).

Life-threatening magnesium toxicity is extremely rare with correct dosing and proper monitoring of the patient during magnesium sulphate therapy. Nevertheless, maternal deaths from magnesium overdose have been reported from the US (Pritchard et al, 1984) and from South Africa (Richards et al, 1985). In addition, magnesium toxicity from overdose nearly led to maternal deaths in 2 other reports (Sibai et al, 1981).

CHAPTER 3: OBJECTIVES, RESEARCH QUESTIONS, HYPOTHESIS, AND OPERATIONAL DEFINITIONS

3.1 General Objective

To evaluate the safety and effectiveness of using clinical parameters to signal cessation of postpartum magnesium sulphate (MgSO4) in patients with severe preeclampsia.

3.2 Specific objectives

3.2.1 To compare the outcomes of MgSO4 therapy as a postpartum seizures prophylaxis for conventional 24 hours and early cessation based on clinical parameters.

3.2.2 To determine the optimal duration of MgSO4 therapy in patient with severe preeclampsia.

3.3 Research Questions

Is there any difference in the outcome among postnatal mothers who received MgSO4 for 24 hours and early cessation of MgSO4 based on clinical parameters?

3.4 Research Hypothesis

There is no difference between using MgSO4 postpartum for 24 hours or early cessation based on clinical parameters.

3.5 Operational definitions

3.5.1 Hypertension

Hypertension in Pregnancy is defined as a systolic blood pressure (BP) of 140mm Hg and/or a diastolic BP of 90 mmHg. An increase of 15 mmHg and 30 mmHg of diastolic and systolic BP levels above baseline BP respectively are no longer recognized as hypertension if absolute values are below 140/90 mmHg. Nevertheless, this warrants close observation, especially if proteinuria and hyperuricaemia are also present. Korotkoff V should now be used as the cut-off point for diastolic BP, and Korotkoff IV utilized only when Korotkoff V is absent.

3.5.2 Proteinuria

Significant proteinuria in pregnancy is defined as 300 mg protein in a 24 hour urine sample, or a spot urine protein-creatinine ratio 30 mg/mmol. If the dipstick is the only test available, 1+ (30 mg/dl) are often, but not always, associated with 300 mg/day proteinuria. Significant proteinuria reflects advanced disease, associated with poorer prognosis.

3.5.3 Classification

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) (Brown et al, 2001).

a). Preeclampsia/eclampsia: clinically diagnosed in the presence of de novo hypertension after gestational week 20, and one or more of the following:

i. Significant proteinuria.
ii. Renal insufficiency: serum creatinine 90 ìmol/l or oliguria.
iii. Liver disease: raised transaminases and/or severe right upper quadrant or epigastric pain.
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.

This is followed by normalisation of the BP by three months postpartum. Oedema is no longer part of the definition of preeclampsia. Either excessive weight gain or failure to gain weight in pregnancy may herald the onset of preeclampsia.

b). Gestational hypertension: hypertension alone, detected for the first time after 20 weeks pregnancy. The definition is changed to "transient" when pressure normalizes postpartum.

c). Chronic hypertension: hypertension diagnosed prior to gestational week 20; or presence of hypertension preconception, or *de novo hypertension in late gestation that fails to resolve* postpartum.

d). Preeclampsia superimposed on chronic hypertension:
This can be diagnosed by the appearance of any of the following in a woman with chronic hypertension:

i) *De novo proteinuria after gestational week 20*
ii) A sudden increase in the severity of hypertension
iii) Appearance of features of preeclampsia-eclampsia, and
iv) A sudden increase in proteinuria in women who have preexisting proteinuria early in gestation

(**Reference** *: Clinical Practice Guidelines, MOH :Management of Hypertension 3rd Edition,February 2008) .*

CHAPTER FOUR: METHODOLOGY

4.1 Study design, Setting and Duration.

This study was a randomized controlled trial study with single blinded trial. It was a study to compare the safety and effectiveness of giving postpartum MgSO4 for 24 hours and early cessation based on clinical parameters among postnatal mothers who received MgSO4 before delivery in HRPZ11 and HUSM. Patients' recruitment began from December 2009 until September 2010.

4.2 Reference population

All postnatal mothers who received IV MgSO4 before delivery at Labour Room HRPZII and Labour Room HUSM.

4.3 Source population / Sampling frame

All postnatal mothers who received IV MgSO4 before delivery at Labour Room HRPZII and Labour Room HUSM from December 2009 until September 2010.

4.4 Inclusion criteria

All patients with severe preeclampsia
BP = 160/110 and
Proteinuria = 2+ and/ or
Symptomatic (frontal headache, visual disturbance, epigastric pain, nausea, vomiting)
All severe preeclampsia superimposed on chronic hypertension

4.5 Exclusion criteria

Mild Preeclampsia
Eclampsia
Underlying seizure disorder

4.6 Sampling method

Block Randomization was used to determine treatment group allocation.104 individuals randomized into two treatment groups of A and B, in blocks of 4. Block of 4 would give 6 combinations of AABB, ABAB, BBAA, BABA, ABBA, and BAAB. Every combination will be assigned a number of 1, 2, 3, 4, 5 and 6 respectively. A series of random number will be generated using table of random number (**Appendix A**). 26 appropriate consecutive numbers will be used to assign to list of 104 participants (i.e. 26 numbers x 4 blocks).

After completing randomization method as described above, a list of 104 participants will be generated with assigned randomized treatment group (**Appendix B**). This list would determine which treatment group every participant will be allocated to. Every participant recruited will be placed in consecutive manner one after the other until 102 participants were finally recruited. The total number of the participants recruited in this study was 102.

STUDY PROTOCOL

Figure 2 Flow chart of the study.

4.7 Sample size calculation

Objective 1:

To compare the outcomes of giving MgSO4 as a postpartum seizures prophylaxis for conventional 24 hours and to stop MgSO4 based on

clinical parameters

Comparing two proportion (Using PS software, Dupont + Plummer version 3.0.2)

We are planning a study of independent cases and controls with 1 control per case. Prior data indicate that the failure rate among controls is 0.02 **(Ascarelli et al, 1998).**

If the true failure rate for experimental subjects is 0.2, we will need to study 46 **experimental** subjects and 46 **control** subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8.

The Type I error probability associated with this test of this null hypothesis is 0.05.

I will choose sample size as 92 in view of limitation with time and power.

With the anticipation of non-response, I will take additional 10%, so that the total sample will be 102

Objective 2:

To determine the optimal duration of MgSO4 therapy in pregnant women with hypertensive disorders

Use PS software (Dupont & Plummer version 3.0.2) to calculate sample size based on comparing 2 means

With 80% power and alpha 0.05

SD = 8.5 hours **(Fontenot et al, 2005)**

To detect the difference of 4 hours

Therefore, need 79 participants in each study group (with 10% non-response)

4.8 Participants' recruitment

This randomized controlled trial study was conducted at the labour room HRPZII and HUSM between December 2009 and September 2010 (10 months). The protocol was approved by Ethic Committee Ministry of Health and HUSM. All patients with the diagnosis of severe preeclampsia at the time of delivery were invited to participate. Patients were classified according to the Ministry of Health Hypertension Guideline. Patients with mild preeclampsia, eclampsia and a history of seizure disorder were excluded from this investigation.

All patients received intravenous magnesium sulphate as a seizure prophylaxis before delivery period consisting of a 4-g loading dose and a 1-g per hour maintenance dose. After delivery, they were randomized into two groups, intervention and control group. The control group received a 1-g per hour maintenance dose for 24 hours postpartum. The intervention group received a 1-g per hour maintenance dose for 12 hours postpartum. Once minimum therapy had been delivered, 4 clinical parameters were used to determine whether intravenous magnesium sulphate could be discontinued.

These criteria included; absence of persistent headache, visual changes, and epigastric pain; greater than 50% of the hourly postpartum blood pressures less than 150mmHg systolic and less than 100mmHg diastolic (including the hour immediately before medication discontinuation); no indication for acute antihypertensive therapy within the preceding 2 hours (systolic blood pressure greater than or equal to 160 mm Hg or diastolic blood pressure greater than or equal to 110 mm Hg); and spontaneous diuresis of more than 25 mL per hour for 2