ATENCION PRENATAL DURANTE EL EMBARAZO Y SU EFECTO SOBRE RESULTADOS MATERNA Y FETAL

ANTENATAL CARE BOOKING DURING PREGNANCY AND ITS EFFECT ON MATERNAL AND FETAL OUTCOMES

Thesis Submitted for partial fulfillment of the requirements of doctoral thesis in Obstetrics and Gynecology

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INTRODUCTION AND RATIONALE

Hypertension is a frequently encountered complication of pregnancy and has a number of possible etiologies. Its onset may predate a pregnancy or develop during the antenatal, intrapartum or post-partum course. In a minority of cases it is associated with proteinuria, and this usually indicates a multi-system disease, also known as pre-eclampsia. This condition remains a leading cause of maternal and perinatal mortality, and is responsible worldwide for over 200,000 maternal deaths each year. However, hypertension alone may be the first signs of pre-eclampsia and therefore cannot be presumed innocent. In addition it is increasingly recognized that chronic hypertension has associated perinatal problems **(Shennan, 2007).**

Pre-eclampsia is a major cause of maternal and fetal mortality and morbidity. The incidence of pre-eclampsia is 2-10%, depending on the population studied and definitions of pre-eclampsia **(Confidential Enquiries into Maternal Deaths, 2001; Confidential Enquiry into Stillbirths and Deaths in Infancy, 2001; American College of Obstetricians and Gynecologists [ACOG], 2002).**

Pre-eclampsia is classically defined as hypertension of at least 140/90 mmHg measured on 2 separate occasions at least 4 h apart and arising de novo in previously normotensive women after the twentieth week of gestation, accompanied by significant proteinuria, all of which are resolved by 6 weeks post-partum. Such a definition, whilst appropriate in the research setting, excludes the presence of symptoms, therefore many clinicians employ a diagnosis that relies upon 2 or more, of the following symptoms being present; hypertension of at least 140/90 mmHg on 2 separate occasions at least 4 h apart, significant proteinuria 0.3 g/l of protein per 24 h [0.5 g/24 h], and symptoms including headache, photophobia, visual disturbance, epigastric pain, alteration in the conscious state **(Magee et al., 2008).**

Also, many clinicians consider that rises in the diastolic blood pressure of 15 mmHg and the systolic blood pressure of greater than 30 mmHg above booking values should be regarded as significant if other features of pre-eclampsia syndrome are present

(Hayman, 2004). The National Institute for Clinical Excellence (NICE) guidelines on antenatal care have reduced the number of antenatal visits recommended for healthy woman at low risk **(NICE, 2003).** As the randomized controlled trials on which this recommendation was based were never powered to identify important outcomes such as mortality, and as the failure to identify and act on known risk factors at booking contributes to deaths from pre-eclampsia, it is important to define risk at the beginning of pregnancy **(Confidential Enquiries into Maternal Deaths, 2001).**

We may therefore have underestimated the importance of antenatal care booking of risk factors for early onset pre-eclampsia, a type with considerable maternal and perinatal morbidity and mortality. Many risk factors that can be assessed at antenatal care booking including history (age, parity, previous pre-eclampsia, family history of pre-eclampsia, multiple pregnancy, time between pregnancies, and pre-existing medical conditions as; insulin dependent diabetes (IDDM), chronic hypertension, renal disease, autoimmune disease and antiphospholipid syndrome) and physical examination (body mass index (BMI), blood pressure, and proteinuria) **(Mattar and Sibai, 2000; Roberts and Catov, 2008).**

In one systematic review of controlled studies, it was found that antiphospholipid antibodies, a history of pre-eclampsia, pre-existing diabetes, multiple pregnancy, family history, nulliparity, a raised BMI before pregnancy or at booking, maternal age > 40, renal disease, hypertension, ≥ 10 years since the last pregnancy, and raised blood pressure at antenatal care booking all increased the risk of a woman developing pre-eclampsia **(Duckitt and Harrington, 2005).**

This prospective study was carried out to reach an overall estimate for the importance of antenatal care booking of the risk of pre-eclampsia. This provides an evidence base from which healthcare professionals can assess each pregnant woman's risk of pre-eclampsia at her booking visit and tailor her antenatal care according to need.

AIM OF THE WORK

The aim of this work is to evaluate the antenatal care booking during pregnancy and its effects on maternal and fetal outcomes.

STUDY OBJECTIVES

- To evaluate the adequacy of antenatal care booking visits during pregnancy.
- To evaluate the effects of antenatal care booking on maternal and fetal outcomes.

STUDY QUESTIONS

- Are the antenatal care booking visits during pregnancy of the studied patients adequate or not?
- What are the effects of antenatal care booking on maternal and fetal outcomes?

STUDY HYPOTHESES

- The antenatal care booking visits during pregnancy of the studied patients are inadequate.
- Antenatal care booking had significant effects of on maternal and fetal outcomes.

HYPERTENSIVE DISORDERS DURING PREGNANCY

How pregnancy incites or aggravates hypertension remains unsolved despite decades of intensive research. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. Hypertensive disorders complicate 5 to 10 percent of all pregnancies, and together they are one member of the deadly triad—along with hemorrhage and infection—that contributes greatly to maternal morbidity and mortality. Of these disorders, the preeclampsia syndrome, either alone or superimposed on chronic hypertension, is the most dangerous. New-onset hypertension during pregnancy—termed gestational hypertension—is followed by signs and symptoms of preeclampsia almost half the time, and preeclampsia is identified in 3.9 percent of all pregnancies **(Martin et al., 2012).**

The World Health Organization (WHO) systematically reviews maternal mortality worldwide, and in developed countries, 16 percent of maternal deaths were reported to be due to hypertensive disorders **(Khan et al., 2006).** This proportion is greater than three other leading causes that include hemorrhage—13 percent, abortion—8 percent, and sepsis—2 percent. In the United States from 1998 to 2005, **Berg and colleagues (2010**) reported that 12.3 percent of 4693 pregnancy-related maternal deaths were caused by preeclampsia or eclampsia. The rate was similar to that of 10 percent for maternal deaths in France from 2003 through 2007 **(Saucedo et al., 2013).** Importantly, more than half of these hypertension-related deaths were preventable **(Berg et al., 2005).**

TERMINOLOGY AND DIAGNOSIS

In this country for the past two decades, pregnancy hypertension was considered using the terminology and classification promulgated by the Working Group of the **National High Blood Pressure Education Program—NHBPEP (2000).**

To update these, a Task Force was appointed by President James Martin for the **American College of Obstetricians and Gynecologists (2013b)** to provide evidence-based recommendations for clinical practice.

The basic classification was retained, as it describes four types of hypertensive disease:

1. Gestational hypertension—evidence for the preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum
2. Preeclampsia and eclampsia syndrome
3. Chronic hypertension of any etiology
4. Preeclampsia superimposed on chronic hypertension.

Importantly, this classification differentiates the preeclampsia syndrome from other hypertensive disorders because it is potentially more ominous. This concept aids interpretation of studies that address the etiology, pathogenesis, and clinical management of pregnancy-related hypertensive disorders.

Diagnosis of Hypertensive Disorders

Hypertension is diagnosed empirically when appropriately taken blood pressure exceeds 140 mm Hg systolic or 90 mm Hg diastolic. Korotkoff phase V is used to define diastolic pressure. Previously, incremental increases of 30 mm Hg systolic or 15 mm Hg diastolic from mid-pregnancy blood pressure values had also been used as diagnostic criteria, even when absolute values were < 140/90 mm Hg. These incremental changes are no longer recommended criteria because evidence shows that such women are not likely to experience increased adverse pregnancy outcomes **(Levine et al., 2000; North et al., 1999).** That said, women who have a rise in pressure of 30 mm Hg systolic or 15 mm Hg diastolic should be observed more closely because eclamptic seizures develop in some of these women whose blood pressures have stayed < 140/90 mm Hg **(Alexander et al., 2006).**

A sudden rise in mean arterial pressure later in pregnancy—also known as "delta hypertension"—may also signify preeclampsia even if blood pressure is < 140/90 mm Hg **(Macdonald-Wallis et al., 2012; Vollaard et al., 2007).**

Concept of "Delta Hypertension"

The systolic and diastolic blood pressure levels of 140/90 mm Hg have been arbitrarily used since the 1950s to define “hypertension” in non-pregnant individuals. These levels were selected by insurance companies for a group of middle-aged men. It seems more realistic to define normal-range blood pressures that fall between an upper and lower limit for blood pressure measurements for a particular population—such as young, healthy, pregnant women. A schematic example is shown in **Figure 1** using arbitrary blood pressure readings. Data curves for both women show blood pressure measurements near the 25th percentile until 32 weeks. These begin to rise in patient B, who by term has substantively increased blood pressures. However, her pressures are still < 140/90 mm Hg, and thus she is considered to be “normotensive.” This rather acute increase in blood pressure is termed as “delta hypertension.” Some of these women will develop eclamptic seizures or HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome while still normotensive.

GESTATIONAL HYPERTENSION

This diagnosis is made in women whose blood pressures reach 140/90 mm Hg or greater for the first time after midpregnancy, but in whom proteinuria is not identified **(Table I).** Almost half of these women subsequently develop preeclampsia syndrome, which includes findings such as headaches or epigastric pain, proteinuria, and thrombocytopenia. Even so, when blood pressure increases appreciably, it is dangerous to both mother and fetus to ignore this rise only because proteinuria has not yet developed.

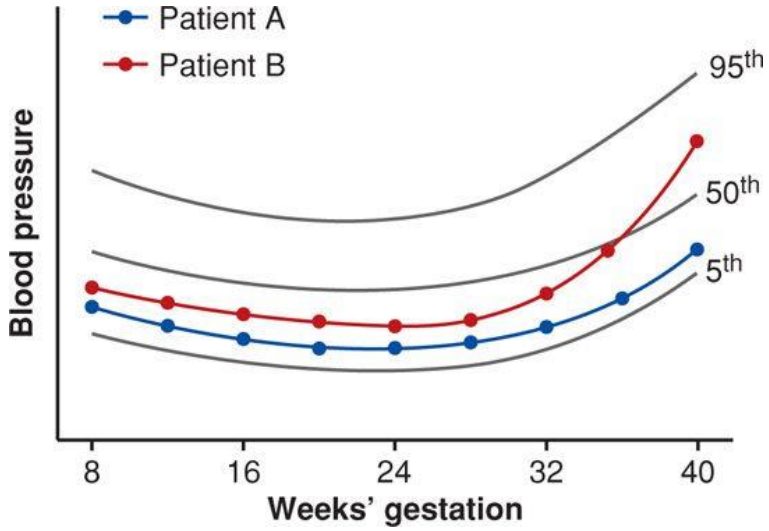

FIGURE 1. Schematic shows normal reference ranges for blood pressure changes across pregnancy. Patient A (blue) has blood pressures near the 20th percentile throughout pregnancy. Patient B (red) has a similar pattern with pressures at about the 25th percentile until about 36 weeks when blood pressure begins to increase. By term, it is substantively higher and in the 75th percentile, but she is still considered "normotensive."

TABLE I. Diagnostic Criteria for Pregnancy-Associated Hypertension:

Condition	Criteria Required
Gestational hypertension	BP > 140/90 mmHg after 20 weeks in previously normotensive women
Preeclampsia—Hypertension and:	
Proteinuria	• ≥ 300 mg/24h, or • Protein: creatinine ratio ≥ 0.3 or • Dipstick 1+ persistent[a] ***or***
Thrombocytopenia	• Platelets < 100,000/μL
Renal insufficiency	• Creatinine > 1.1 mg/dL or doubling of baseline[b]
Liver involvement	• Serum transaminase levels[c] twice normal
Cerebral symptoms	• Headache, visual disturbances, convulsions
Pulmonary edema	—

[a]Recommended only if sole available test.
[b]No prior renal disease.
[c]AST (aspartate aminotransferase) or ALT (alanine aminotransferase).
Modified from the American College of Obstetricians and Gynecologists, 2013b.

as transient hypertension if evidence for preeclampsia does not develop and the blood pressure returns to normal by 12 weeks postpartum.

PREECLAMPSIA SYNDROME

Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually every organ system. And, although preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important diagnostic criterion. Thus, proteinuria is an objective marker and reflects the system-wide endothelial leak, which characterizes the preeclampsia syndrome **(Lindheimer et al., 2008a).**

Abnormal protein excretion is arbitrarily defined by 24-hour urinary excretion exceeding 300 mg; a urine protein: creatinine ratio ≥ 0.3; or persistent 30 mg/dL (1+ dipstick) protein in random urine samples **(Lindheimer et al., 2008a).** None of these values is sacrosanct, and urine concentrations vary widely during the day, as do dipstick readings. Thus, assessment may show a dipstick value of 1+ to 2+ from concentrated urine specimens from women who excrete < 300 mg/day. It is likely that determination of spot urine: creatinine ratio is a suitable replacement for a 24-hour urine measurement. It is now appreciated that overt proteinuria may not be a feature in some women with the preeclampsia syndrome **(Sibai et al., 2009).**

Because of this, the **Task Force (2013)** suggested other diagnostic criteria, which are shown in **Table I.** Evidence of multiorgan involvement may include thrombocytopenia, renal dysfunction, hepatocellular necrosis ("liver dysfunction"), central nervous system perturbations, or pulmonary edema.

Indicators of Preeclampsia Severity

The markers listed in **Table I** are also used to classify preeclampsia syndrome severity. Although many use a dichotomous "mild" and "severe" classification, the **Task Force (2013)** discourages the use of "mild preeclampsia." It is problematic that there are criteria for the diagnosis of "severe" preeclampsia, but the default classification is either implied or specifically termed as "mild," "less severe," or "non-severe". There are no

generally agreed-on criteria for “moderate” preeclampsia—an elusive third category. The criteria listed in **Table II,** which are categorized as “severe” versus “non-severe.” Importantly, while it is pragmatic that non-severe classifications include “moderate” and “mild,” these have not been specifically defined **(Alexander et al., 2003; Lindheimer et al., 2008b).**

Some symptoms are considered to be ominous. Headaches or visual disturbances such as scotomata can be premonitory symptoms of eclampsia. Epigastric or right upper quadrant pain frequently accompanies hepatocellular necrosis, ischemia, and edema that ostensibly stretches Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels. Finally, thrombocytopenia is also characteristic of worsening preeclampsia as it signifies platelet activation and aggregation as well as microangiopathic hemolysis. Other factors indicative of severe preeclampsia include renal or cardiac involvement and obvious fetal-growth restriction, which also attests to its duration. The more profound these signs and symptoms, the less likely they can be temporized, and the more likely delivery will be required. A caveat is that differentiation between non-severe and severe gestational hypertension or preeclampsia can be misleading because what might be apparently mild disease may progress rapidly to severe disease **(Lindheimer et al., 2008a).**

TABLE II. Indicators of Severity of Gestational Hypertensive Disorders: [a]

Abnormality	Nonsevere[b]	Severe
Diastolic BP	< 110 mm Hg	≥ 110 mm Hg
Systolic BP	< 160 mm Hg	≥ 160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (< 100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

[a]Compare with criteria in Table 1.
[b]Includes "mild" and "moderate" hypertension not specifically defined.
[c]Most disregard degrees of proteinuria as being nonsevere or severe.
BP = blood pressure.

ECLAMPSIA

In a woman with preeclampsia, a convulsion that cannot be attributed to another cause is termed eclampsia. The seizures are generalized and may appear before, during, or after labor. The proportion who do not develop seizures until after 48 hours postpartum

approximates 10 percent **(Sibai et al., 2005).** In some reports, up to a fourth of eclamptic seizures develop beyond 48 hours postpartum **(Chames et al., 2002).** Experiences from Parkland Hospital, however, are that delayed postpartum eclampsia continues to occur in about 10 percent of cases **(Alexander et al., 2006).** This lower percentage was also found in 222 women with eclampsia from The Netherlands **(Zwart et al., 2008).**

PREECLAMPSIA SUPERIMPOSED ON CHRONIC HYPERTENSION

Regardless of its cause, any chronic hypertensive disorder predisposes a woman to develop superimposed preeclampsia syndrome. Chronic underlying hypertension is diagnosed in women with documented blood pressures ≥ 140/90 mm Hg before pregnancy or before 20 weeks' gestation, or both. Hypertensive disorders can create difficult problems with diagnosis and management in women who are not first seen until after mid-pregnancy. This is because blood pressure normally decreases during the second and early third trimesters in both normotensive and chronically hypertensive women. Thus, a woman with previously undiagnosed chronic vascular disease who is seen before 20 weeks frequently has blood pressures within the normal range. During the third trimester, however, as blood pressures return to their originally hypertensive levels, it may be difficult to determine whether hypertension is chronic or induced by pregnancy. Even a careful search for evidence of preexisting end-organ damage may be futile, as many of these women have mild disease and no evidence of ventricular hypertrophy, retinal vascular changes, or renal dysfunction (**Lawlor et al., 2005).**

In some women with chronic hypertension, their blood pressure increases to obviously abnormal levels, and this is typically after 24 weeks. If new-onset or worsening baseline hypertension is accompanied by new-onset proteinuria or other findings listed in **Table I,** then superimposed preeclampsia is diagnosed. Compared with "pure" preeclampsia, superimposed preeclampsia commonly develops earlier in pregnancy. It also tends to be more severe and often is accompanied by fetal-growth restriction. The same criteria shown in **Table II** are also used to further characterize severity of superimposed preeclampsia.

INCIDENCE AND RISK FACTORS

Preeclampsia Syndrome

Young and nulliparous women are particularly vulnerable to developing preeclampsia, whereas older women are at greater risk for chronic hypertension with superimposed preeclampsia. The incidence is markedly influenced by race and ethnicity—and thus by genetic predisposition. By way of example, in nearly 2400 nulliparas enrolled in a Maternal-Fetal Medicine Units (MFMU) Network study, the incidence of preeclampsia was 5 percent in white, 9 percent in Hispanic, and 11 percent in African-American women **(Myatt et al., 2012a; 2012b).**

Other factors include environmental, socioeconomic, and even seasonal influences **(Spencer et al., 2009).** With consideration for these vicissitudes, in several worldwide studies reviewed by **Staff and coworkers (2014),** the incidence of preeclampsia in nulliparous populations ranged from 3 to 10 percent. The incidence of preeclampsia in multiparas is also variable but is less than that for nulliparas. Specifically, population studies from Australia, Canada, Denmark, Norway, Scotland, Sweden, and Massachusetts indicate an incidence of 1.4 to 4 percent **(Roberts et al., 2011).**

There are several other risk factors associated with preeclampsia. These include obesity, multifetal gestation, maternal age, hyperhomocysteinemia, and metabolic syndrome **(Conde-Agudelo et al., 2000; Walker et al., 2000; Scholten et al., 2013).** The relationship between maternal weight and the risk of preeclampsia is progressive. It increases from 4.3 percent for women with a body mass index (BMI) < 20 kg/m2 to 13.3 percent in those with a BMI > 35 kg/m2 **(Table III and Figure 2).**

TABLE III. Adverse Pregnancy Effects in Overweight and Obese Women:

Complication	Prevalence (%) in Women with Normal BMI 20–24.9 n = 176,923	Increased Complications (Odds Ratio[a])	
		Overweight BMI 25–29.9 n = 79,014	Obese BMI > 30 n = 31,276
Gestational diabetes	0.8	1.7–3.5	3.0–3.6
Preeclampsia	0.7	1.5–1.9	2.1
Postterm pregnancy	0.13	1.2[b]	1.7
Emergency cesarean delivery	7.8	1.3–1.4	1.7–1.8
Elective cesarean delivery	4.0	1.2	1.3–1.4
Postpartum hemorrhage	10.4	1.04–1.2	1.0–1.4
Pelvic infection	0.7	1.2	1.3
Urinary tract infection	0.7	1.2	1.4
Wound infection	0.4	1.3	2.2
Fetal macrosomia	9.0	1.6	2.4
Stillbirth	0.4	1.4	1.4–1.6
Thrombosis	—	1.6	0.97[b]

[a]Odds ratios (99% CI) are significant except when denoted.
[b]Not significantly different.
BMI = body mass index.
Data from Ovesen, 2011; Sebire, 2001.

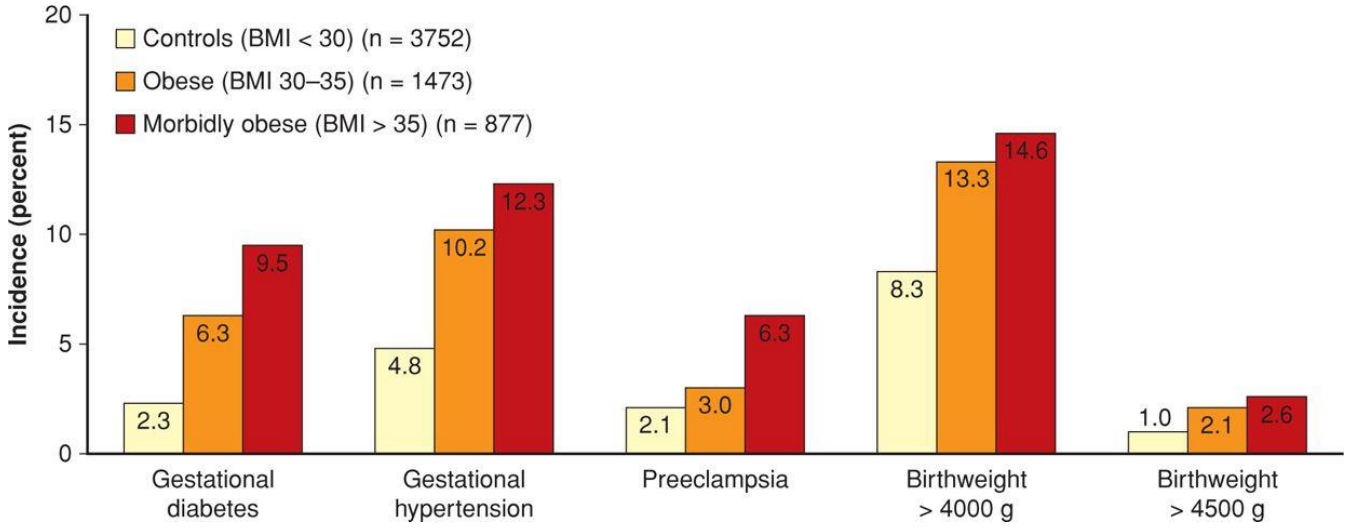

FIGURE 2. Incidence of selected pregnancy outcomes in 16,102 women enrolled in the FASTER (First- and Second-Trimester Evaluation of Risk) trial according to body mass index (BMI) status **(Adapted from Weiss et al., 2004).**

In women with a twin gestation compared with those with singletons, the incidence of gestational hypertension—13 versus 6 percent, and the incidence of preeclampsia—13 versus 5 percent, are both significantly increased **(Sibai et al., 2000).** It is interesting that this latter incidence is unrelated to zygosity **(Maxwell et al., 2001).**

Although smoking during pregnancy causes various adverse pregnancy outcomes, ironically, it has consistently been associated with a reduced risk for hypertension during pregnancy **(Bainbridge et al., 2005).**

Kraus and associates (2013) posit that this is because smoking upregulates placental adrenomedullin expression, which regulates volume homeostasis.Women with preeclampsia in the first pregnancy are at greater risk in a second pregnancy compared with women normotensive during their first pregnancy **(McDonald et al., 2009).**

And conversely, in the woman who was normotensive during her first pregnancy, the incidence of preeclampsia in a subsequent pregnancy is much lower than for a first pregnancy. In a population-based retrospective cohort analysis, **Getahun and colleagues (2007)** studied almost 137,000 second pregnancies in such women. The incidence for preeclampsia in secundigravida white women was 1.8 percent compared with 3 percent in African-American women.

Eclampsia

Presumably because it is somewhat preventable by adequate prenatal care, the incidence of eclampsia has decreased over the years in areas where health care is more readily available. In countries with adequate resources, its incidence averages 1 in 2000 deliveries. **Ventura and associates (2000)** estimated that the incidence in the United States in 1998 was 1 in 3250 births. According to the **Royal College of Obstetricians and Gynecologists (2006),** it approximates 1 in 2000 in the United Kingdom. Akkawi and coworkers (2009) reported it to be 1 in 2500 in Dublin, **Andersgaard and associates (2006)** as 1 per 2000 for Scandinavia, and **Zwart and colleagues (2008)** as 1 per 1600 for The Netherlands.

ETIOPATHOGENESIS

Any satisfactory theory concerning the etiology and pathogenesis of preeclampsia must account for the observation that gestational hypertensive disorders are more likely to develop in women with the following characteristics:

- Are exposed to chorionic villi for the first time or are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole
- Have preexisting conditions of endothelial cell activation or inflammation such as diabetes or renal or cardiovascular disease
- Are genetically predisposed to hypertension developing during pregnancy.

A fetus is not a requisite for preeclampsia to develop. And, although chorionic villi are essential, they need not be intrauterine. For example, **Worley and associates (2008)** reported a 30-percent incidence in women with an extrauterine pregnancy exceeding 18 weeks' gestation. Regardless of precipitating etiology, the cascade of events leading to the preeclampsia syndrome is characterized by abnormalities that result in vascular endothelial damage with resultant vasospasm, transudation of plasma, and ischemic and thrombotic sequelae.

Phenotypic Expression of Preeclampsia Syndrome

The preeclampsia syndrome is widely variable in its clinical phenotypic expression. There are at least two major subtypes differentiated by whether or not remodeling of uterine spiral arterioles by endovascular trophoblastic invasion is defective. This concept has given rise to the "two-stage disorder" theory of preeclampsia etiopathogenesis. The two-stage disorder includes "maternal and placental preeclampsia." According to **Redman and coworkers (2014),** stage 1 is caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome. Importantly, stage 2 is susceptible to modification by preexisting maternal conditions that are manifest by endothelial cell activation or inflammation. Such conditions include cardiovascular or renal disease, diabetes, obesity, immunological disorders, or hereditary influences. Such compartmentalization is artificial, and it seems logical to us that

preeclampsia syndrome presents clinically as a spectrum of worsening disease. Moreover, evidence is accruing that many "isoforms" exist. Examples include differences in maternal and fetal characteristics, placental findings, and hemodynamic findings **(Valensise et al., 2008; Phillips et al., 2010; van der Merwe et al., 2010).**

ETIOLOGY

Writings describing eclampsia have been traced as far back as 2200 BC **(Lindheimer et al., 2014).** And, an imposing number of mechanisms have been proposed to explain its cause. Those currently considered important include:

1. Placental implantation with abnormal trophoblastic invasion of uterine vessels
2. Immunological maladaptive tolerance between maternal, paternal (placental), and fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors including inherited predisposing genes and epigenetic influences.

Abnormal Trophoblastic Invasion

Normal implantation is characterized by extensive remodeling of the spiral arterioles within the decidua basalis as shown schematically in **Figure 3.** Endovascular trophoblasts replace the vascular endothelial and muscular linings to enlarge the vessel diameter. The veins are invaded only superficially. In some cases of preeclampsia, however, there may be incomplete trophoblastic invasion. With this, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The deeper myometrial arterioles do not lose their endothelial lining and musculoelastic tissue, and their mean external diameter is only half that of corresponding vessels in normal placentas **(Fisher et al., 2014).** In general, the magnitude of defective trophoblastic

invasion is thought to correlate with severity of the hypertensive disorder **(Madazli et al., 2000).**

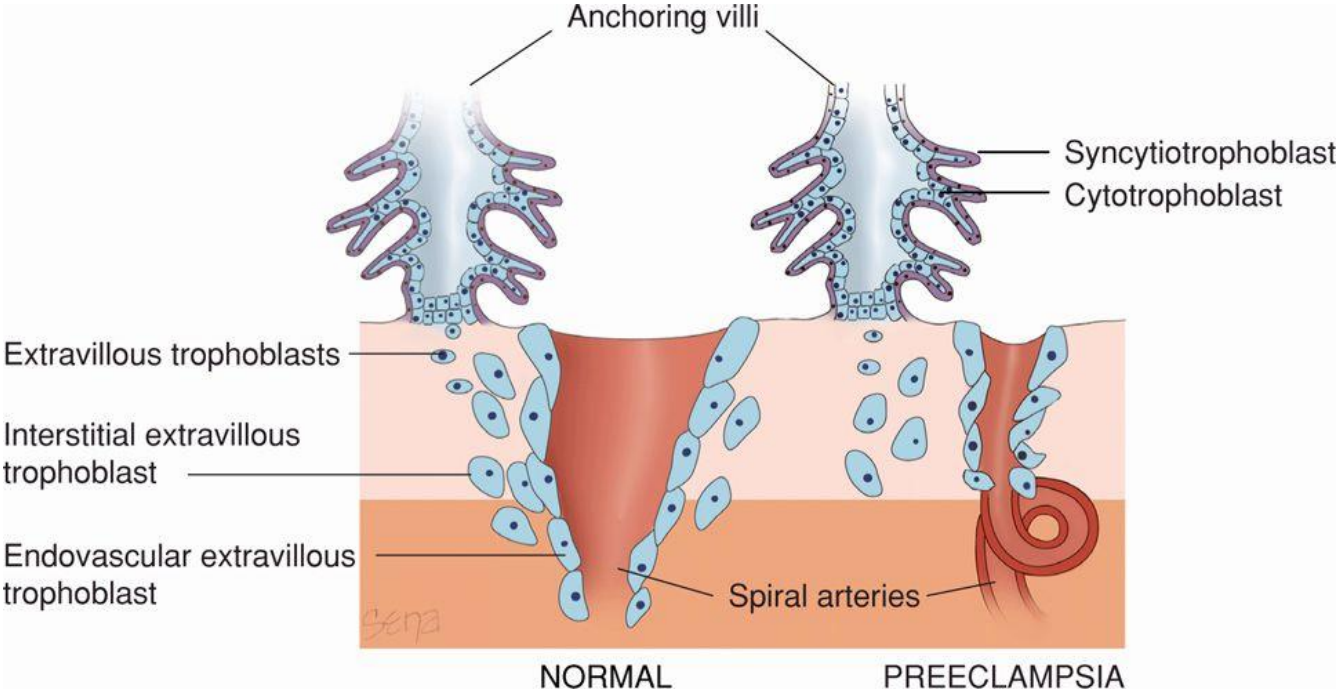

FIGURE 3. Schematic representation of normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, there is defective implantation characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small-caliber vessel with high resistance to flow.

Using electron microscopy, **De Wolf and coworkers (1980)** examined arteries taken from the implantation site. They reported that early preeclamptic changes included endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, and medial necrosis. Lipid accumulated first in myointimal cells and then within macrophages.

These lipid-laden cell changes, shown in **Figure 4,** were referred to as atherosis. **Nelson and colleagues (2014)** completed placental examination in more than 1200

women with preeclampsia. These investigators reported that vascular lesions including spiral arteriole narrowing, atherosis, and infarcts were more common in placentas from women diagnosed with preeclampsia before 34 weeks.

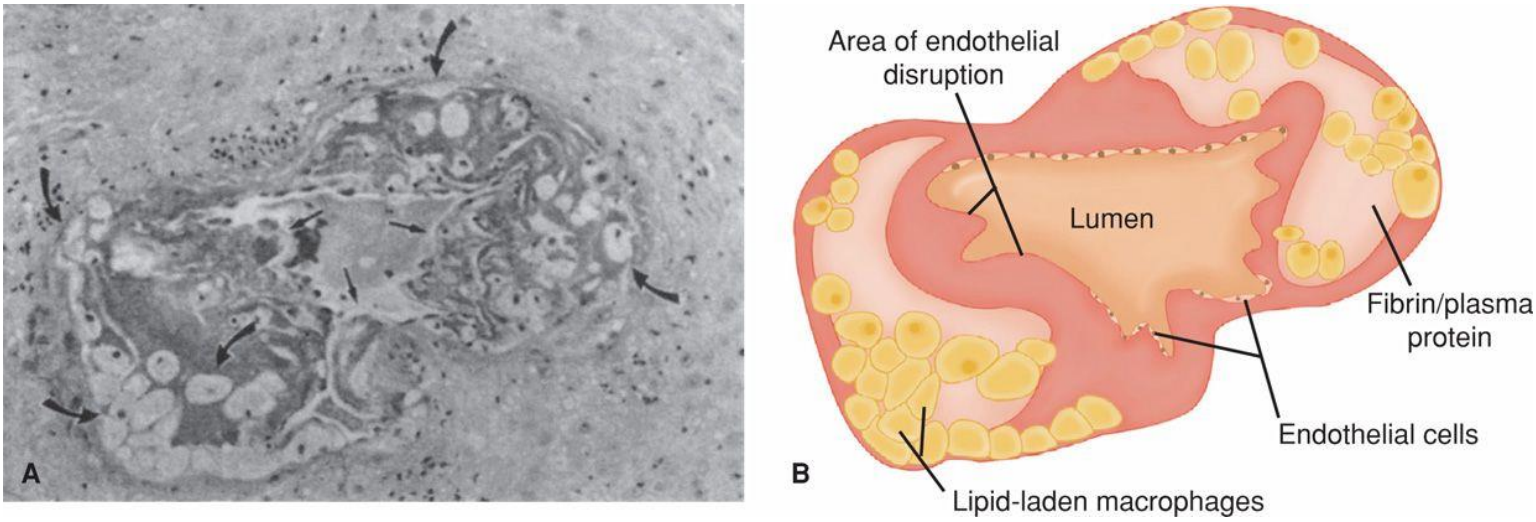

FIGURE 4. Atherosis in a blood vessel from a placental bed. A. Photomicrograph shows disruption of the endothelium that result in a narrowed lumen because of subendothelial accumulation of plasma proteins and foamy macrophages. Some of the foamy macrophages are shown by curved arrows and straight arrows highlight areas of endothelial disruption. **B.** Schematic diagram of the photomicrograph **(Adapted from Rogers et al., 1999).**

Thus, the abnormally narrow spiral arteriolar lumen likely impairs placental blood flow. **McMahon and colleagues (2014)** have provided evidence that decreased soluble antiangiogenic growth factors may be involved in faulty endovascular remodeling.

Diminished perfusion and a hypoxic environment eventually lead to release of placental debris or microparticles that incite a systemic inflammatory response **(Lee et al., 2012; Redman et al., 2012). Fisher and Roberts (2014)** have provided an elegant review of the molecular mechanisms involved in these interactions.

Defective placentation is posited to further cause the susceptible (pregnant) woman to develop gestational hypertension, the preeclampsia syndrome, preterm delivery, a growth-restricted fetus, and/or placental abruption **(McElrath et al., 2008; Kovo et al., 2010; Brosens et al., 2011; Nelson et al., 2014).** In addition, **Staff and coworkers (2013)** have hypothesized that acute atherosis identifies a group of women at increased risk for later atherosclerosis and cardiovascular disease.

Immunological Factors

Loss of maternal immune tolerance to paternally derived placental and fetal antigens, or perhaps its dysregulation, is another theory cited to account for preeclampsia syndrome **(Erlebacher et al., 2013).** Certainly, the histological changes at the maternal-placental interface are suggestive of acute graft rejection. Some of the factors possibly associated with dysregulation include "immunization" from a previous pregnancy, some inherited human leukocyte antigen (HLA) and natural killer (NK)-cell receptor haplotypes, and possibly shared susceptibility genes with diabetes and hypertension **(Fukui et al., 2012; Ward et al., 2014).**

Inferential data also suggest preeclampsia to be an immune-mediated disorder. For example, the risk of preeclampsia is appreciably enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites might be impaired. In this scenario, the first pregnancy would carry a higher risk. Tolerance dysregulation might also explain an increased risk when the paternal antigenic load is increased, that is, with two sets of paternal chromosomes—a "double dose" **(Bdolah et al., 2006).**

Namely, women with molar pregnancies have a high incidence of early-onset preeclampsia. Women with a trisomy 13 fetus also have a 30- to 40-percent incidence of preeclampsia. These women have elevated serum levels of antiangiogenic factors, and the gene for one of these factors, sFlt-1, is on chromosome 13 **(Bdolah et al., 2006).** Conversely, women previously exposed to paternal antigens, such as a prior pregnancy with the same partner, are "immunized" against preeclampsia. This phenomenon is not as apparent in women with a prior abortion.

Strickland and associates (1986) studied more than 29,000 pregnancies at Parkland Hospital. These investigators reported that hypertensive disorder rates were decreased in women who previously had miscarried compared with nulligravidas. However, the difference, although statistically significant, was not great—22 versus 25 percent. Other studies have shown that multiparas impregnated by a new consort have an increased risk of preeclampsia **(Mostello et al., 2002).**

Redman and colleagues (2014) reviewed the possible role of immune maladaptation in preeclampsia pathophysiology. In women destined to be preeclamptic, extravillous trophoblasts early in pregnancy express reduced amounts of immunosuppressive nonclassic HLA G. Black women more commonly have the 1597ΔC allele that further predisposes to preeclampsia **(Loisel et al., 2013).**

Zhou and coworkers (2012b) have shown this to be associated with high levels of placental oxidative products. These changes may contribute to defective placental vascularization in stage 1 of the preeclampsia syndrome. During normal pregnancy, T-helper (Th) lymphocytes are produced so that type 2 activity is increased in relation to type 1—termed type 2 bias **(Redman et al., 2012; 2014).**

Th2 cells promote humoral immunity, whereas Th1 cells stimulate inflammatory cytokine secretion. Beginning in the early second trimester in women who develop preeclampsia, Th1 action is increased and the Th1/Th2 ratio changes. Contributors to an enhanced immunologically mediated inflammatory reaction are stimulated by placental microparticles and by adipocytes **(Redman et al., 2012; 2014).**

Endothelial Cell Activation

In many ways, inflammatory changes are believed to be a continuation of the stage 1 changes caused by defective placentation. In response to placental factors released by ischemic changes or by any other inciting cause, a cascade of events begins **(Davidge et al., 2014).** Thus, antiangiogenic and metabolic factors and other

inflammatory mediators are thought to provoke endothelial cell injury **(Davidge et al., 2014).**

Endothelial cell dysfunction may result from an extreme activated state of leukocytes in the maternal circulation **(Faas et al., 2000; Gervasi et al., 2001).** Briefly, cytokines such as tumor necrosis factor-α (TNF-α) and the interleukins (IL) may contribute to the oxidative stress associated with preeclampsia. This 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. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in atherosis and shown in **Figure 4;** activation of microvascular coagulation manifest by thrombocytopenia; and increased capillary permeability manifest by edema and proteinuria **(Task Force, 2013).**

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. Unfortunately, dietary supplementation with vitamins E (α-tocopherol) and C (ascorbic acid) to prevent preeclampsia has thus far proven unsuccessful **(Task Force, 2013).**

Nutritional Factors

John and colleagues (2002) showed that in the general population, a diet high in fruits and vegetables with antioxidant activity is associated with decreased blood pressure. **Zhang and associates (2002)** reported that the incidence of preeclampsia was doubled in women whose daily intake of ascorbic acid was less than 85 mg. These studies were followed by randomized trials to study dietary supplementation.

Villar and coworkers (2006) showed that calcium supplementation in populations with a low dietary calcium intake had a small effect to lower perinatal mortality rates but no effect on preeclampsia incidence (p. 748). According to the 2013

Task Force, in several trials, supplementation with the antioxidant vitamins C or E showed no benefits.

Genetic Factors

From a hereditary viewpoint, preeclampsia is a multifactorial, polygenic disorder. In their comprehensive review, **Ward and Taylor (2014)** cite an incident risk for preeclampsia of 20 to 40 percent for daughters of preeclamptic mothers; 11 to 37 percent for sisters of preeclamptic women; and 22 to 47 percent for twins. In a study by **Nilsson and colleagues (2004)** that included almost 1.2 million Swedish births, there was a genetic component for gestational hypertension and for preeclampsia. They also reported 60-percent concordance in monozygotic female twin pairs.

The hereditary predisposition for preeclampsia likely is the result of interactions of literally hundreds of inherited genes—both maternal and paternal—that control myriad enzymatic and metabolic functions throughout every organ system. Plasma-derived factors may induce some of these genes in preeclampsia **(Mackenzie et al., 2012).**

Thus, the clinical manifestation in any given woman with the preeclampsia syndrome will occupy a spectrum. In this regard, phenotypic expression will differ among similar genotypes depending on interactions with environmental factors **(Yang et al., 2013).**

Candidate Genes

Hundreds of genes have been studied for their possible association with preeclampsia **(Buurma et al., 2013; Ward et al., 2014).** Several of those that may have positive significant association with preeclampsia are listed in **Table IV.** Polymorphisms of the genes for Fas receptor, hypoxia-inducible factor-1α protein (HIF-1α), IL-1β, lymphotoxin-α, transforming growth factor beta 3 (TGF-β3), apolipoprotein E (ApoE), and TNF-α have also been studied with varying results **(Hefler et al., 2001; Lachmeijer et al., 2001; Livingston et al., 2001; Borowski et al., 2009; Wilson et al., 2009; Jamalzei et al., 2013).**

Because of the heterogeneity of the preeclampsia syndrome and especially of the other genetic and environmental factors that interact with its complex phenotypic expression, it is doubtful that any one candidate gene will be found responsible. Indeed, **Majander and associates (2013)** have linked preeclampsia predisposition to fetal genes on chromosome 18.

TABLE IV. Genes with Possible Associations with Preeclampsia Syndrome:

Gene (Polymorphism)	Function Affected
MTHFR (C677T)	Methylene tetrahydrofolate reductase
F5 (Leiden)	Factor V_{Leiden}
AGT (M235T)	Angiotensinogen
HLA (Various)	Human leukocyte antigens
NOS3 (Glu 298 Asp)	Endothelial nitric oxide
F2 (G20210A)	Prothrombin (factor II)
ACE (I/D[at]Intron 16)	Angiotensin-converting enzyme
CTLA4	Cytotoxic T-lymphocyte-associated protein
LPL	Lipoprotein lipase
SERPINE1	Serine peptidase inhibitor

Data from Buurma, 2013; Staines-Urias, 2012; Ward, 2014.

Other Genetic Variables

An extensive list of other variables affect genotypic and phenotypic expression of the preeclampsia syndrome. Some include maternal and paternal genotypes, associated disorders, genomic ethnicity, gene-gene interactions, epigenetic phenomena, and gene-environmental interactions. Combinations of these are infinite. Ethnoracial factors are

important as discussed regarding the high incidence of preeclampsia in African-American women. It may be that Latina women have a lower prevalence because of interactions of American Indian and white race genes **(Shahabi et al., 2013).**

PATHOGENESIS

Vasospasm

The concept of vasospasm with preeclampsia was advanced by Volhard (1918) based on his 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. Endothelial activation causes vascular constriction with increased 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 and associates (2002)** have also demonstrated disruption of endothelial junctional proteins. **Suzuki and coworkers (2003)** described ultrastructural changes in the subendothelial region of resistance arteries in preeclamptic women. The much larger venous circuit is similarly involved, and with diminished blood flow because of maldistribution, ischemia of the surrounding tissues can lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. One important clinical correlate is the markedly attenuated blood volume seen in women with severe preeclampsia **(Zeeman et al., 2009).**

Endothelial Cell Injury

During the past two decades, endothelial cell injury has become the centerpiece in the contemporary understanding of preeclampsia pathogenesis. In this scheme, protein factor(s)—likely placental—are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. Many of the facets of the clinical

syndrome of preeclampsia are thought to result from these widespread endothelial cell changes **(Davidge et al., 2014).**

Grundmann and associates (2008) have reported that circulating endothelial cell—CEC—levels are elevated fourfold in the peripheral blood of preeclamptic women. Similarly, **Petrozella and colleagues (2012)** demonstrated increased levels of circulating endothelial microparticles—EMPs—in preeclamptic women.

Intact endothelium has anticoagulant properties, and endothelial cells blunt the response of vascular smooth muscle to agonists by releasing nitric oxide. Damaged or activated endothelial cells may produce less nitric oxide and secrete substances that promote coagulation and increase 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 endothelial activation. These latter substances are transferable, and serum from women with preeclampsia stimulates some of these substances in greater amounts. It seems likely that multiple factors in plasma of preeclamptic women combine to have these vasoactive effects **(Myers et al., 2007; Walsh et al., 2009).**

Prostaglandins/ Pressor Responses

Pregnant women normally develop refractoriness to infused vasopressors. Women with early preeclampsia, however, have increased vascular reactivity to infused norepinephrine and angiotensin II. Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension **(Abdul-Karim et al., 1961).** Several prostanoids are thought to be central to preeclampsia syndrome pathophysiology. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to decreased vascular responsiveness mediated by endothelial prostaglandin synthesis. For example, compared with normal pregnancy, endothelial prostacyclin

(PGI2) production is decreased in preeclampsia. This action appears to be mediated by phospholipase A2 **(Davidge et al., 2014).**

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. These changes are apparent as early as 22 weeks in women who later develop preeclampsia **(Chavarria et al., 2003).**

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. 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. It also is produced by fetal endothelium, and here it is increased in response to preeclampsia, diabetes, and sepsis **(Parra et al., 2001; von Mandach et al., 2003).**

The effects of nitric oxide production in preeclampsia are unclear **(Davidge et al., 2014).** It appears that the syndrome is associated with decreased endothelial nitric oxide synthase expression, thus increasing nitric oxide inactivation. These responses may be race related, with African-American women producing more nitric oxide **(Wallace et al., 2009).**

Endothelins

These 21-amino acid peptides are potent vasoconstrictors, and endothelin-1 (ET-1) is the primary isoform produced by human endothelium **(George et al., 2011).** Plasma ET-1 levels are increased in normotensive pregnant women, but women with preeclampsia have even higher levels **(Ajne et al., 2003).**

According to **Taylor and Roberts (1999),** the placenta is not the source of increased ET-1 concentrations, and they likely arise from systemic endothelial activation. Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations **(Sagsoz et al., 2003).**

Angiogenic and Antiangiogenic Proteins

Placental vasculogenesis is evident by 21 days after conception. There is an ever-expanding list of pro- and antiangiogenic substances involved in placental vascular development. The families of vascular endothelial growth factor (VEGF) and angiopoietin (Ang) are most extensively studied. Angiogenic imbalance is used to describe excessive amounts of antiangiogenic factors that are hypothesized to be stimulated by worsening hypoxia at the uteroplacental interface **(Karumanchi et al., 2014).**

Trophoblast of women destined to develop preeclampsia overproduces at least two antiangiogenic peptides that enter the maternal circulation **(Karumanchi et al., 2014):**

1. Soluble Fms-like tyrosine kinase 1 (sFlt-1) is a variant of the Flt-1 receptor for placental growth factor (PlGF) and for VEGF. Increased maternal sFlt-1 levels inactivate and decrease circulating free PlGF and VEGF concentrations, leading to endothelial dysfunction **(Maynard et al., 2003).** As shown in **Figure 5,** sFlt-1 levels begin to increase in maternal serum months before preeclampsia is evident. **Haggerty and colleagues (2012)** observed that these high levels in the second trimester were associated with a doubling of the risk for preeclampsia. This divergence from normal levels appears to occur even sooner with early-onset preeclampsia **(Vatten et al., 2012).**

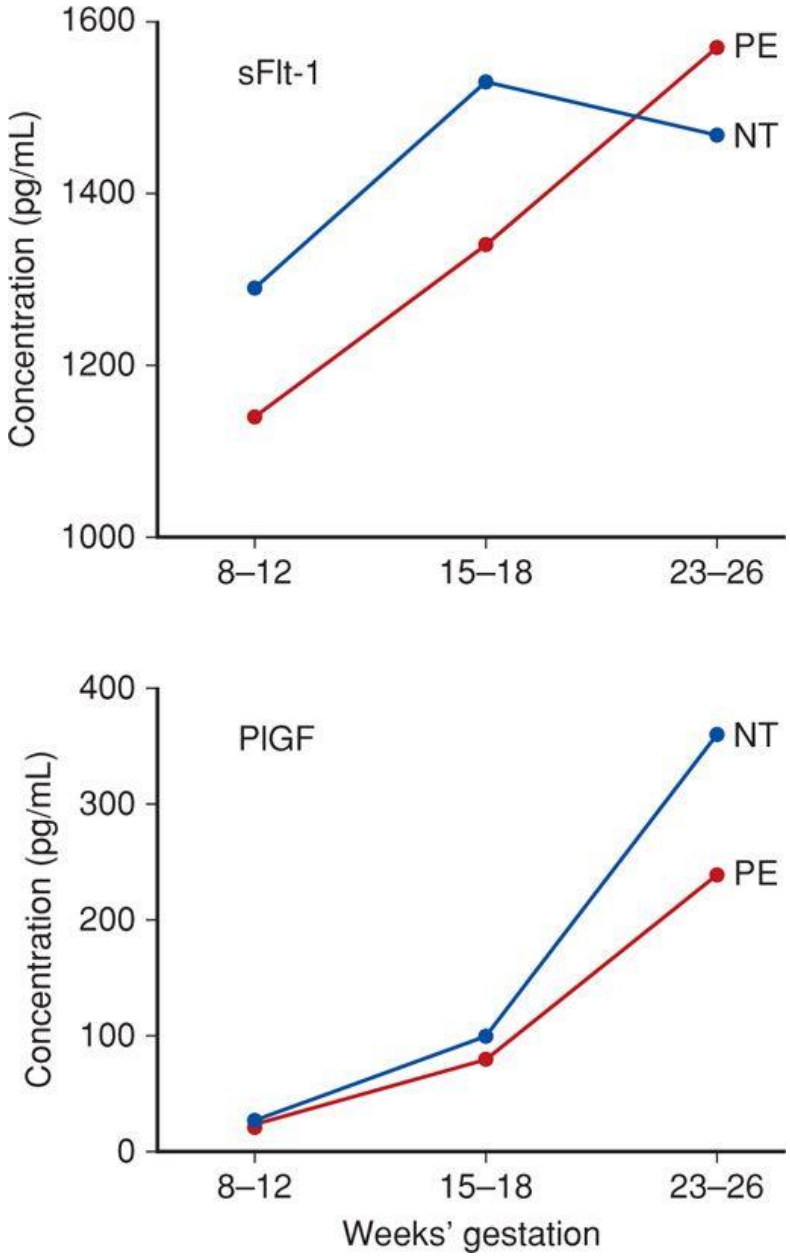

FIGURE 5. Angiogenic and antiangiogenic factors in normotensive (NT) and preeclamptic (PE) women across pregnancy. Both pairs of factors are significantly divergent by 23 to 26 weeks. sFlt = soluble Fms-like tyrosine kinase 1; PlGF = placental growth factor **(Adapted from Myatt, 2013).**

2. Soluble endoglin (sEng) is a placenta-derived 65-kDa molecule that blocks endoglin, which is a surface coreceptor for the TGFβ family. Also called CD105, this soluble form of endoglin inhibits various TGFβ isoforms from binding to endothelial receptors and

results in decreased endothelial nitric oxide-dependent vasodilatation **(Levine et al., 2006; Venkatesha et al., 2006).** Serum levels of sEng also begin to increase months before clinical preeclampsia develops **(Haggerty et al., 2012).**

The cause of placental overproduction of antiangiogenic proteins remains an enigma. Concentrations of the soluble forms are not increased in the fetal circulation or amnionic fluid, and their levels in maternal blood dissipate after delivery **(Staff et al., 2007).** Research currently is focused on immunological mechanisms, oxidative stress, mitochondrial pathology, and hypoxia genes **(Karumanchi et al., 2014).**

Clinical research is directed at use of antiangiogenic proteins in the prediction and diagnosis of preeclampsia. In a systematic review, **Widmer and associates (2007)** concluded that third-trimester elevation of sFlt-1 levels and decreased PlGF concentrations correlate with preeclampsia development after 25 weeks. These results require verification in prospective studies. Subsequently, **Haggerty and coworkers (2012)** reported that doubling of expressions of sFlt-1 and sEng increased the preeclampsia risk 39 and 74 percent, respectively.

PATHOPHYSIOLOGY

Although the cause of preeclampsia remains unknown, evidence for its manifestation begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately result in multiorgan involvement with a clinical spectrum ranging from an attenuated manifestation to one of cataclysmic deterioration that is life threatening for both mother and fetus. These are thought to be a consequence of endothelial dysfunction, vasospasm, and ischemia.

Although the many maternal consequences of the preeclampsia syndrome are usually described in terms of individual organ systems, they frequently are multiple, and they overlap clinically.

Cardiovascular System

Severe disturbances of normal cardiovascular function are common with preeclampsia syndrome. These are related to: (1) increased cardiac afterload caused by hypertension; (2) cardiac preload, which is affected negatively by pathologically diminished hypervolemia of pregnancy and is increased by intravenous crystalloid or oncotic solutions; and (3) endothelial activation with interendothelial extravasation of intravascular fluid into the extracellular space and importantly, into the lungs **(Melchiorre et al., 2013).**

Hemodynamic Changes and Cardiac Function

The cardiovascular aberrations of pregnancy-related hypertensive disorders vary depending on several modifiers. These factors include hypertension severity, underlying chronic disease, preeclampsia severity, and in which part of the clinical spectrum these are studied. In some women, these cardiovascular changes may precede hypertension onset **(De Paco et al., 2008; Khalil et al., 2012; Melchiorre et al., 2013).**

Nevertheless, with the clinical onset of preeclampsia, cardiac output declines, due at least in part to increased peripheral resistance. When assessing cardiac function in preeclampsia, consideration is given to echocardiographic measures of myocardial function and to clinically relevant ventricular function. Serial echocardiographic studies have documented in preeclampsia evidence for ventricular remodeling that is accompanied by diastolic dysfunction in 40 percent of women **(Melchiorre et al., 2012).** In some of these women, functional differences persisted up to 16 months after delivery **(Evans et al., 2011).**

Ventricular Function

Ventricular remodeling was judged to be an adaptive response to maintain normal contractility with the increased after-load of preeclampsia. In the otherwise healthy pregnant woman, these changes are usually clinically inconsequential. But when combined with underlying ventricular dysfunction—for example, concentric ventricular hypertrophy from chronic hypertension—further diastolic dysfunction may cause cardiogenic pulmonary edema. Despite the relatively high frequency of diastolic

dysfunction with preeclampsia, in most women clinical cardiac function is appropriate. This has been shown by several studies in which ventricular function was assessed using invasive hemodynamic methods **(Hibbard et al., 2014).**

Importantly, both normally pregnant women and those with preeclampsia syndrome can have normal or slightly hyperdynamic ventricular function **(Figure 6).** Thus, both have a cardiac output that is appropriate for left-sided filling pressures. Data from preeclamptic women obtained by invasive hemodynamic studies are confounded because of the heterogeneity of populations and interventions that also may significantly alter these measurements. Some of these are crystalloid infusions, antihypertensive agents, and magnesium sulfate. Ventricular function studies of preeclamptic women from several investigations are shown in **Figure 7.** Although cardiac function was hyperdynamic in all women, filling pressures were dependent on the volume of intravenous fluids. Specifically, aggressive hydration resulted in overtly hyperdynamic ventricular function in most women. However, this was accompanied by elevated pulmonary capillary wedge pressures. In some of these women, pulmonary edema may develop despite normal ventricular function because of an alveolar endothelial-epithelial leak. This is compounded by decreased oncotic pressure from a low serum albumin concentration **(American College of Obstetricians and Gynecologists, 2012b).**

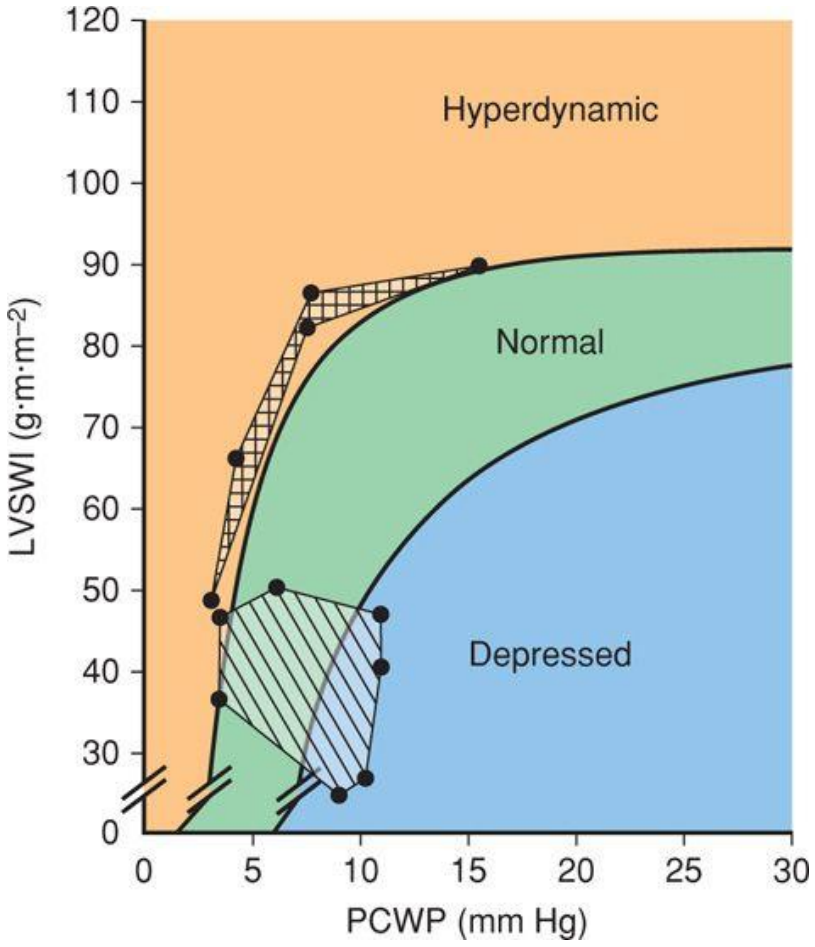

FIGURE 6. Ventricular function in normally pregnant women (striped area) and in women with eclampsia (boxed area) is plotted on a Braunwald ventricular function curve. Normal values are from Clark, 1989, and those for eclampsia are from Hankins, 1984. LVSWI = left ventricular stroke work index; PCWP = pulmonary capillary wedge pressure.

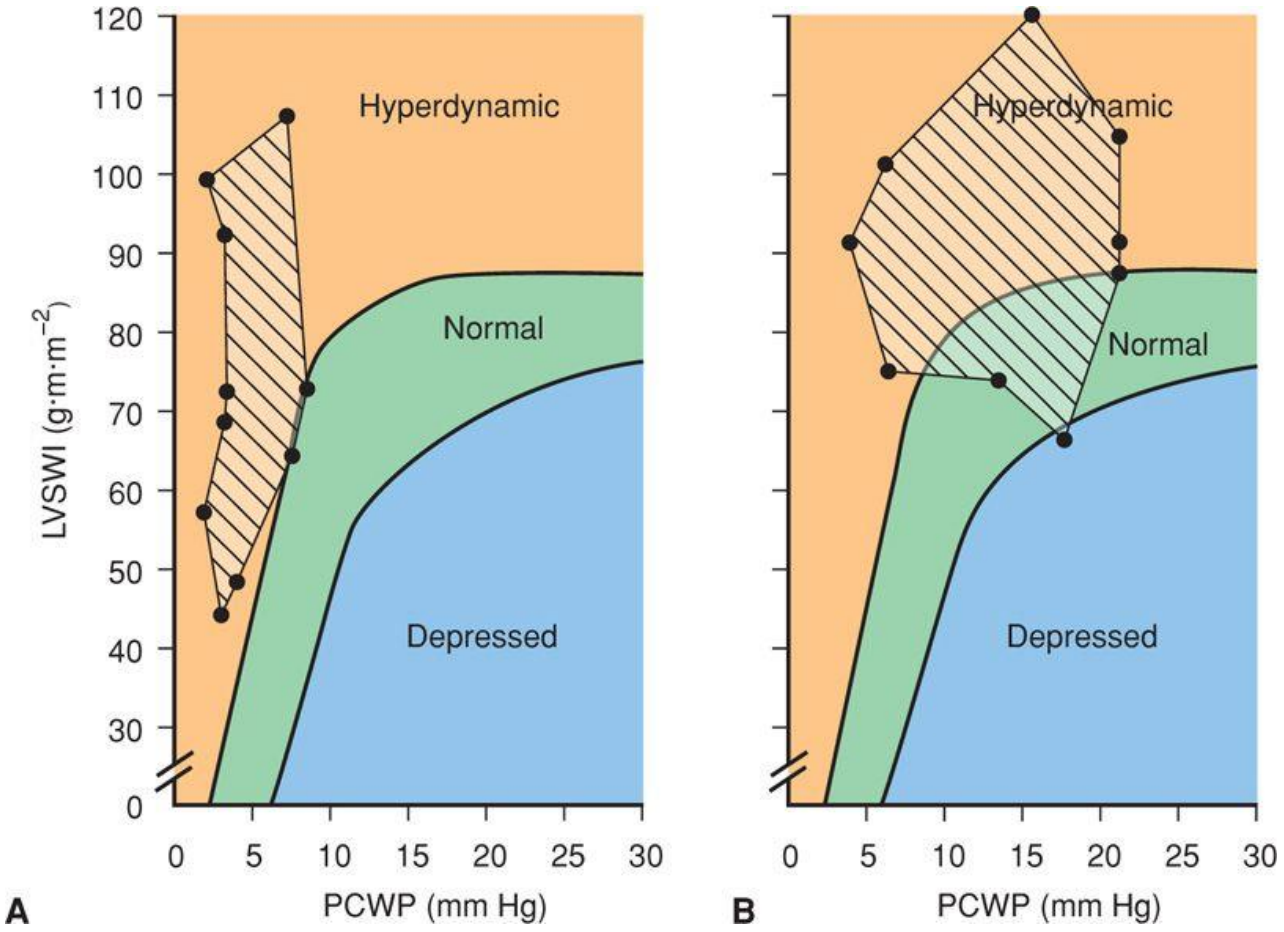

FIGURE 7. Ventricular function in women with severe preeclampsia–eclampsia plotted on the Braunwald ventricular function curve. The pulmonary capillary wedge pressures (PCWP) are lower in those managed with restricted fluid administration (striped area in A) compared with women managed with aggressive fluid therapy (striped area in B). In those managed with aggressive fluid infusions, eight developed pulmonary edema despite normal to hyperdynamic ventricular function in all but one. LVSWI = left ventricular stroke work index **(data for A adapted from Hankins et al., 1984; data for B adapted from Phelan et al., 1982).**

Thus, increased cardiac output and hyperdynamic ventricular function is largely a result of low wedge pressures and not a result of augmented myocardial contractility. By comparison, women given appreciably larger volumes of fluid commonly had filling

pressures that exceeded normal, but their ventricular function remained hyperdynamic because of concomitantly increased cardiac output. From these studies, it is reasonable to conclude that aggressive fluid administration to otherwise normal women with severe preeclampsia substantially elevates normal left-sided filling pressures and increases a physiologically normal cardiac output to hyperdynamic levels **(American College of Obstetricians and Gynecologists, 2012b).**

Blood Volume

For nearly 100 years, hemoconcentration has been a hallmark of eclampsia. This was not precisely quantified until **Zeeman and colleagues (2009)** expanded the previous observations of **Pritchard and associates (1984)** and showed in eclamptic women that the normally expected hypervolemia is severely curtailed **(Figure 8).** Women of average size should have a blood volume of nearly 4500 mL during the last several weeks of a normal pregnancy. In nonpregnant women, this volume approximates only 3000 mL. With eclampsia, however, much or all of the anticipated normal excess 1500 mL is lost. Such hemoconcentration results from generalized vasoconstriction that follows endothelial activation and leakage of plasma into the interstitial space because of increased permeability. In women with preeclampsia, and depending on its severity, hemoconcentration is usually not as marked. Women with gestational hypertension, but without preeclampsia, usually have a normal blood volume **(Silver et al., 1998).**

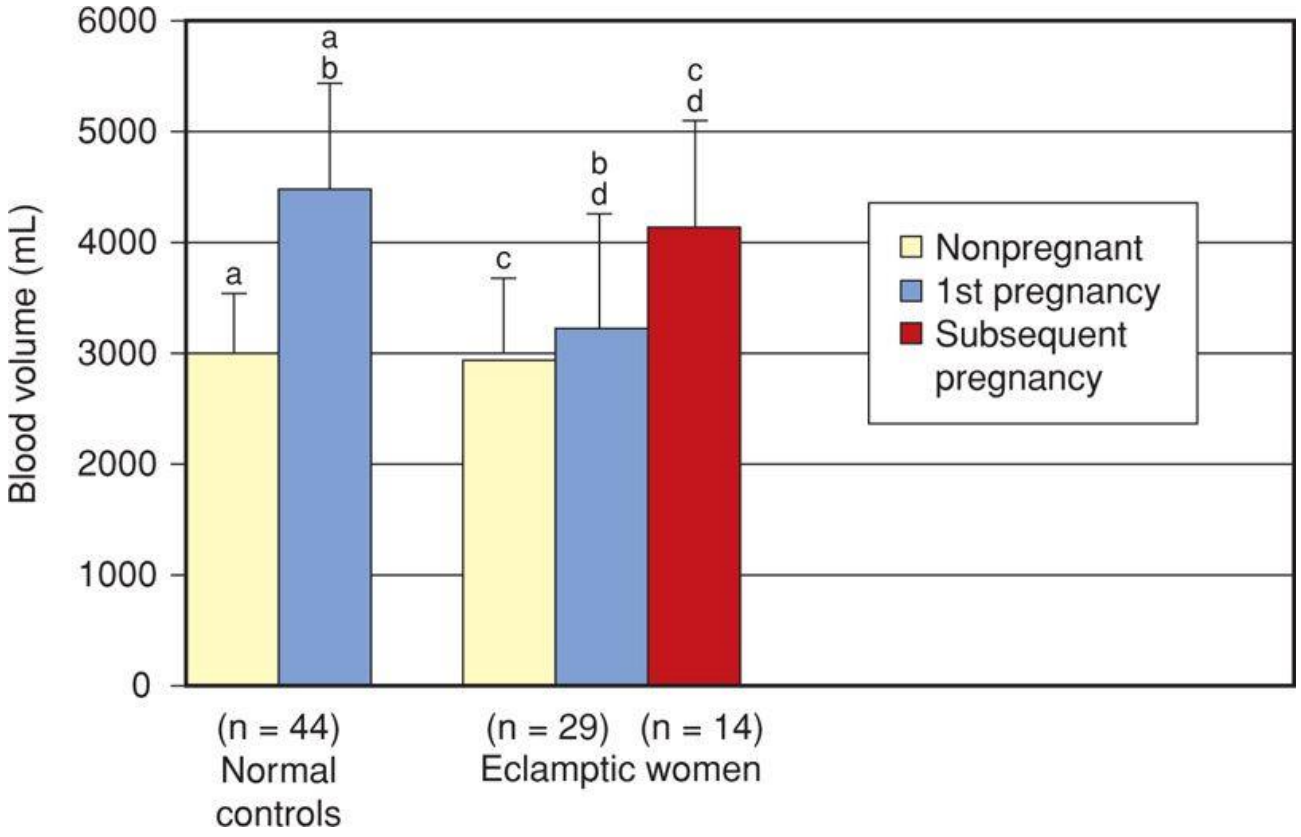

FIGURE 8. The two bar graphs on the left compare mean blood volumes in non-pregnant and term normally pregnant women. On the right, graphs display values for a group of 29 women with eclampsia and their non-pregnant values. The red bar reflects values for a subset of 14 who had a subsequent normotensive pregnancy. Extensions above bars represent one standard deviation. Comparison between values with identical lowercase letters, that is, a-a, b-b, c-c, d-d, are significant $p < 0.001$ **(Adapted from Zeeman et al., 2009).**

For women with severe hemoconcentration, it was once taught that an acute fall in hematocrit suggested resolution of preeclampsia. In this scenario, hemodilution follows endothelial healing with return of interstitial fluid into the intravascular space. Although

this is somewhat correct, it is important to recognize that a substantive cause of this fall in hematocrit is usually the consequence of blood loss at delivery. It may also partially result from increased erythrocyte destruction as subsequently described. Vasospasm and endothelial leakage of plasma may persist for a variable time after delivery as the endothelium is restored to normalcy. As this takes place, vasoconstriction reverses, and as the blood volume increases, the hematocrit usually falls. Thus, women with eclampsia are sensitive to vigorous fluid therapy administered in an attempt to expand the contracted blood volume to normal pregnancy levels or are sensitive to amounts of blood loss at delivery that are considered normal for a normotensive woman **(Zeeman et al., 2009).**

Hematological Changes

Several hematological abnormalities are associated with the preeclampsia syndrome. Among those commonly identified is thrombocytopenia, which at times may become severe enough to be life threatening. Occasionally, the levels of some plasma clotting factors may be decreased, and erythrocytes display abnormal morphology and undergo rapid hemolysis **(Heilmann et al., 2007).**

Thrombocytopenia

Decreased platelet concentrations with eclampsia were described as early as 1922 by Stancke. The platelet count is routinely measured in women with any form of gestational hypertension. The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of the preeclampsia syndrome and the frequency with which platelet counts are performed **(Hupuczi et al., 2007).**

Overt thrombocytopenia—defined by a platelet count < 100,000/μL—indicates severe disease **(Table II).** In general, the lower the platelet count, the higher the rates of maternal and fetal morbidity and mortality. In most cases, delivery is advisable because thrombocytopenia usually continues to worsen. After delivery, the platelet count may continue to decline for the first day or so. It then usually increases progressively to reach a normal level within 3 to 5 days. In some instances with HELLP syndrome, the platelet count continues to fall after delivery. If these do not reach a nadir until 48 to 72 hours,

then preeclampsia syndrome may be incorrectly attributed to one of the thrombotic microangiopathies **(George et al., 2013).**

Other Platelet Abnormalities

In addition to thrombocytopenia, there are myriad other platelet alterations described with the preeclampsia syndrome. These were reviewed by **Kenny and coworkers (2014)** and include platelet activation with increased α-degranulation producing β-thromboglobulin, factor 4, and increased clearance. Paradoxically, in most studies, in vitro platelet aggregation is decreased compared with the normal increase characteristic of pregnancy. This likely is due to platelet "exhaustion" following in vivo activation. Although the cause is unknown, immunological processes or simply platelet deposition at sites of endothelial damage may be implicated. Platelet-bound and circulating platelet-bindable immunoglobulins are increased, which suggest platelet surface alterations.

Neonatal Thrombocytopenia

Severe thrombocytopenia does not develop in the fetus or infant born to preeclamptic women despite severe maternal thrombocytopenia. Importantly, maternal thrombocytopenia in hypertensive women is not a fetal indication for cesarean delivery **(Kenny et al., 2014).**

Hemolysis

Severe preeclampsia is frequently accompanied by evidence of hemolysis as manifest by elevated serum lactate dehydrogenase levels and decreased haptoglobin levels. Other evidence comes from schizocytosis, spherocytosis, and reticulocytosis in peripheral blood. These derangements result in part from microangiopathic hemolysis caused by endothelial disruption with platelet adherence and fibrin deposition. **Sanchez-Ramos and colleagues (1994)** described increased erythrocyte membrane fluidity with HELLP syndrome. **Cunningham and coworkers (1995)** postulated that these changes were due to serum lipid alterations, and **Mackay and associates (2012)** found

substantively decreased long-chain fatty acid content in erythrocytes of pre-eclamptic women. Erythrocytic membrane changes, increased adhesiveness, and aggregation may also promote a hypercoagulable state **(Gamzu et al., 2001).**

HELLP Syndrome

Subsequent to reports of hemolysis and thrombocytopenia with severe preeclampsia, descriptions followed that abnormally elevated serum liver transaminase levels were commonly found and were indicative of hepatocellular necrosis **(Chesley et al., 1978). Weinstein (1982)** referred to this combination of events as the HELLP syndrome—and this moniker now is used worldwide. Also, and as shown in **Table II,** facets of the HELLP syndrome are included in criteria that differentiate severe from non-severe preeclampsia.

Coagulation Changes

Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia **(Kenny et al., 2014).**

Some of these changes include increased factor VIII consumption, increased levels of fibrinopeptides A and B and of D-dimers, and decreased levels of regulatory proteins—antithrombin III and protein C and S. Except for thrombocytopenia, coagulation aberrations generally are mild and are seldom clinically significant **(Kenny et al., 2014).**

Unless there is associated placental abruption, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy. Fibrin degradation products such as d-dimers are elevated only occasionally. Fibronectin, a glycoprotein associated with vascular endothelial cell basement membrane, is elevated in women with preeclampsia **(Brubaker et al., 1992).**

As preeclampsia worsens, so do abnormal findings with thromboelastography **(Pisani-Conway et al., 2013).** Despite these changes, routine laboratory assessments of coagulation, including prothrombin time, activated partial thromboplastin time, and plasma fibrinogen level, were found to be unnecessary in the management of pregnancy-associated hypertensive disorders **(Barron et al., 1999).**

Endocrine Changes

Plasma levels of renin, angiotensin II, angiotensin 1–7, aldosterone, and atrial natriuretic peptide are substantively increased during normal pregnancy. Deoxycorticosterone (DOC) is a potent mineralocorticoid that is also increased remarkably in normal pregnancy. This compound results from conversion of plasma progesterone to DOC rather than increased maternal adrenal secretion. Because of this, DOC secretion is not reduced by sodium retention or hypertension. This may explain why women with preeclampsia retain sodium. In pregnancy, the mineralocorticoid receptor becomes less sensitive to aldosterone **(Armanini et al., 2012).**

Vasopressin levels are similar in non-pregnant, normally pregnant, and preeclamptic women even though the metabolic clearance is increased in the latter two **(Dürr et al., 1999).** Atrial natriuretic peptide is released during atrial wall stretching from blood volume expansion, and it responds to cardiac contractility. Serum levels rise in pregnancy, and its secretion is further increased in women with preeclampsia **(Borghi et al., 2000; Luft et al., 2009).** Levels of its precursor—proatrial natriuretic peptide—are also increased in preeclampsia **(Sugulle et al., 2012).**

Fluid/ Electrolyte Changes and Volume Homeostasis

The normal pregnancy-induced extra- and intracellular volume increases that are accompanied by vasodilatation undergo further complex shifts with the preeclampsia syndrome. In addition to blood volume changes shown in **Figure 8,** there are many hormonal, fluid, and electrolyte aberrations. In women with severe preeclampsia, the volume of extracellular fluid, manifest as edema is usually much greater than that in 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. This reduction creates a filtration imbalance and further displaces intravascular fluid into the surrounding interstitium **(Davidge et al., 2014).**

Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with those of normal pregnant women. This may not be the case if there has been vigorous diuretic therapy, sodium restriction, or administration of free water with sufficient oxytocin to produce anti-diuresis. 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—metabolic acidosis—and the rate at which carbon dioxide is exhaled—respiratory acidosis **(Davidge et al., 2014).**

Renal Changes

During normal pregnancy, renal blood flow and glomerular filtration rate are increased appreciably. With development of preeclampsia, there may be a number of reversible anatomical and pathophysiological changes. Of clinical importance, renal perfusion and glomerular filtration are reduced. Levels that are much less than normal nonpregnant values are infrequent and are the consequence of severe disease. A small degree of decreased glomerular filtration may result from reduced plasma volume. Most of the decrement, however, is from increased renal afferent arteriolar resistance that may be elevated up to fivefold **(Cornelis et al., 2011; Conrad et al., 2014).**

There are also morphological changes characterized by glomerular endotheliosis blocking the filtration barrier. Diminished filtration causes serum creatinine levels to rise to values seen in non-pregnant individuals, that is, 1 mg/mL, and sometimes even higher **(Lindheimer et al., 2008a).** Abnormal values usually begin to normalize 10 days or later after delivery. In most pre-eclamptic women, urine sodium concentration is elevated. Urine osmolality, urine: plasma creatinine ratio, and fractional excretion of sodium also indicate that a prerenal mechanism is involved **(Spaan et al., 2012a).**

Kirshon and coworkers (1988) infused dopamine intravenously into oliguric women with preeclampsia, and this renal vasodilator stimulated increased urine output, fractional sodium excretion, and free water clearance. As was shown in **Figure 7,** sodium-containing crystalloid infusion increases left ventricular filling pressure, and although oliguria temporarily improves, rapid infusions may cause clinically apparent pulmonary edema. Intensive intravenous fluid therapy is not indicated as "treatment" for preeclamptic women with oliguria. Exceptions are diminished urine output from hemorrhage or fluid loss from vomiting or fever.

Plasma uric acid concentration is typically elevated in preeclampsia. The elevation exceeds the reduction in glomerular filtration rate and likely is also due to enhanced tubular reabsorption. At the same time, preeclampsia is associated with diminished urinary excretion of calcium, perhaps because of increased tubular reabsorption. Another possibility is from increased placental urate production compensatory to increased oxidative stress **(Spaan et al., 2012a).**

Proteinuria

As shown in **Table I,** some degree of proteinuria will establish the diagnosis of preeclampsia syndrome. Proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. For example, 10 to 15 percent of women with HELLP syndrome did not have proteinuria at presentation **(Sibai et al., 2004).** In another report, 17 percent of eclamptic women did not have proteinuria by the time of seizures **(Zwart et al., 2008).** Problematically, the optimal method of establishing abnormal levels of either urine protein or albumin remains to be defined. **Chen and associates (2008)** have shown that clean-catch and catheterized urine specimens correlate well. But dipstick qualitative determinations depend on urinary concentration and are notorious for false-positive and -negative results.

For a 24-hour quantitative specimen, the "consensus" threshold value used is > 300 mg/24 h **(Task Force, 2013). Tun and colleagues (2012)** have shown equivalent efficacy using protein excretion of 165 mg in a 12-hour sample. Importantly, these values

have not been irrefutably established. Determination of urinary protein: creatinine ratio may supplant the cumbersome 24-hour quantification **(Kyle et al., 2008; Morris et al., 2012; Ethridge et al., 2013).**

In a systematic review, **Papanna and associates (2008)** concluded that random urine protein: creatinine ratios that are below 130 to 150 mg/g, that is, 0.13 to 0.15, indicate a low likelihood of proteinuria exceeding 300 mg/day. Midrange ratios, that is, 300 mg/g or 0.3 have poor sensitivity and specificity. **Stout and colleagues (2013)** found that values < 0.08 or > 1.19 had negative- or positive-predictive values of 86 and 96 percent, respectively. At this time, most recommend that with midrange ratio values, 24-hour protein excretion should be quantified.

There are several methods used to measure proteinuria, and none detect all of the various proteins normally excreted **(Nayeri et al., 2013).** A more accurate method involves measurement of albumin excretion. Albumin filtration exceeds that of larger globulins, and with glomerular disease such as preeclampsia, most of the protein in urine is albumin. There are test kits that permit rapid measurement of urinary albumin:creatinine ratios in an outpatient setting **(Kyle et al., 2008).**

Although worsening or nephrotic-range proteinuria has been considered by most to be a sign of severe disease, this does not appear to be the case **(Airoldi et al., 2007).** Certainly, this concept was not accepted by the 2013 Task Force. Finally, increasing proteinuria is more common in multifetal pregnancy complicated by preeclampsia **(Zilberberg et al., 2013).**

Kidney Anatomical Changes

Sheehan and Lynch (1973) commonly found changes identifiable at autopsy by light and electron microscopy in the kidneys of eclamptic women. Glomeruli are enlarged by approximately 20 percent, they are “bloodless,” and capillary loops variably are dilated and contracted. Endothelial cells are swollen—termed glomerular capillary

endotheliosis by **Spargo and associates (1959).** Endothelial cells are often so swollen that they block or partially block the capillary lumens **(Figure 9).** Homogeneous subendothelial deposits of proteins and fibrin-like material are seen.

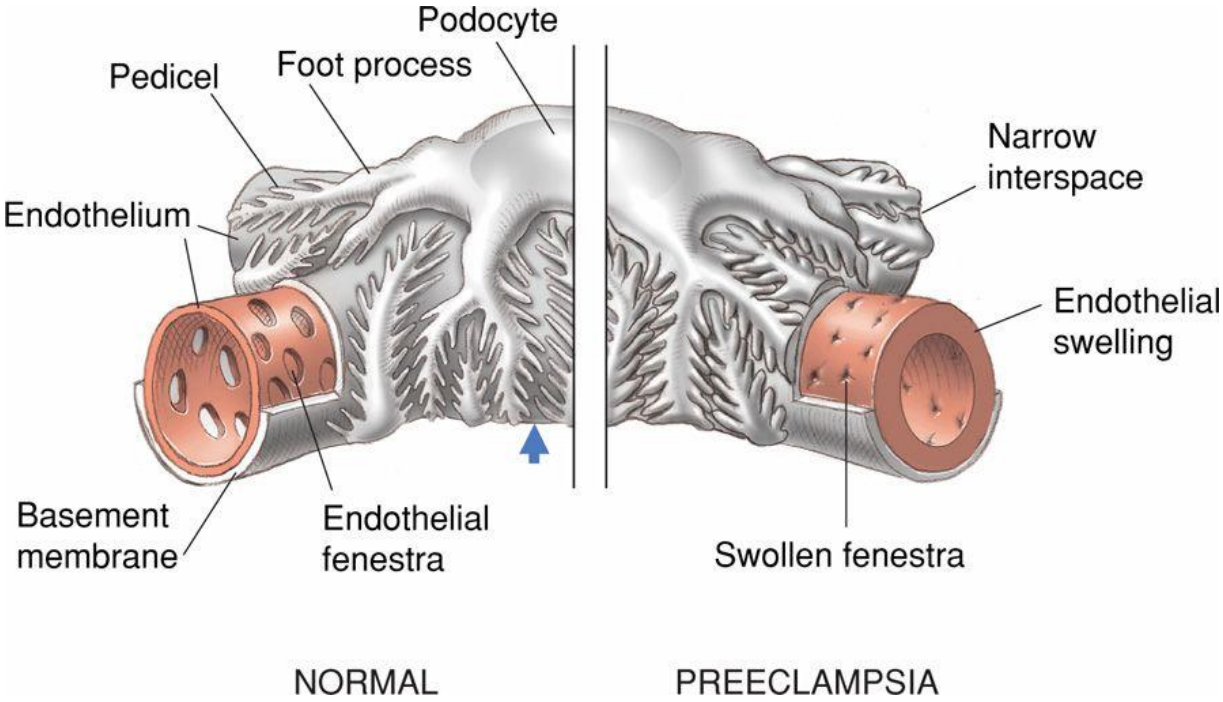

FIGURE 9. Schematic showing glomerular capillary endotheliosis. The capillary of the normal glomerulus shown on the left has wide endothelial fenestrations, and the pedicels emanating from the podocytes are widely spaced (arrow). The illustration on the right is of a glomerulus with changes induced by the preeclampsia syndrome. The endothelial cells are swollen and their fenestrae narrowed, as are the pedicels that now abut each other.

Endothelial swelling may result from angiogenic factor "withdrawal" caused by free angiogenic proteins complexing with the circulating antiangiogenic protein receptor **(Eremina et al., 2007; Karumanchi et al., 2009; Conrad et al., 2014).**

The angiogenic proteins are crucial for podocyte health, and their inactivation leads to podocyte dysfunction and endothelial swelling. One marker of this is excretion of podocyte proteins such as nephrin, podocalyxin, and βig-h3 (transforming growth factor, β-induced) **(Wang et al., 2012b).**

Also, eclampsia is characterized by increased excretion of urinary podocytes, a phenomenon shared by other proteinuric disorders **(Garrett et al., 2013).** Of interest, podocytes are epithelia, and thus renal pathology involves both endothelial and epithelial cells **(Figure 9) (Wagner et al., 2012).**

Acute Kidney Injury

Rarely is acute tubular necrosis caused by preeclampsia alone. Although mild degrees are encountered in neglected cases, clinically apparent renal failure is invariably induced by coexistent hemorrhage with hypovolemia and hypotension. This is usually caused by severe obstetrical hemorrhage for which adequate blood replacement is not given. **Drakeley and coworkers (2002)** described 72 women with preeclampsia and renal failure. Half had HELLP syndrome and a third had placental abruption. **Haddad and colleagues (2000)** reported that 5 percent of 183 women with HELLP syndrome had kidney injury. Half of these, however, also had a placental abruption, and most had postpartum hemorrhage. Rarely, irreversible renal cortical necrosis develops.

Hepatic Changes

Hepatic changes in women with fatal eclampsia were described in 1856 by Virchow. The characteristic lesions were regions of periportal hemorrhage in the liver periphery. In their elegant autopsy studies, **Sheehan and Lynch (1973)** described that some degree of hepatic infarction accompanied hemorrhage in almost half of women who died with eclampsia. These corresponded with reports that had appeared during the 1960s describing elevated serum hepatic transaminase levels. Along with the earlier observations by **Pritchard and associates (1954),** who described hemolysis and thrombocytopenia with eclampsia, this constellation of hemolysis, hepatocellular necrosis, and thrombocytopenia was later termed HELLP syndrome by **Weinstein et al., (1985)** to call attention to its seriousness.

Lesions as extensive as those shown in **Figure 10** are unusual, even in the autopsy series by **Sheehan and Lynch (1973).** From a pragmatic point, liver involvement with preeclampsia may be clinically significant in several circumstances.

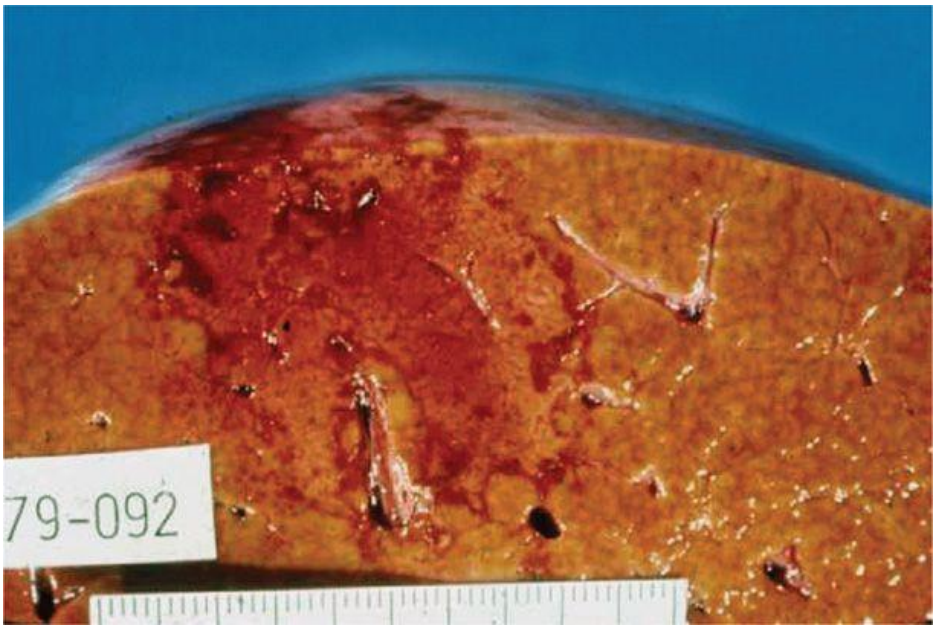

FIGURE 10. Gross liver specimen from a woman with preeclampsia who died from aspiration pneumonitis. Periportal hemorrhagic necrosis was seen microscopically **(Adapted from Cunningham et al., 1993).**

First, symptomatic involvement is considered a sign of severe disease. It typically manifests by moderate to severe right-upper quadrant or midepigastric pain and tenderness. In many cases, such women also have elevated levels of serum aminotransferase, namely, aspartate aminotransferase (AST) or alanine aminotransferase (ALT). In some cases, however, the amount of hepatic tissue involved with infarction may be surprisingly extensive yet still clinically insignificant. Infarction may be worsened by hypotension from obstetrical hemorrhage, and it occasionally causes hepatic failure—so-called shock liver **(Alexander et al., 2009).**

Second, asymptomatic elevations of serum hepatic transaminase levels—AST and ALT—are also considered markers for severe preeclampsia. Values seldom exceed 500 U/L, but have been reported to be greater than 2000 U/L in some women. In general, serum levels inversely follow platelet levels, and they both usually normalize within 3 days following delivery. In a third example of liver involvement, hemorrhagic infarction may extend to form a hepatic hematoma. These in turn may extend to form a subcapsular hematoma that may rupture. They can be identified using computed tomography (CT)

scanning or magnetic resonance (MR) imaging as shown in **Figure 11.** Unruptured hematomas are probably more common than clinically suspected and are more likely to be found with HELLP syndrome **(Carlson et al., 2004; Vigil-De Gracia et al., 2012).**

Although once considered a surgical condition, contemporaneous management usually consists of observation and conservative treatment of hematomas unless hemorrhage is ongoing. In some cases, however, prompt surgical intervention may be lifesaving. **Vigil-De Gracia and coworkers (2012)** reviewed 180 cases of hepatic hematoma or rupture. More than 90 percent had HELLP syndrome, and in 90 percent, the capsule had ruptured. The maternal mortality rate was 22 percent, and the perinatal mortality rate was 31 percent. In rare cases, liver transplant is necessary **(Wicke et al., 2004).**

Lastly, acute fatty liver of pregnancy is sometimes confused with preeclampsia. It too has an onset in late pregnancy, and often there is accompanying hypertension, elevated serum transaminase and creatinine levels, and thrombocytopenia **(Sibai et al., 2007a; Nelson et al., 2013).**

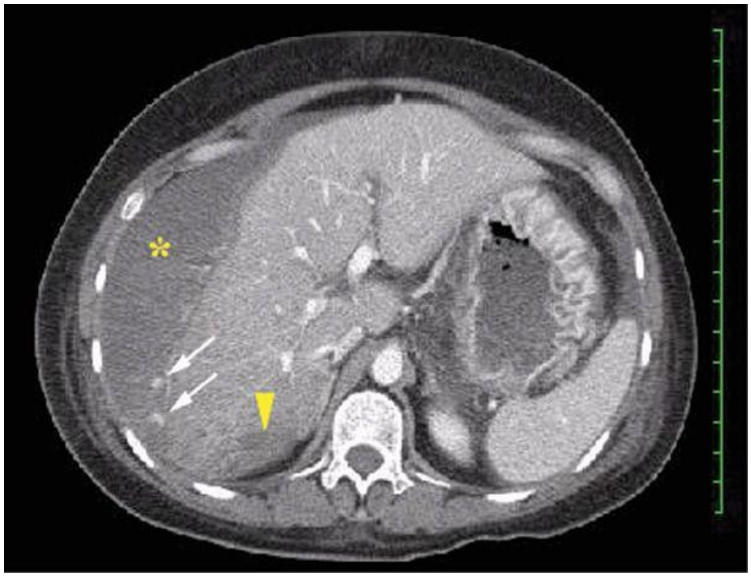

FIGURE 11. Abdominal CT imaging performed postpartum in a woman with severe HELLP syndrome and right-upper quadrant pain. A large subcapsular hematoma (asterisk) is seen confluent with intrahepatic infarction and hematoma (arrowhead). Numerous flame-shaped hemorrhages are seen at the hematoma interface (arrows).

HELLP Syndrome

There is no universally accepted strict definition of this syndrome, and thus its incidence varies by investigator. When it is identified, the likelihood of hepatic hematoma and rupture is substantially increased. In a multicenter study, **Haddad and colleagues (2000)** described 183 women with HELLP syndrome of whom 40 percent had adverse outcomes including two maternal deaths. The incidence of subcapsular liver hematoma was 1.6 percent. Other complications included eclampsia—6 percent, placental abruption—10 percent, acute kidney injury—5 percent, and pulmonary edema—10 percent. Other serious complications included stroke, coagulopathy, acute respiratory distress syndrome, and sepsis.

Women with preeclampsia complicated by the HELLP syndrome typically have worse outcomes than those without these findings **(Kozic et al., 2011; Martin et al., 2012; 2013).** In their review of 693 women with HELLP syndrome, **Keiser and coworkers (2009)** reported that 10 percent had concurrent eclampsia.

Sep and associates (2009) also described a significantly increased risk for complications in women with HELLP syndrome compared with those with "isolated preeclampsia." These included eclampsia—15 versus 4 percent; preterm birth—93 versus 78 percent; and perinatal mortality rate—9 versus 4 percent, respectively. Because of these marked clinical differences, these investigators postulate that HELLP syndrome has a distinct pathogenesis. Others have shown a difference in the ratio of anti-angiogenic and inflammatory acute-phase proteins in these two conditions and have reached similar conclusions **(Reimer et al., 2013). Sibai and Stella (2009)** have discussed some of these aspects under the rubric of "atypical preeclampsia-eclampsia."

Pancreatic Changes

According to **Sheehan and Lynch (1973),** there are no convincing data that the pancreas has special involvement with preeclampsia syndrome. If so, the occasional case reports of concurrent hemorrhagic pancreatitis are likely unrelated. That said, severe hemoconcentration may predispose to pancreatic inflammation **(Swank et al., 2012).**

Neurological Changes

Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia. The earliest anatomical descriptions of brain involvement came from autopsy specimens, but CT- and MR-imaging and Doppler studies have added many important insights into cerebrovascular involvement.

Neuroanatomical Lesions

Most gross anatomical descriptions of the brain in eclamptic women are taken from eras when mortality rates were high. One consistent finding was that brain pathology accounted for only about a third of fatal cases such as the one shown in **Figure 12.** In fact, most deaths were from pulmonary edema, and brain lesions were coincidental. Thus, although gross intracerebral hemorrhage was seen in up to 60 percent of eclamptic women, it was fatal in only half of these **(Sheehan et al., 1973; Richards et al., 1988).** As shown in **Figure 13,** other principal lesions found at autopsy of eclamptic women were cortical and subcortical petechial hemorrhages. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages. Other frequently described major lesions include subcortical edema, multiple non-hemorrhagic areas of “softening” throughout the brain, and hemorrhagic areas in the white matter. There also may be hemorrhage in the basal ganglia or pons, often with rupture into the ventricles.

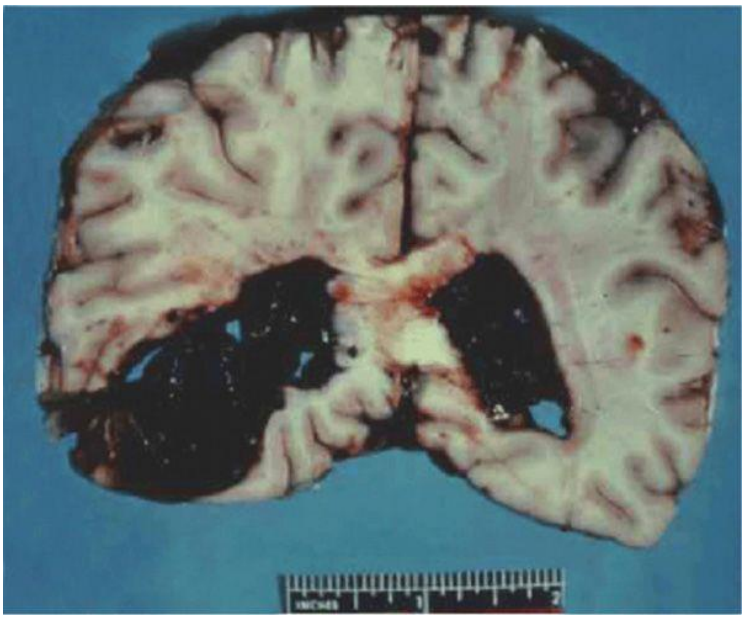

FIGURE 12. This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.

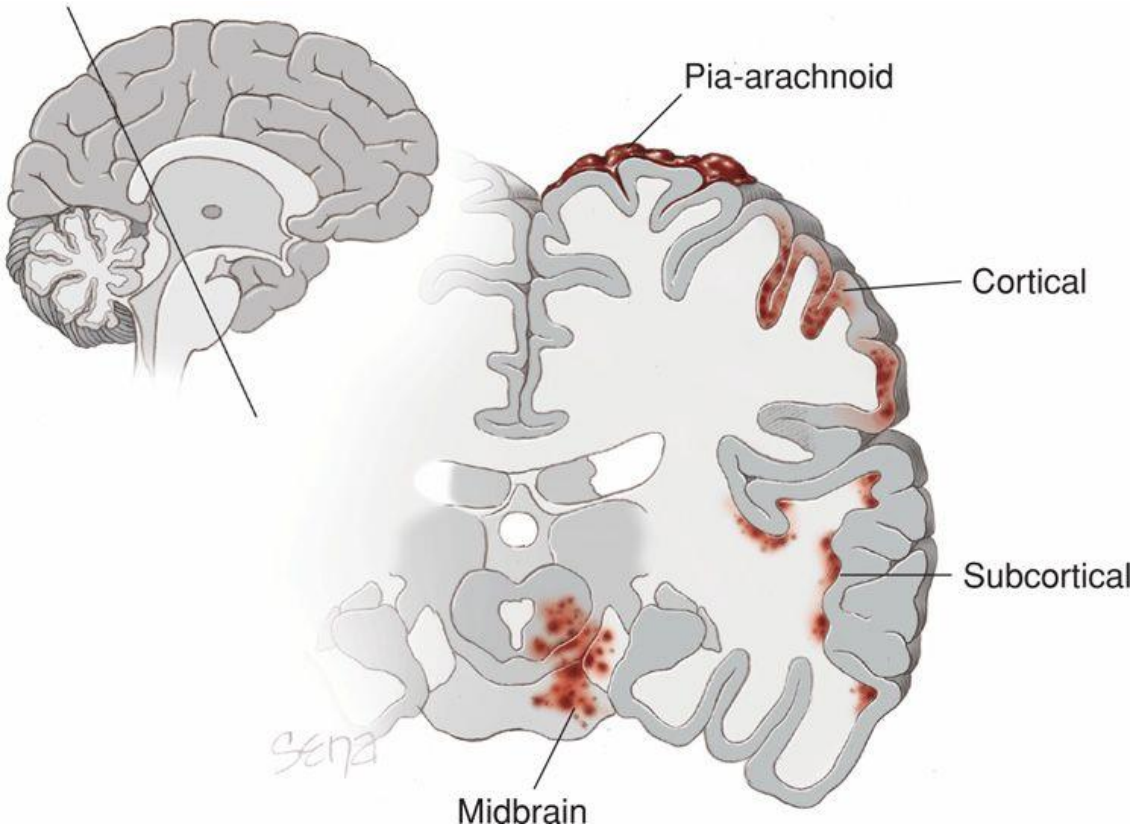

FIGURE 13. Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed **(Adapted from Sheehan et al., 1973).**

Cerebrovascular Pathophysiology

Clinical, pathological, and neuroimaging findings have led to two general theories to explain cerebral abnormalities with eclampsia. Importantly, endothelial cell dysfunction that characterizes the preeclampsia syndrome likely plays a key role in both. The first theory suggests that in response to acute and severe hypertension, cerebrovascular overregulation leads to vasospasm **(Trommer et al., 1988).**

This presumption is based on the angiographic appearance of diffuse or multifocal segmental narrowings suggestive of vasospasm. In this scheme, diminished cerebral blood flow is hypothesized to result in ischemia, cytotoxic edema, and eventually tissue infarction. Although this theory was widely embraced for many years, there is little objective evidence to support it. The second theory is that sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity **(Schwartz et al., 2000).**

Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level, disruption of end-capillary pressure causes increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings. This leads to vasogenic edema. This theory is incomplete because very few eclamptic women have mean arterial pressures that exceed limits of autoregulation—approximately 160 mm Hg. It seems reasonable to conclude that the most likely mechanism is a combination of the two. Thus, a preeclampsia-associated interendothelial cell leak develops at blood pressure (hydraulic) levels much lower than those usually causing vasogenic edema and is coupled with a loss of upper-limit autoregulation **(Zeeman et al., 2009).**

With imaging studies, these changes manifest as facets of the reversible posterior leukoencephalopathy syndrome. This subsequently became referred to as the posterior

reversible encephalopathy syndrome—PRES. This term is misleading because although PRES lesions principally involve the posterior brain—the occipital and parietal cortices—in at least a third of cases, they also involve other brain areas **(Zeeman et al., 2004a; Edlow et al., 2013).** The most frequently affected region is the parietooccipital cortex—the boundary zone of the anterior, middle, and posterior cerebral arteries. Also, in most cases, these lesions are reversible **(Cipolla et al., 2014).**

Cerebral Blood Flow

Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure. In nonpregnant individuals, this mechanism protects the brain from hyperperfusion when mean arterial pressures increase to as high as 160 mm Hg. These are pressures far greater than those seen in all but a very few women with eclampsia. Thus, to explain eclamptic seizures, it was theorized that autoregulation must be altered by pregnancy. Although species differences must be considered, studies by **Cipolla and colleagues (2007; 2009 and 2014)** have convincingly shown that autoregulation is unchanged across pregnancy in rodents. That said, some, but not others, have provided evidence of impaired autoregulation in women with preeclampsia **(van Veen et al., 2013; Janzarik et al., 2014).**

Zeeman and associates (2003) showed that cerebral blood flow during the first two trimesters of normal pregnancy is similar to nonpregnant values, but thereafter, it significantly decreases by 20 percent during the last trimester. These investigators also documented significantly increased cerebral blood flow in women with severe preeclampsia compared with that of normotensive pregnant women. Taken together, these findings suggest that eclampsia occurs when cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage, which leads to perivascular edema characteristic of the preeclampsia syndrome. In this regard, eclampsia is an example of the posterior reversible encephalopathy syndrome **(Zeeman et al., 2004b).**

Neurological Manifestations

There are several neurological manifestations of the preeclampsia syndrome. Each signifies severe involvement and requires immediate attention. First, headache and scotomata are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes **(Sibai, 2005).**

According to **Sibai (2005)** and **Zwart and coworkers (2008),** 50 to 75 percent of women have headaches and 20 to 30 percent have visual changes preceding eclamptic convulsions. The headaches may be mild to severe and intermittent to constant. They are unique in that they do not usually respond to traditional analgesia, but they do improve after magnesium sulfate infusion is initiated.

Convulsions are a second potential manifestation and are diagnostic for eclampsia. These are caused by excessive release of excitatory neurotransmitters—especially glutamate; massive depolarization of network neurons; and bursts of action potentials **(Meldrum et al., 2002).** Clinical and experimental evidence suggest that extended seizures can cause significant brain injury and later brain dysfunction. As a third manifestation, blindness is rare with preeclampsia alone, but it complicates eclamptic convulsions in up to 15 percent of women. Blindness has been reported to develop up to a week or more following delivery **(Chambers et al., 2004).** There are at least two types of blindness. Last, generalized cerebral edema may develop and is usually manifest by mental status changes that vary from confusion to coma. This situation is particularly dangerous because fatal transtentorial herniation may result **(Chambers et al., 2004).**

Neuroimaging Studies

With CT imaging, localized hypodense lesions at the gray- and white-matter junction, primarily in the parietooccipital lobes, are typically found in eclampsia. Such lesions may also be seen in the frontal and inferior temporal lobes, the basal ganglia, and thalamus. The spectrum of brain involvement is wide, and increasing involvement can be identified with CT imaging. Edema of the occipital lobes or diffuse cerebral edema may cause symptoms such as blindness, lethargy, and confusion **(Cunningham et al., 2000).**

In the latter cases, widespread edema shows as a marked compression or even obliteration of the cerebral ventricles. Such women may develop signs of impending life-threatening transtentorial herniation. Several MR imaging acquisitions are used to study eclamptic women. Common findings are hyperintense T2 lesions—posterior reversible encephalopathy syndrome (PRES)—in the subcortical and cortical regions of the parietal and occipital lobes **(Figure 14).** There is also relatively common involvement of the basal ganglia, brainstem, and cerebellum **(Zeeman et al., 2004a; Brewer et al., 2013).** Although these PRES lesions are almost universal in women with eclampsia, their incidence in women with preeclampsia is less frequent. They are more likely to be found in women who have severe disease and who have neurological symptoms **(Schwartz et al., 2000).** And although usually reversible, a fourth of these hyperintense lesions represent cerebral infarctions that have persistent findings **(Loureiro et al., 2003; Zeeman et al., 2004a).**

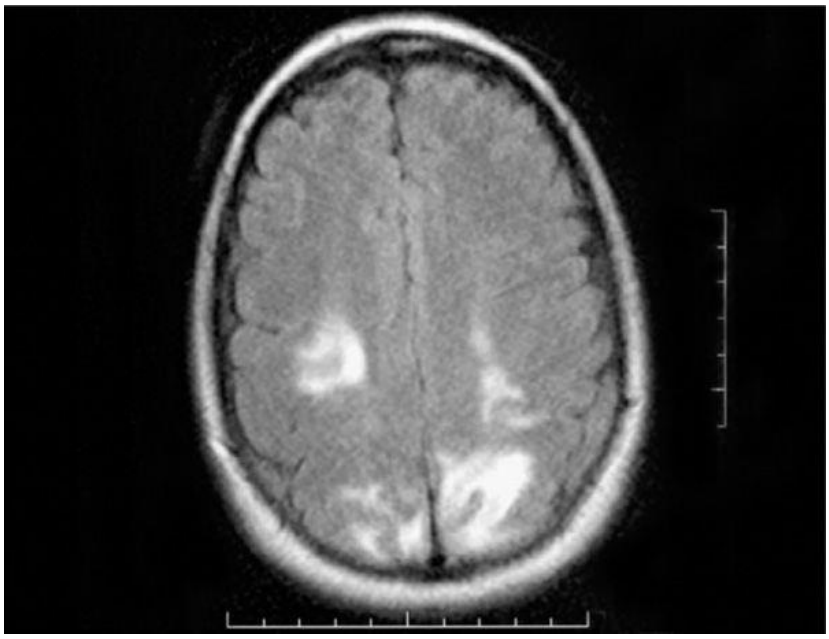

FIGURE 14. Cranial magnetic resonance imaging in a nullipara with eclampsia. Multilobe T2-FLAIR high-signal lesions are apparent. FLAIR = fluid-attenuated inversion recovery **(Adapted from Zeeman et al., 2004a).**

Visual Changes and Blindness

Scotomata, blurred vision, or diplopia are common with severe preeclampsia and eclampsia. These usually improve with magnesium sulfate therapy and/or lowered blood pressure. Blindness is less common, is usually reversible, and may arise from three potential areas. These are the visual cortex of the occipital lobe, the lateral geniculate nuclei, and the retina. In the retina, pathological lesions may be ischemia, infarction, or detachment. Occipital blindness is also called amaurosis—from the Greek dimming. Affected women usually have evidence of extensive occipital lobe vasogenic edema on imaging studies. Of 15 women cared for at Parkland Hospital, occipital blindness lasted from 4 hours to 8 days, but it resolved completely in all cases. Rarely, extensive cerebral infarctions may result in total or partial visual defects **(Figure 15) (Roos et al., 2012).**

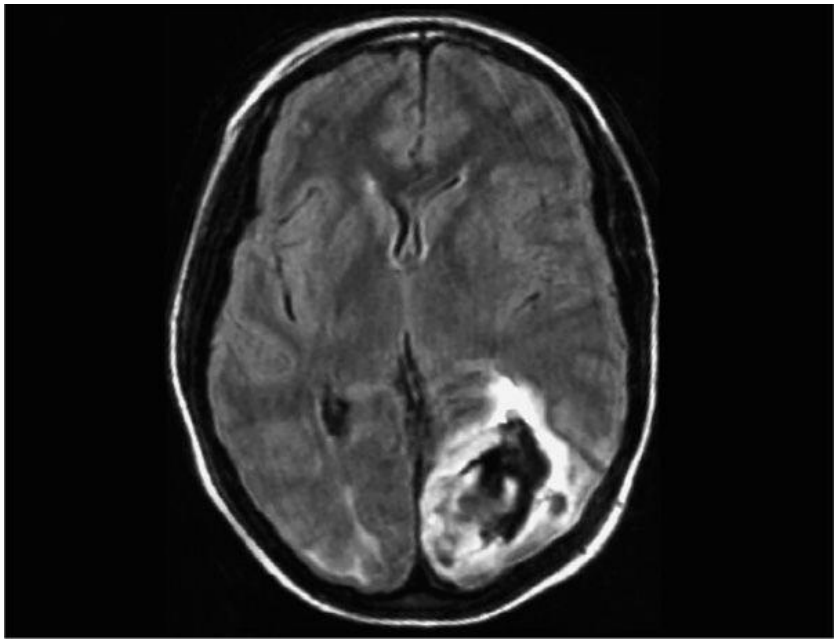

FIGURE 15. Cranial magnetic resonance imaging performed 3 days postpartum in a woman with eclampsia and HELLP syndrome. Neurovisual defects persisted at 1 year, causing job disability **(Adapted from Murphy et al., 2005).**

Blindness from retinal lesions is caused either by serous retinal detachment or rarely by retinal infarction, which is termed Purtscher retinopathy **(Figure 16).** Serous retinal detachment is usually unilateral and seldom causes total visual loss. In fact, asymptomatic serous retinal detachment is relatively common. In most cases of

eclampsia-associated blindness, visual acuity subsequently improves, but if caused by retinal artery occlusion, vision may be permanently impaired **(Lara-Torre et al., 2002; Roos et al., 2012).** In some women, these findings are additive. **Moseman and Shelton (2002)** described a woman with permanent blindness due to a combination of retinal infarctions and bilateral lesions in the lateral geniculate nuclei.

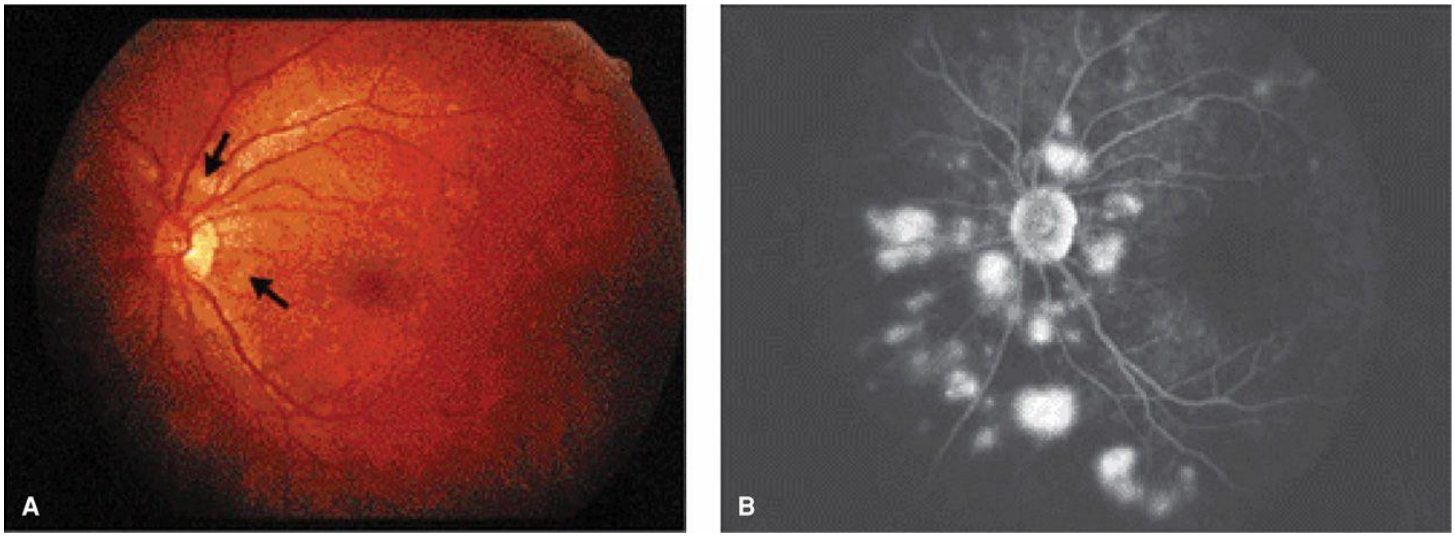

FIGURE 16. Purtscher retinopathy caused by choroidal ischemia and infarction in preeclampsia syndrome. A. Ophthalmoscopy shows scattered yellowish, opaque lesions of the retina (arrows). **B.** The late phase of fluorescein angiography shows areas of intense hyperfluorescence representing pooling of extravasated dye **(Adapted from Lam et al., 2001).**

Cerebral Edema

Clinical manifestations suggesting widespread cerebral edema are worrisome. During 13 years at Parkland Hospital, 10 of 175 women with eclampsia were diagnosed with symptomatic cerebral edema. Symptoms ranged from lethargy, confusion, and blurred vision to obtundation and coma. In most cases, symptoms waxed and waned. Mental status changes generally correlated with the degree of involvement seen with CT

and MR imaging studies. These women are very susceptible to sudden and severe blood pressure elevations, which can acutely worsen the already widespread vasogenic edema. Thus, careful blood pressure control is essential. In the 10 women with generalized edema, three became comatose and had imaging findings of impending transtentorial herniation. One of these three died from herniation. Consideration is given for treatment with mannitol or dexamethasone **(Cunningham et al., 2000).**

Uteroplacental Perfusion

Of immense clinical importance, compromised uteroplacental perfusion is almost certainly a major culprit in the increased perinatal morbidity and mortality rates. Thus, measurement of uterine, intervillous, and placental blood flow would likely be informative. Attempts to assess these in humans have been hampered by several obstacles that include inaccessibility of the placenta, the complexity of its venous effluent, and the need for radioisotopes or invasive techniques. Measurement of uterine artery blood flow velocity has been used to estimate resistance to uteroplacental blood flow. Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. By the completion of placentation, impedance to uterine artery blood flow is markedly decreased, but with abnormal placentation, abnormally high resistance persists **(Ghidini et al., 2008; Everett et al., 2012; Napolitano et al., 2012).**

Earlier studies were done to assess this by measuring peak systolic:diastolic velocity ratios from uterine and umbilical arteries in preeclamptic pregnancies. The results were interpreted as showing that in some cases, but certainly not all, there was increased resistance. Another Doppler waveform—uterine artery "notching"—has been reported to be associated with increased risks for preeclampsia or fetal-growth restriction **(Groom et al., 2009).** In the MFMU Network study reported by **Myatt and colleagues (2012a),** however, notching had a low predictive value except for early-onset severe disease.

Matijevic and Johnson (1999) measured resistance in uterine spiral arteries. Impedance was higher in peripheral than in central vessels—a so-called ring-like

distribution. Mean resistance was higher in all women with preeclampsia compared with that in normotensive controls. **Ong and associates (2003)** used MR imaging and other techniques to assess placental perfusion ex vivo in the myometrial arteries removed from women with preeclampsia or fetal-growth restriction. These investigators confirmed that in both conditions myometrial arteries exhibited endothelium-dependent vasodilatory response. Moreover, other pregnancy conditions are also associated with increased resistance. One major adverse effect is fetal-growth restriction **(Urban et al., 2007).**

Pimenta and colleagues (2013) assessed placental vascularity using a three-dimensional power Doppler histogram. These researchers described the placental vascularity index, which was decreased in women with any pregnancy-associated hypertensive disorders—11.1 percent compared with 15.2 percent in normal controls.

Despite these findings, evidence for compromised uteroplacental circulation is found in only a few women who go on to develop preeclampsia. Indeed, when preeclampsia develops during the third trimester, only a third of women with severe disease have abnormal uterine artery velocimetry **(Li et al., 2005).**

In a study of 50 women with HELLP syndrome, only a third had abnormal uterine artery waveforms **(Bush et al., 2001).** In general, the extent of abnormal waveforms correlates with severity of fetal involvement **(Ghidini et al., 2008; Groom et al., 2009).**

PREDICTION AND PREVENTION

PREDICTION

Measurement during early pregnancy—or across pregnancy—of various biological, biochemical, and biophysical markers implicated in preeclampsia syndrome pathophysiology has been proposed to predict its development. Attempts have been made to identify early markers of faulty placentation, impaired placental perfusion, endothelial cell activation and dysfunction, and activation of coagulation. For the most, these have resulted in testing strategies with poor sensitivity and with poor positive-predictive value for preeclampsia **(Lindheimer et al., 2008b; Odibo et al., 2013; Conde-Agudelo et al.,**

2014). Currently, no screening tests are predictably reliable, valid, and economical **(Kleinrouweler et al., 2012).** There are, however, combinations of tests, some yet to be adequately evaluated, that may be promising **(Kuc et al., 2011; Olsen et al., 2012; Dugoff et al., 2013; Navaratnam et al., 2013).**

The list of predictive factors evaluated during the past three decades is legion. Although most have been evaluated in the first half of pregnancy, some have been tested as predictors of severity in the third trimester **(Rana et al., 2012; Chaiworapongsa et al., 2013; Mosimann et al., 2013).** Others have been used to forecast recurrent preeclampsia **(Demers et al., 2014).** Some of these tests are listed in **Table V,** which is by no means all inclusive. **Conde-Agudelo and coworkers (2014)** have recently provided a thorough review of many of these testing strategies.

TABLE V. Predictive Tests for Development of the Preeclampsia Syndrome:

Testing Related To:	Examples
Placental perfusion/ vascular resistance	Roll-over test, isometric handgrip or cold pressor test, pressor response to aerobic exercise, angiotensin-II infusion, midtrimester mean arterial pressure, platelet angiotensin-II binding, renin, 24-hour ambulatory blood pressure monitoring, uterine artery or fetal transcranial Doppler velocimetry
Fetal-placental unit endocrine dysfunction	Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), estriol, pregnancy-associated protein A (PAPP A), inhibin A, activin A, placental protein 13, corticotropin-releasing hormone, A disintegrin, ADAM-12, kisspeptin
Renal dysfunction	Serum uric acid, microalbuminuria, urinary calcium or kallikrein, microtransferrinuria, *N*-acetyl-β-glucosaminidase, cystatin C, podocyturia
Endothelial dysfunction/ oxidant stress	Platelet count and activation, fibronectin, endothelial adhesion molecules, prostaglandins, prostacyclin, MMP-9, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteine, lipids, insulin resistance, antiphospholipid antibodies, plasminogen activator-inhibitor (PAI), leptin, p-selectin, angiogenic factors such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), endoglin
Others	Antithrombin-III(AT-3), atrial natriuretic peptide (ANP), β_2-microglobulin, haptoglobin, transferrin, ferritin, 25-hydroxyvitamin D, genetic markers, cell-free fetal DNA, serum and urine proteomics and metabolomic markers, hepatic aminotransferases

ADAM12 = ADAM metallopeptidase domain 12; MMP = matrix metalloproteinase.
Adapted from Conde-Agudelo, 2014.

Vascular Resistance Testing and Placental Perfusion:

Most of these are cumbersome, time consuming, and overall inaccurate.

Provocative Pressor Tests

Three tests have been extensively evaluated to assess the blood pressure rise in response to a stimulus. The roll-over test measures the hypertensive response in women at 28 to 32 weeks who are resting in the left lateral decubitus position and then roll over to the supine position. Increased blood pressure signifies a positive test. The isometric exercise test employs the same principle by squeezing a handball **(Rana et al., 2012).**

The angiotensin II infusion test is performed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified. In their updated meta-analysis, **Conde-Agudelo and associates (2014)** found sensitivities of all three tests to range from 55 to 70 percent, and specificities approximated 85 percent.

Uterine Artery Doppler Velocimetry

Faulty trophoblastic invasion of the spiral arteries, which is depicted in **Figure 2,** results in diminished placental perfusion and upstream increased uterine artery resistance. Increased uterine artery velocimetry determined by Doppler ultrasound in the first two trimesters should provide indirect evidence of this process and thus serve as a predictive test for preeclampsia **(Gebb et al., 2009a; 2009b; Groom et al., 2009).**

Increased flow resistance results in an abnormal waveform represented by an exaggerated diastolic notch. These have value for fetal-growth restriction but not preeclampsia **(American College of Obstetricians and Gynecologists, 2013a).** Several flow velocity waveforms—alone or in combination—have been investigated for preeclampsia prediction. In some of these, predictive values for early-onset preeclampsia were promising **(Herraiz et al., 2012).** At this time, however, none is suitable for clinical use **(Kleinrouweler et al., 2012; Myatt et al., 2012a; Conde-Agudelo et al., 2014).**

Pulse Wave Analysis

Like the uterine artery, finger arterial pulse "stiffness" is an indicator of cardiovascular risk. Investigators have preliminarily evaluated its usefulness in preeclampsia prediction **(Vollebregt et al., 2009).**

Fetal-Placental Unit Endocrine Function

Several serum analyses that have been proposed to help predict preeclampsia**.** Newer ones are continuously added. Many of these gained widespread use in the 1980s to identify fetal malformations and were also found to be associated with other pregnancy abnormalities such as neural-tube defects and aneuploidy. Although touted for hypertension prediction, in general, none of these tests has been shown to be clinically beneficial for that purpose **(Kanasaki et al., 2008; Kenny et al., 2009; Jeyabalan et al., 2009).**

Tests of Renal Function

Serum Uric Acid

One of the earliest laboratory manifestations of preeclampsia is hyperuricemia **(Powers et al., 2006).** It likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption, and decreased secretion **(Lindheimer et al., 2008a).** It is used by some to define preeclampsia, but **Cnossen and coworkers (2006)** reported that its sensitivity ranged from 0 to 55 percent, and specificity was 77 to 95 percent.

Microalbuminuria

As a predictive test for preeclampsia, microalbuminuria has sensitivities ranging from 7 to 90 percent and specificities between 29 and 97 percent (Conde-Agudelo, 2014).

Poon and colleagues (2008) likewise found unacceptable sensitivity and specificity for urine albumin:creatinine ratios.

Endothelial Dysfunction and Oxidant Stress

Endothelial activation and inflammation are major participants in the pathophysiology of the preeclampsia syndrome. As a result, compounds such as those are found in circulating blood of affected women, and some have been assessed for their predictive value.

Fibronectins

These high-molecular-weight glycoproteins are released from endothelial cells and extracellular matrix following endothelial injury **(Chavarria et al., 2002).** More than 30 years ago, plasma concentrations were reported to be elevated in women with preeclampsia. Following their systematic review, however, **Leeflang and associates (2007)** concluded that neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia.

Coagulation Activation

Thrombocytopenia and platelet dysfunction are integral features of preeclampsia. Platelet activation causes increased destruction and decreased concentrations, and mean platelet volume rises because of platelet immaturity. Although markers of coagulation activation are increased, the substantive overlap with levels in normotensive pregnant women stultifies their predictive value **(Kenny et al., 2014).**

Oxidative Stress

Increased levels of lipid peroxides coupled with decreased antioxidant activity have raised the possibility that markers of oxidative stress might predict preeclampsia. For example, malondialdehyde is a marker of lipid peroxidation. Other markers are various prooxidants or their potentiators.

These include iron, transferrin, and ferritin; blood lipids, including triglycerides, free fatty acids, and lipoproteins; and antioxidants such as ascorbic acid and vitamin E **(Powers et al., 2000; Bainbridge et al., 2005; Mackay et al., 2012).** These have not been found to be predictive, and treatment to prevent preeclampsia with some of them has been studied **(Conde-Agudelo et al., 2014).**

Hyperhomocysteinemia causes oxidative stress and endothelial cell dysfunction and is characteristic of preeclampsia. Although women with elevated serum homocysteine levels at mid-pregnancy had a three- to fourfold risk of preeclampsia, these tests have not been shown to be clinically useful predictors **(Zeeman et al., 2003; D'Anna et al., 2004; Mignini et al., 2005).**

Angiogenic Factors

Evidence has accrued that an imbalance between proangiogenic and antiangiogenic factors is related to preeclampsia pathogenesis. Serum levels of some proangiogenic factors—vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)—begin to decrease before clinical preeclampsia develops. And, recall as shown in **Figure 4** that at the same time levels of some antiangiogenic factors such as sFlt-1 and sEng become increased **(Maynard et al., 2008).** In one study, these abnormalities were identified coincidentally with rising uterine artery Doppler resistance **(Coolman et al., 2012).**

Conde-Agudelo and colleagues (2014) reviewed the predictive accuracy of some of these factors for severe preeclampsia. Sensitivities for all cases of preeclampsia ranged from 30 to 50 percent, and specificity was about 90 percent. Their predictive accuracy was higher for early-onset preeclampsia. These preliminary results suggest a clinical role for preeclampsia prediction.

However, until this role is better substantiated, their general clinical use is not currently recommended **(Boucoiran et al., 2013; Kleinrouweler et al., 2012; Widmer et al., 2007).** Automated assays are being studied, and the World Health Organization (WHO) began a multicenter trial in 2008 to evaluate these factors **(Sunderji et al., 2009).**

Cell-Free Fetal DNA

Cell-free fetal DNA can be detected in maternal plasma. It has been reported that fetal-maternal cell trafficking is increased in pregnancies complicated by preeclampsia. It is hypothesized that cell-free DNA is released by accelerated apoptosis of cytotrophoblasts. From their review, **Conde-Agudelo and associates (2014)** concluded that cell-free fetal DNA quantification is not yet useful for prediction purposes.

Proteomic, Metabolomic, and Transcriptomic Markers

Methods to study serum and urinary proteins and cellular metabolites have opened a new vista for preeclampsia prediction. Preliminary studies indicate that these may become useful **(Bahado-Singh et al., 2013; Carty et al., 2011; Liu et al., 2013; Myers et al., 2013).**

PREVENTION

Various strategies used to prevent or modify preeclampsia severity have been evaluated. Some are listed in **Table VI.** In general, none of these has been found to be convincingly and reproducibly effective.

TABLE VI. Some Methods to Prevent Preeclampsia That Have Been Evaluated in Randomized Trials:

Dietary manipulation—	Calcium or fish oil	Low-salt diet

	supplementation		
Exercise—	Stretching	Increase physical activity	
Cardiovascular drugs—	Anti-hypertensive drugs	Diuretics	
Anti-oxidants—	α-tocopherol (vitamin E)	Vitamin D	Ascorbic acid (vitamin C)
Anti-thrombotic drugs—low-dose aspirin	Aspirin/dipyridamole	Aspirin + heparin	Aspirin + ketanserin

Modified from ***Staff et al. 2014.***

Dietary and Lifestyle Modifications

A favorite of many theorists and faddists for centuries, dietary "treatment" for preeclampsia has produced some interesting abuses as chronicled by **Chesley (1978).** Low-Salt Diet. One of the earliest research efforts to prevent preeclampsia was salt restriction **(De Snoo et al., 1937).** This interdiction was followed by years of inappropriate diuretic therapy. Although these practices were discarded, it ironically was not until relatively recently that the first randomized trial was done and showed that a sodium-restricted diet was ineffective in preventing preeclampsia in 361 women **(Knuist et al., 1998).** Guidelines from the **United Kingdom National Institute for Health and Clinical Excellence (2010)** recommend against salt restrictions.

Calcium Supplementation

Studies performed in the 1980s outside the United States showed that women with low dietary calcium intake were at significantly increased risk for gestational hypertension. Calcium supplementation has been studied in several trials, including one by the National Institute of Child Health and Human Development (NICHD) that included more than 4500 nulliparous women **(Levine et al., 1997).** In one recent meta-

analysis, **Patrelli and coworkers (2012)** reported that increased calcium intake lowered the risk for preeclampsia in high-risk women. In aggregate, most of these trials have shown that unless women are calcium deficient, supplementation has no salutary effects **(Staff et al., 2014).**

Fish Oil Supplementation

Cardioprotective fatty acids found in some fatty fishes are plentiful in diets of Scandinavians and American Eskimos. The most common dietary sources are EPA—eicosapentaenoic acid, ALA—alpha-linoleic acid, and DHA—docosahexaenoic acid. With proclamations that supplementation with these fatty acids would prevent inflammatory-mediated atherogenesis, it was not a quantum leap to posit that they might also prevent preeclampsia. Unfortunately, randomized trials conducted thus far have shown no such benefits **(Olsen et al., 2000; Makrides et al., 2006; Olafsdottir et al., 2006; Zhou et al., 2012a).**

Exercise

There are a few studies done to assess the protective effects of physical activity on preeclampsia. In their systematic review, **Kasawara and associates (2012)** reported a trend toward risk reduction with exercise. More research is needed in this area **(Staff et al., 2014).**

Anti-hypertensive Drugs

Because of the putative effects of sodium restriction, diuretic therapy became popular with the introduction of chlorothiazide. In their meta-analysis, **Churchill and colleagues (2007)** summarized nine randomized trials that included more than 7000 pregnancies. They found that women given diuretics had a decreased incidence of edema and hypertension but not of preeclampsia. Because women with chronic hypertension are at high risk for preeclampsia, several randomized trials—only a few placebo-controlled—have been done to evaluate various antihypertensive drugs to reduce the incidence of

superimposed preeclampsia. A critical analysis of these trials by **Staff and coworkers (2014)** failed to demonstrate salutary effects.

Anti-oxidants

There are inferential data that an imbalance between oxidant and antioxidant activity may play an important role in the pathogenesis of preeclampsia. Thus, naturally occurring antioxidants—vitamins C, D, and E—might decrease such oxidation. Indeed, women who developed preeclampsia were found to have reduced plasma levels of these antioxidants **(Raijmakers et al., 2004; De-Regil et al., 2012).**

There have now been several randomized studies to evaluate vitamin supplementation for women at high risk for preeclampsia **(Poston et al., 2006; Rumbold et al., 2006; Villar et al., 2007).** The one by the MFMU Network included almost 10,000 low-risk nulliparas **(Roberts et al., 2009).** None of these studies showed reduced preeclampsia rates in women given vitamins C and E compared with those given placebo. The recent meta-analysis by **De-Regil and colleagues (2012)** likewise showed no benefits of vitamin D supplementation.

The rationale for the use of statins to prevent preeclampsia is that they stimulate hemoxygenase-1 expression that inhibits sFlt-1 release. There are preliminary animal data that statins may prevent hypertensive disorders of pregnancy. The MFMU Network plans a randomized trial to test pravastatin for this purpose **(Costantine et al., 2013).**

Anti-thrombotic Agents

There are sound theoretical reasons that antithrombotic agents might reduce the incidence of preeclampsia. The syndrome is characterized by vasospasm, endothelial cell dysfunction, and inflammation, as well as activation of platelets and the coagulation-hemostasis system. Moreover, prostaglandin imbalance(s) may be operative, and other sequelae include placental infarction and spiral artery thrombosis **(Nelson et al., 2014).**

Low-Dose Aspirin

In oral doses of 50 to 150 mg daily, aspirin effectively inhibits platelet thromboxane A2 biosynthesis but has minimal effects on vascular prostacyclin production. However, clinical trials have shown limited benefits. For example, results in **Table VII** are from the MFMU Network, and none of the outcomes shown were significantly improved. Some reports are more favorable. For example, the Paris Collaborative Group performed a meta-analysis that included 31 randomized trials involving 32,217 women **(Askie et al., 2007).**

For women assigned to receive anti-platelet agents, the relative risk for development of preeclampsia, superimposed preeclampsia, preterm delivery, or any adverse pregnancy outcome was significantly decreased by 10 percent. Another review and meta-analysis reported marginal benefits for low-dose aspirin and severe preeclampsia **(Roberge et al., 2012).**

A recent small Finnish multicenter trial included 152 women at high risk for preeclampsia **(Villa et al., 2013).** Although there were no benefits to low-dose aspirin, the accompanying meta-analysis reported a lowering of risk. **The 2013 Task Force** recommended the use of low-dose aspirin in some high-risk women to prevent preeclampsia.

TABLE VII. Maternal-Fetal Medicine Units Network Trial of Low-Dose Aspirin in Women at High Risk for Preeclampsia:

Risk Factors	No.	Preeclampsia (%)[a] Aspirin	Placebo
Normotensive, no proteinuria	1613	14.5	17.7
Proteinuria plus hypertension	119	31.7	22.0
Proteinuria only	48	25.0	33.3
Hypertension only	723	24.8	25.0
Insulin-dependent diabetes	462	18.3	21.6
Chronic hypertension	763	26.0	24.6
Multifetal gestation	678	11.5	15.9
Previous preeclampsia	600	16.7	19.0

[a]No statistically significant difference for any comparison between groups.
Data from Caritis, 1998.

Low-Dose Aspirin plus Heparin

In women with lupus anticoagulant, treatment with low-dose aspirin and heparin mitigates thrombotic sequelae. Because of the high prevalence of placental thrombotic lesions found with severe preeclampsia, observational trials have been done to evaluate such treatments for affected women **(Staff et al., 2014).**

Sergis and associates (2006) reviewed effects of prophylaxis with low-molecular-weight heparin plus low-dose aspirin on pregnancy outcomes in women with a history of severe early-onset preeclampsia and low-birth weight neonates. They reported better pregnancy outcomes in women given low-molecular-weight heparin plus low-dose aspirin compared with those given low-dose aspirin alone. Similar findings were reported in a trial that included 139 women with thrombophilia and a history of early-onset preeclampsia **(de Vries et al., 2012).** Despite these small trials, evidence is insufficient to recommend these regimens to prevent preeclampsia **(National Institute for Health and Clinical Excellence, 2010).**

MANAGEMENT

Pregnancy complicated by gestational hypertension is managed based on severity, gestational age, and presence of preeclampsia. With preeclampsia, management varies with the severity of endothelial cell injury and multi-organ dysfunction. Preeclampsia cannot always be diagnosed definitively. Thus, the **Task Force of the American College of Obstetricians and Gynecologists (2013b)** recommends more frequent prenatal visits if preeclampsia is "suspected." Increases in systolic and diastolic blood pressure can be either normal physiological changes or signs of developing pathology. Increased surveillance permits more prompt recognition of ominous changes in blood pressure, critical laboratory findings, and clinical signs and symptoms.

The basic management objectives for any pregnancy complicated by preeclampsia are: (1) termination of pregnancy with the least possible trauma to mother and fetus, (2) birth of an infant who subsequently thrives, and (3) complete restoration of health to the mother. In many women with preeclampsia, especially those at or near term, all three objectives are served equally well by induction of labor. One of the most important clinical questions for successful management is precise knowledge of fetal age **(Macdonald-Wallis et al., 2012).**

Early Diagnosis of Preeclampsia

Traditionally, the frequency of prenatal visits is increased during the third trimester, and this aids early detection of preeclampsia. Women without overt hypertension, but in whom early developing preeclampsia is suspected during routine prenatal visits, are seen more frequently. The protocol used successfully for many years at Parkland Hospital for women with new-onset diastolic blood pressures > 80 mm Hg but < 90 mm Hg or with sudden abnormal weight gain of more than 2 pounds per week includes, at minimum, return visits at 7-day intervals. Outpatient surveillance is continued unless overt hypertension, proteinuria, headache, visual disturbances, or epigastric discomfort supervene. Women with overt new-onset hypertension—either diastolic pressures ≥ 90 mm Hg or systolic pressures ≥ 140 mm Hg—are admitted to determine if the increase is due to preeclampsia, and if so, to evaluate its severity. Women with persistent severe disease are generally delivered. Conversely, women with

apparently mild disease can often be managed as outpatients, although there should be a low threshold for continued hospitalization for the nullipara, especially if there is proteinuria **(Conde-Agudelo et al., 2014).**

Evaluation

Hospitalization is considered at least initially for women with new-onset hypertension, especially if there is persistent or worsening hypertension or development of proteinuria. A systematic evaluation is instituted to include the following **(Macdonald-Wallis et al., 2012):**

- Detailed examination, which is followed by daily scrutiny for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain
- Weight determined daily.
- Analysis for proteinuria or urine protein: creatinine ratio on admittance and at least every 2 days thereafter.
- Blood pressure readings in the sitting position with an appropriate-size cuff every 4 hours, except between 2400 and 0600 unless previous readings had become elevated **(Cnossen et al., 2006).**
- Measurements of plasma or serum creatinine and hepatic aminotransferase levels and a hemogram that includes platelet quantification. The frequency of testing is determined by hypertension severity. Some recommend measurement of serum uric acid and lactic acid dehydrogenase levels and coagulation studies. However, the value of these tests has been called into question **(Thangaratinam et al., 2006).**
- Evaluation of fetal size and well-being and amnionic fluid volume, with either physical examination or sonography **(Conde-Agudelo et al., 2014).**

Goals of management include early identification of worsening preeclampsia and development of a management plan for timely delivery. If any of these observations lead to a diagnosis of severe preeclampsia as previously defined by the criteria in **Table II,** further management is subsequently described. Reduced physical activity throughout

much of the day is likely beneficial, but as the **2013 Task Force** concluded, absolute bed rest is not desirable. Ample protein and calories should be included in the diet, and sodium and fluid intake should not be limited or forced. Further management depends on: (1) preeclampsia severity, (2) gestational age, and (3) condition of the cervix. Fortunately, many cases are sufficiently mild and near enough to term that they can be managed conservatively until labor commences spontaneously or until the cervix becomes favorable for labor induction. Complete abatement of all signs and symptoms, however, is uncommon until after delivery. Almost certainly, the underlying disease persists until delivery is accomplished **(Conde-Agudelo et al., 2014).**

Consideration for Delivery

Termination of pregnancy is the only cure for preeclampsia. Headache, visual disturbances, or epigastric pain are indicative that convulsions may be imminent, and oliguria is another ominous sign. Severe preeclampsia demands anticonvulsant and frequently antihypertensive therapy, followed by delivery. Treatment is identical to that described subsequently for eclampsia. The prime objectives are to forestall convulsions, to prevent intracranial hemorrhage and serious damage to other vital organs, and to deliver a healthy newborn. When the fetus is preterm, the tendency is to temporize in the hope that a few more weeks in utero will reduce the risk of neonatal death or serious morbidity from prematurity. Such a policy certainly is justified in milder cases. Assessments of fetal well-being and placental function are performed, especially when the fetus is immature. Most recommend frequent performance of various tests to assess fetal well-being as described by the **American College of Obstetricians and Gynecologists (2012a).** These include the nonstress test or the biophysical profile. Measurement of the lecithin-sphingomyelin (L/S) ratio in amnionic fluid may provide evidence of lung maturity.

With moderate or severe preeclampsia that does not improve after hospitalization, delivery is usually advisable for the welfare of both mother and fetus. This is true even when the cervix is unfavorable **(Tajik et al., 2012).**

Labor induction is carried out, usually with preinduction cervical ripening from a prostaglandin or osmotic dilator. Whenever it appears that induction almost certainly will not succeed or attempts have failed, then cesarean delivery is indicated. For a woman near term, with a soft, partially effaced cervix, even milder degrees of preeclampsia probably carry more risk to the mother and her fetus-infant than does induction of labor **(Tajik et al., 2012).**

The decision to deliver late-preterm fetuses is not clear. **Barton and coworkers (2009)** reported excessive neonatal morbidity in women delivered before 38 weeks despite having stable, mild, non-proteinuric hypertension. The Netherlands study of 4316 newborns delivered between 340/7 and 366/7 weeks also described substantive neonatal morbidity in these cases **(Langenveld et al., 2011).** Most of these deliveries were before 36 weeks, and the higher cesarean delivery rates were associated with more respiratory complications. Conversely, one randomized trial of 756 women with mild preeclampsia supported delivery after 37 weeks **(Koopmans et al., 2009).**

Elective Cesarean Delivery

Once severe preeclampsia is diagnosed, labor induction and vaginal delivery have traditionally been considered ideal. Temporization with an immature fetus is considered subsequently. Several concerns, including an unfavorable cervix, a perceived sense of urgency because of preeclampsia severity, and a need to coordinate neonatal intensive care, have led some to advocate cesarean delivery. **Alexander and colleagues (1999)** reviewed 278 singleton liveborn neonates weighing 750 to 1500 g delivered of women with severe preeclampsia at Parkland Hospital. In half of the women, labor was induced, and the remainder underwent cesarean delivery without labor. Induction was successful in accomplishing vaginal delivery in a third, and it was not harmful to the very- low-

birthweight infants. **Alanis and associates (2008)** reported similar observations. The results of a systematic review also confirmed these conclusions **(Le Ray et al., 2009).**

Hospitalization versus Outpatient Management

For women with mild to moderate stable hypertension—whether or not preeclampsia has been confirmed—surveillance is continued in the hospital, at home for some reliable patients, or in a day-care unit. At least intuitively, reduced physical activity throughout much of the day seems beneficial.

Several observational studies and randomized trials have addressed the benefits of inpatient care and outpatient management. Somewhat related, **Abenhaim and coworkers (2008)** reported a retrospective cohort study of 677 non-hypertensive women hospitalized for bed rest because of threatened preterm delivery. When outcomes of these women were compared with those of the general obstetrical population, bed rest was associated with a significantly reduced relative risk—RR 0.27—of developing preeclampsia.

In a review of two small randomized trials totaling 106 women at high risk for preeclampsia, prophylactic bed rest for 4 to 6 hours daily at home was successful in significantly lowering the incidence of preeclampsia but not gestational hypertension **(Meher et al., 2006).**

These and other observations support the claim that restricted activity alters the underlying pathophysiology of the preeclampsia syndrome. That said, complete bed rest is not recommended by the **2013 Task Force.** First, this is pragmatically unachievable because of the severe restrictions it places on otherwise well women. Also, it likely also predisposes to thromboembolism **(Knight et al., 2007).**

High-Risk Pregnancy Unit

Most hospitalized women have a beneficial response characterized by amelioration or improvement of hypertension. These women are not “cured,” and nearly 90 percent have recurrent hypertension before or during labor. By 2013, more than

10,000 nulliparas with mild to moderate early-onset hypertension during pregnancy had been managed successfully in this unit. Provider costs—not charges—for this relatively simple physical facility, modest nursing care, no drugs other than iron and folate supplements, and few essential laboratory tests are minimal compared with the cost of neonatal intensive care for a preterm infant. None of these women have suffered thromboembolic disease.

Home Health Care

Many clinicians believe that further hospitalization is not warranted if hypertension abates within a few days, and this has legitimized third-party payers to deny hospitalization reimbursement. Consequently, many women with mild to moderate hypertension are managed at home. Outpatient management may continue as long as preeclampsia syndrome does not worsen and fetal jeopardy is not suspected. Sedentary activity throughout the greater part of the day is recommended. These women are instructed in detail to report symptoms. Home blood pressure and urine protein monitoring or frequent evaluations by a visiting nurse may prove beneficial. Caution is exercised regarding use of certain automated home blood pressure monitors **(Lo et al., 2002; Ostchega et al., 2012).**

In an observational study by **Barton and associates (2002),** 1182 nulliparas with mild gestational hypertension—20 percent had proteinuria—were managed with home health care. Their mean gestational ages were 32 to 33 weeks at enrollment and 36 to 37 weeks at delivery. Severe preeclampsia developed in approximately 20 percent, about 3 percent developed HELLP syndrome, and two women had eclampsia. Perinatal outcomes were generally good. In approximately 20 percent, there was fetal-growth restriction, and the perinatal mortality rate was 4.2 per 1000.

Several prospective studies have been designed to compare continued hospitalization with either home health care or a day-care unit. In a pilot study from Parkland Hospital, **Horsager and colleagues (1995)** randomly assigned 72 nulliparas with new-onset hypertension from 27 to 37 weeks either to continued hospitalization or

to outpatient care. In all of these women, proteinuria had receded to less than 500 mg per day when they were randomized. Outpatient management included daily blood pressure monitoring by the patient or her family. Weight and dipstick spot urine protein determinations were evaluated three times weekly.

A home health nurse visited twice weekly, and the women were seen weekly in the clinic. Perinatal outcomes were similar in each group. The only significant difference was that women in the home care group developed severe preeclampsia significantly more frequently than hospitalized women—42 versus 25 percent. A larger randomized trial reported by **Crowther and coworkers (1992)** included 218 women with mild gestational non-proteinuric hypertension. After evaluation, half remained hospitalized, whereas the other half was managed as outpatients. As shown in **Table VIII,** the mean duration of hospitalization was 22.2 days for women with inpatient management compared with only 6.5 days in the home-care group. Preterm delivery before 34 and before 37 weeks was increased twofold in the outpatient group, but maternal and infant outcomes otherwise were similar.

TABLE VIII. Randomized Clinical Trials Comparing Hospitalization versus Routine Care for Women with Mild Gestational Hypertension or Preeclampsia:

	Maternal Characteristics—Admission					Maternal Characteristics—Delivery				Perinatal Outcomes		
Study Groups	No.	$Para_0$ (%)	Chronic HTN (%)	EGA (wk)	Prot (%)	EGA (wk)	< 37 wk (%)	< 34 wk (%)	Mean Hosp (d)	Mean BW (g)	SGA (%)	PMR (%)
Crowther (1992)	218[a]											
Hospitalization	110	13	14	35.3	0	38.3	12	1.8	22.2	3080	14	0
Outpatient	108	13	17	34.6	0	38.2	22	3.7	6.5	3060	14	0
Tuffnell (1992)	54											
Day Unit	24	57	23	36	0	39.8	—	—	1.1	3320	—	0
Usual Care	30	54	21	36.5	21	39	—	—	5.1	3340	—	0
Turnbull (2004)	374[b]											
Hospitalization	125	63	0	35.9	22	39	—	—	8.5	3330	3.8	0
Day Unit	249	62	0	36.2	22	39.7	—	—	7.2	3300	2.3	0

[a]Excluded women with proteinuria at study entry.
[b]Included women with ≤ 1+ proteinuria.
BW = birthweight; EGA = estimated gestational age; HTN = hypertension; $Para_0$ = nulliparas; PMR = perinatal mortality rate; Prot = proteinuria; SGA = small for gestational age.

Another approach, popular in European countries, is day care **(Milne et al., 2009).** This approach has been evaluated by several investigators. In the study by **Tuffnell and associates (1992),** 54 women with hypertension after 26 weeks' gestation were assigned to either day care or routine outpatient management **(Table VIII).** Progression to overt preeclampsia and labor inductions were significantly increased in the routine management group. **Turnbull and coworkers (2004)** enrolled 395 women who were randomly assigned to either day care or inpatient management **(Table VIII).** Almost 95 percent had mild to moderate hypertension. Of enrolled women, 288 were without proteinuria, and 86 had ≥ 1+ proteinuria. There were no perinatal deaths, and none of the women developed eclampsia or HELLP syndrome. Surprisingly, costs for either scheme were not significantly different. Perhaps not surprisingly, general satisfaction favored day care.

Anti-hypertensive Therapy for Mild to Moderate Hypertension

The use of antihypertensive drugs in attempts to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various types and severities of hypertensive disorders has been of considerable interest. Drug treatment for early mild preeclampsia has been disappointing as shown in representative randomized trials listed in **Table IX. Sibai and colleagues (1987a)** evaluated the effectiveness of labetalol and hospitalization compared with hospitalization alone in 200 nulliparas with gestational hypertension from 26 to 35 weeks' gestation. Although women given labetalol had significantly lower mean blood pressures, there were no differences between the groups in terms of mean pregnancy prolongation, gestational age at delivery, or birthweight. The cesarean delivery rates were similar, as were the number of infants admitted to special-care nurseries. The frequency of growth-restricted infants was doubled in women given labetalol—19 versus 9 percent.

The three other studies listed in **Table IX** were performed to compare labetalol or the calcium-channel blockers, nifedipine and isradipine, with placebo. Except for fewer

episodes of severe hypertension, none of these studies showed any benefits of antihypertensive treatment. Moreover, there may have been treatment-induced adverse fetal growth **(Von Dadelszen et al., 2002).**

TABLE IX. Randomized Placebo-Controlled Trials of Antihypertensive Therapy for Early Mild Gestational Hypertension:

Study	Study Drug (No.)	Pregnancy Prolonged (d)	Severe HTN[a] (%)	Cesarean Delivery (%)	Placental Abruption (%)	Mean Birthweight (g)	Growth Restriction (%)	Neonatal Deaths (No.)
Sibai (1987a)[a] 200 inpatients	Labetalol (100)	21.3	5	36	2	2205	19[c]	1
	Placebo (100)	20.1	15[c]	32	0	2260	9	0
Sibai (1992)[b] 200 outpatients	Nifedipine (100)	22.3	9	43	3	2405	8	0
	Placebo (100)	22.5	18[c]	35	2	2510	4	0
Pickles (1992) 144 outpatients	Labetalol (70)	26.6	9	24	NS	NS	NS	NS
	Placebo (74)	23.1	10	26	NS	NS	NS	NS
Wide-Swensson (1995) 111 outpatients	Isradipine (54)	23.1	22	26	NS	NS	NS	0
	Placebo (57)	29.8	29	19	NS	NS	NS	0

[a]All women had preeclampsia.
[b]Includes postpartum hypertension.
[c]$p < .05$ when study drug compared with placebo.
HTN = hypertension; NS = not stated.

Abalos and associates (2007) reviewed 46 randomized trials of active antihypertensive therapy compared with either no treatment or placebo given to women with mild to moderate gestational hypertension. Except for a halving of the risk for developing severe hypertension, active antihypertensive therapy had no beneficial effects. They further reported that fetal-growth restriction was not increased in treated women. In this vein, it is also controversial whether β-blocking agents cause fetal-growth restriction

if given for chronic hypertension. Thus, any salutary or adverse effects of antihypertensive therapy seem minimal at most **(August et al., 2014; Umans et al., 2014).**

Delayed Delivery

Up through the early 1990s, it was the practice that all women with severe preeclampsia were delivered without delay. During the past 25 years, however, another approach for women with preterm severe preeclampsia has been advocated. This approach calls for "conservative" or "expectant" management with the aim of improving neonatal outcome without compromising maternal safety. Aspects of such management always include careful daily—and usually more frequent—inpatient monitoring of the mother and her fetus.

Expectant Management of Preterm Severe Preeclampsia

Theoretically, antihypertensive therapy has potential application when severe preeclampsia develops before intact neonatal survival is likely. Such management is controversial, and it may be dangerous. In one of the first studies, **Sibai and the Memphis group (1985)** attempted to prolong pregnancy because of fetal immaturity in 60 women with severe preeclampsia between 18 and 27 weeks. The results were disastrous.

The perinatal mortality rate was 87 percent. Although no mothers died, 13 suffered placental abruption, 10 had eclampsia, three developed renal failure, two had hypertensive encephalopathy, and one each had an intracerebral hemorrhage and a ruptured hepatic hematoma. Because of these catastrophic outcomes, the Memphis group redefined their study criteria and performed a randomized trial of expectant versus aggressive management for 95 women who had severe preeclampsia but with more advanced gestations of 28 to 32 weeks **(Sibai et al., 1994).**

Women with HELLP syndrome were excluded from this trial. Aggressive management included glucocorticoid administration for fetal lung maturation followed by

delivery in 48 hours. Expectantly managed women were observed at bed rest and given either labetalol or nifedipine orally if there was severe hypertension. In this study, pregnancy was prolonged for a mean of 15.4 days in the expectant management group. An overall improvement in neonatal outcomes was also reported. Following these experiences, expectant management became more commonly practiced, but with the caveat that women with HELLP syndrome or growth-restricted fetuses were usually excluded. But in a subsequent follow-up observational study, the Memphis group compared outcomes in 133 preeclamptic women with and 136 without HELLP syndrome who presented between 24 and 36 weeks **(Abramovici et al., 1999).**

Women were subdivided into three study groups. The first group included those with complete HELLP syndrome. The second group included women with partial HELLP syndrome—defined as either one or two but not all three of the defining laboratory findings. The third group included women who had severe preeclampsia without HELLP syndrome laboratory findings. Perinatal outcomes were similar in each group, and importantly, outcomes were not improved with procrastination. Despite this, the investigators concluded that women with partial HELLP syndrome and those with severe preeclampsia alone could be managed expectantly.

Sibai and Barton (2007b) reviewed expectant management of severe preeclampsia from 24 to 34 weeks. More than 1200 women were included, and although the average time gained ranged from 5 to 10 days, the maternal morbidity rates were formidable. As shown in **Table X,** serious complications in some of these and in later studies included placental abruption, HELLP syndrome, pulmonary edema, renal failure, and eclampsia. Moreover, perinatal mortality rates averaged 90 per 1000.

Fetal-growth restriction was common, and in the study from The Netherlands by **Ganzevoort and associates (2005a; 2005b),** it was an astounding 94 percent. Perinatal mortality rates are disproportionately high in these growth-restricted infants, but maternal outcomes were not appreciably different from pregnancies in women without growth-restricted fetuses **(Haddad et al., 2007; Shear et al., 2005).**

TABLE X. Maternal and Perinatal Outcomes Reported Since 2005 with Expectant Management of Severe Preeclampsia from 24 to 34 Weeks:

			Maternal Outcomes (%)					Perinatal Outcomes (%)	
Study	No.	Days Gained	Placental Abruption	HELLP	Pulm. Edema	ARF	Eclampsia	FGR	PMR
Oettle (2005)	131[a]	11.6	23	4.6	0.8	2.3	2.3	NS	13.8
Shear (2005)	155	5.3	5.8	27	3.9	NS	1.9	62	3.9
Ganzevoort (2005a, b)	216	11	1.8	18	3.6	NS	1.8	94	18
Sarsam (2008)	35	9.2	5.7	11	2.9	2.9	18	31	2.8
Bombrys (2009)	66	5	11	8	9	3	0	27	1.5
Abdel-Hady (2010)	211	12	3.3	7.6	0.9	6.6	0.9	NS	48
Vigil-De Gracia (2013)	131	10.3	7.6	14	1.5	4.5	0.8	22	8.7
Range	945	5–12	1.8–23	4.6–27	0.9–3.9	2.3–6.6	0.9–18	27–94	1.5–48

[a]Includes one maternal death.
ARF = acute renal failure; EGA = estimated gestational age; FGR = fetal-growth restriction; HELLP = hemolysis, elevated liver enzyme levels, low platelet count syndrome; NS = not stated; PMR = perinatal mortality rate; Pulm. = pulmonary.

The MEXPRE Latin Study was a multicenter trial that randomly assigned 267 women with severe preeclampsia at 28 to 32 weeks to prompt delivery or to expectant management **(Vigil-De Gracia et al., 2013).** The perinatal mortality rate approximated 9 percent in each group, and these investigators found no improvements in composite neonatal morbidity with expectant management. On the other hand, fetal-growth restriction—22 versus 9 percent—and placental abruption—7.6 versus 1.5 percent—were significantly higher in the group managed expectantly.

Barber and associates (2009) conducted a 10-year review of 3408 women with severe preeclampsia from 24 to 32 weeks. They found that increasing lengths of antepartum hospital stays were associated with slight but significantly increased rates of maternal and neonatal morbidity.

Expectant Management of Mid-trimester Severe Preeclampsia

Several small studies have focused on expectant management of severe preeclampsia syndrome before 28 weeks. In their review, **Bombrys and coworkers (2008)** found eight such studies that included nearly 200 women with severe preeclampsia with an onset < 26 completed weeks. Maternal complications were common.

Because there were no neonatal survivors in women presenting before 23 weeks, the **Task Force of the American College of Obstetricians and Gynecologists (2013b)** recommends pregnancy termination. For women with slightly more advanced pregnancies, however, the decision is less clear. For example, at 23 weeks' gestation, the perinatal survival rate was 18 percent, but long-term perinatal morbidity is yet unknown. For women with pregnancies at 24 to 26 weeks, perinatal survival approached 60 percent, and it averaged almost 90 percent for those at 26 weeks.

There have been at least five studies published since 2005 of women with severe mid-trimester preeclampsia who were managed expectantly. Maternal complications developed in 60 percent, and there was one death. Perinatal mortality was 65 percent. At this time, there are no comparative studies attesting to the perinatal benefits of such expectant treatment versus early delivery in the face of serious maternal complications that approach 50 percent **(Budden et al., 2006; Gaugler-Senden et al., 2006; Bombrys et al., 2008; Abdel-Hady et al., 2010; Belghiti et al., 2011).**

Glucocorticoids for Lung Maturation

In attempts to enhance fetal lung maturation, glucocorticoids have been administered to women with severe hypertension who are remote from term. Treatment does not seem to worsen maternal hypertension, and a decrease in the incidence of respiratory distress and improved fetal survival has been cited. That said, there is only one randomized trial of corticosteroids given to hypertensive women for fetal lung maturation. This trial, by **Amorim and colleagues (1999),** included 218 women with severe preeclampsia between 26 and 34 weeks who were randomly assigned to betamethasone or placebo administration. Neonatal complications, including respiratory

distress, intraventricular hemorrhage, and death, were decreased significantly when betamethasone was given compared with placebo. On the heavily weighted negative side, there were two maternal deaths and 18 stillbirths **(Bloom et al., 2003; Alexander et al., 2014).**

Corticosteroids to Ameliorate HELLP Syndrome

Almost 30 years ago, **Thiagarajah and associates (1984)** suggested that glucocorticoids might aid treatment of the laboratory abnormalities associated with HELLP syndrome.

Subsequently, **Tompkins and Thiagarajah (1999) and O'Brien et al. (2002)** and their colleagues reported less than salutary effects. **Martin and coworkers (2003)** reviewed observational outcomes of almost 500 such women treated at their institution and reported salutary results with treatment. Unfortunately, their subsequent randomized trial compared two corticosteroids and did not include a non-treated group **(Isler et al., 2001).**

Since these observational studies, at least two prospective randomized trials have addressed this question. **Fonseca and associates (2005)** randomly assigned 132 women with HELLP syndrome to either dexamethasone or placebo administration. Outcomes assessed included duration of hospitalization, recovery time of abnormal laboratory test results, resolution of clinical parameters, and complications that included acute renal failure, pulmonary edema, eclampsia, and death. None of these was significantly different between the two groups.

In another randomized study, **Katz and coworkers (2008)** assigned 105 postpartum women with HELLP syndrome to treatment with dexamethasone or placebo. They analyzed outcomes similar to the Fonseca study and found no advantage to dexamethasone. Shown in **Figure 17** are recovery times for platelet counts and serum aspartate aminotransferase (AST) levels. These times were almost identical in the two groups.

For these reasons, the **2013 Task Force** does not recommend corticosteroid treatment for thrombocytopenia with HELLP syndrome. A caveat is that in women with dangerously low platelet counts, corticosteroids might serve to increase platelets.

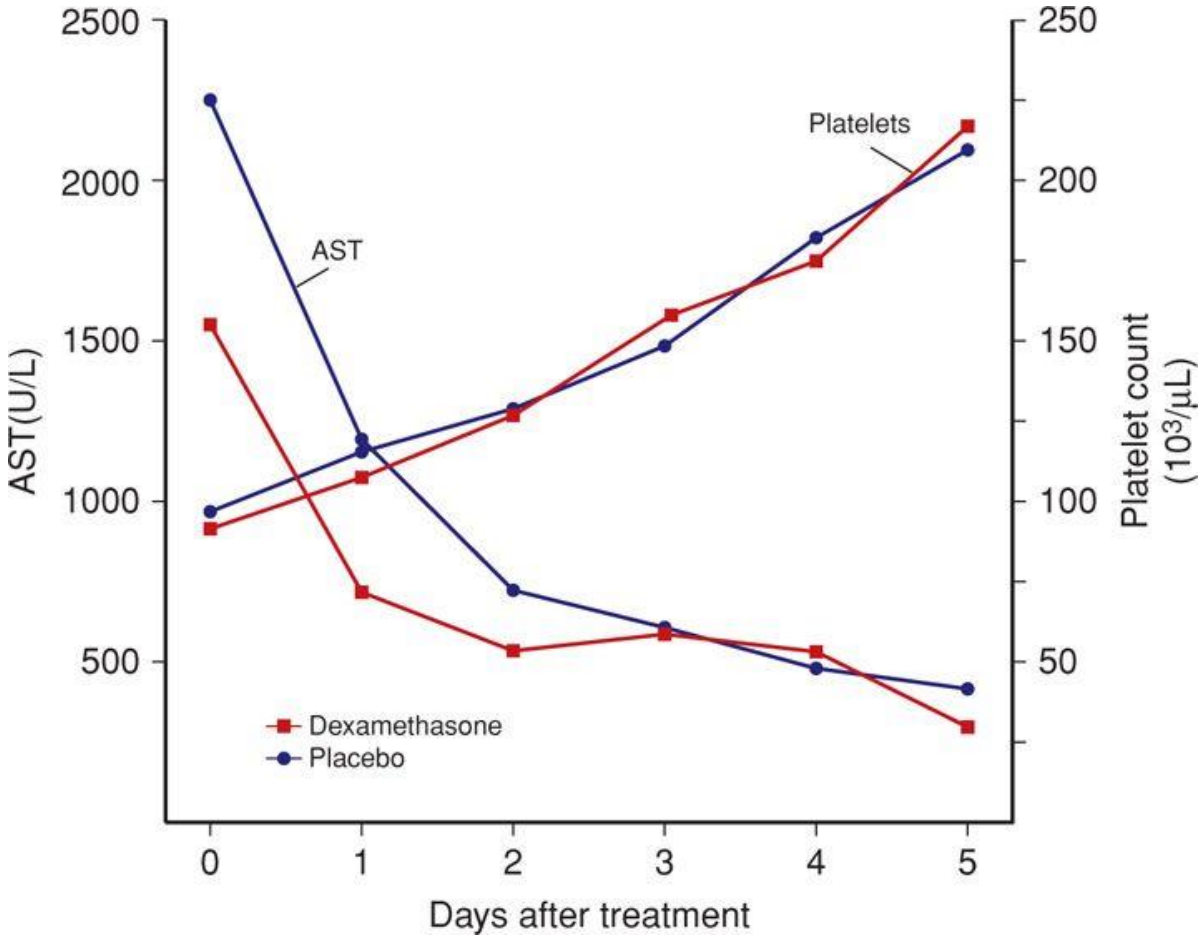

FIGURE 17. Recovery times for platelet counts and serum aspartate aminotransferase (AST) levels in women with HELLP syndrome assigned to receive treatment with dexamethasone or placebo (Data from Katz et al., 2008).

Expectant Management—Risks versus Benefits—Recommendations

These studies do not show overwhelming benefits compared with risks for expectant management of severe preeclampsia in those with gestations from 24 to 32 weeks. The **Society for Maternal-Fetal Medicine (2011)** has determined that such

management is a reasonable alternative in selected women with severe preeclampsia before 34 weeks **(Figure 18).**

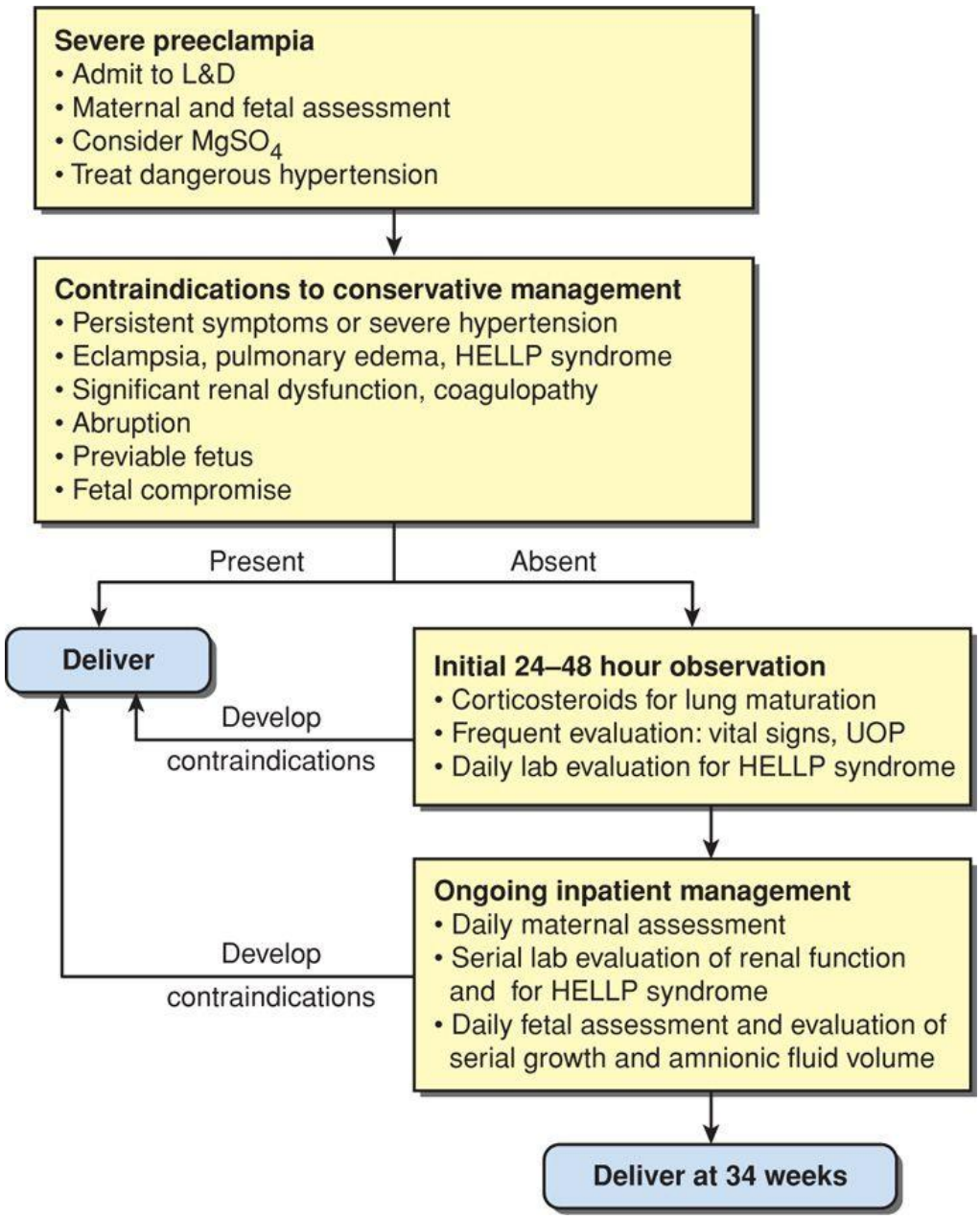

FIGURE 18. Schematic clinical management algorithm for suspected severe preeclampsia at < 34 weeks. HELLP = hemolysis, elevated liver enzyme levels, low platelet count; L&D = labor and delivery; MgSO4 = magnesium sulfate; UOP = urine output **(Adapted from the Society for Maternal-Fetal Medicine, 2011).**

The Task Force of the American College of Obstetricians and Gynecologists (2013b) supports this recommendation. As shown in **Figure 18,** such management calls for in-hospital maternal and fetal surveillance with delivery prompted by evidence for worsening severe preeclampsia or maternal or fetal compromise. Although attempts are made for vaginal delivery in most cases, the likelihood of cesarean delivery increases with decreasing gestational age.

Undoubtedly, the overriding reason to terminate pregnancies with severe preeclampsia is maternal safety. There are no data to suggest that expectant management is beneficial for the mother. Indeed, it seems obvious that a delay to prolong gestation in women with severe preeclampsia may have serious maternal consequences. Notably, placental abruption develops in up to 20 percent, and pulmonary edema in as many as 4 percent. Moreover, there are substantive risks for eclampsia, cerebrovascular hemorrhage, and especially maternal death. These observations are even more pertinent when considered with the absence of convincing evidence that perinatal outcomes are markedly improved by the average prolongation of pregnancy of about 1 week. If undertaken, the caveats that mandate delivery shown in **Table XI** should be strictly heeded.

ECLAMPSIA

Preeclampsia complicated by generalized tonic-clonic convulsions appreciably increases the risk to both mother and fetus. **Mattar and Sibai (2000)** described outcomes in 399 consecutive women with eclampsia from 1977 through 1998. Major maternal complications included placental abruption—10 percent, neurological deficits—7 percent, aspiration pneumonia—7 percent, pulmonary edema—5 percent, cardiopulmonary arrest—4 percent, and acute renal failure—4 percent. Moreover, 1 percent of these women died.

TABLE XI. Indications for Delivery in Women < 34 Weeks' Gestation Managed Expectantly:

Corticosteroid Therapy for Lung Maturation [a] and Delivery after Maternal

Stabilization:

Uncontrolled severe hypertension

Eclampsia

Pulmonary edema

Placental abruption

Disseminated intravascular coagulation

Non-reassuring fetal status

Fetal demise

Corticosteroid Therapy for Lung Maturation—Delay Delivery 48 hr If Possible:

Preterm ruptured membranes or labor

Thrombocytopenia < 100,000/μL

Hepatic transaminase levels twice upper limit of normal

Fetal-growth restriction

Oligohydramnios

Reversed end-diastolic Doppler flow in umbilical artery

Worsening renal dysfunction

[a] *Initial dose only, do not delay delivery.* ***From the Society for Maternal-Fetal Medicine, 2011, and the Task Force of the American College of Obstetricians and Gynecologists, 2013b.***

European maternity units also report excessive maternal and perinatal morbidity and mortality rates with eclampsia. In a report from Scandinavia, **Andersgaard and associates (2006)** described 232 women with eclampsia.

Although there was but a single maternal death, a third of the women experienced major complications that included HELLP syndrome, renal failure, pulmonary edema, pulmonary embolism, and stroke. The **United Kingdom Obstetric Surveillance System (UKOSS)** audit reported by **Knight (2007**) described no maternal deaths in 214 eclamptic women, but five women experienced cerebral hemorrhage.

In The Netherlands, there were three maternal deaths among 222 eclamptic women **(Zwart et al., 2008).** From Dublin, **Akkawi and coworkers (2009)** reported four maternal deaths among 247 eclamptic women **(Akkawi et al., 2009).** Data from Australia are similar **(Thornton et al., 2013).**

Thus, in developed countries, the maternal mortality rate approximates 1 percent in women with eclampsia. In perspective, this is a thousand-fold increase above the overall maternal death rates for these countries. Almost without exception—but at times unnoticed—preeclampsia precedes the onset of eclamptic convulsions. Depending on whether convulsions appear before, during, or after labor, eclampsia is designated as antepartum, intrapartum, or postpartum. Eclampsia is most common in the last trimester and becomes increasingly frequent as term approaches. In more recent years, the incidence of postpartum eclampsia has risen. This is presumably related to improved access to prenatal care, earlier detection of preeclampsia, and prophylactic use of magnesium sulfate **(Chames et al., 2002).**

Importantly, other diagnoses should be considered in women with convulsions more than 48 hours postpartum or in women with focal neurological deficits, prolonged coma, or atypical eclampsia **(Sibai et al., 2009; 2012).**

Immediate Management of Seizure

Eclamptic seizures may be violent, and the woman must be protected, especially her airway. So forceful are the muscular movements that the woman may throw herself out of her bed, and if not protected, her tongue is bitten by the violent action of the jaws. This phase, in which the muscles alternately contract and relax, may last approximately a minute. Gradually, the muscular movements become smaller and less frequent, and finally the woman lies motionless. After a seizure, the woman is postictal, but in some, a coma of variable duration ensues. When the convulsions are infrequent, the woman

usually recovers some degree of consciousness after each attack. As the woman arouses, a semiconscious combative state may ensue. In severe cases, coma persists from one convulsion to another, and death may result. In rare instances, a single convulsion may be followed by coma from which the woman may never emerge. As a rule, however, death does not occur until after frequent convulsions. Finally and also rarely, convulsions continue unabated—status epilepticus—and require deep sedation and even general anesthesia to obviate anoxic encephalopathy. Respirations after an eclamptic convulsion are usually increased in rate and may reach 50 or more per minute in response to hypercarbia, lactic acidemia, and transient hypoxia. Cyanosis may be observed in severe cases. High fever is a grave sign as it likely emanates from cerebrovascular hemorrhage **(Podymow et al., 2010).**

Proteinuria is usually, but not always, present. Urine output may be diminished appreciably, and occasionally anuria develops. There may be hemoglobinuria, but hemoglobinemia is observed rarely. Often, peripheral and facial edema is pronounced, but it may also be absent. As with severe preeclampsia, an increase in urinary output after delivery is usually an early sign of improvement. If there is renal dysfunction, serum creatinine levels should be monitored. Proteinuria and edema ordinarily disappear within a week postpartum. In most cases, blood pressure returns to normal within a few days to 2 weeks after delivery **(Berks et al., 2009).**

The longer hypertension persists postpartum and the more severe it is, the more likely it is that the woman also has chronic vascular disease **(Podymow et al., 2010).** In antepartum eclampsia, labor may begin spontaneously shortly after convulsions ensue and may progress rapidly. If the convulsions occur during labor, contractions may increase in frequency and intensity, and the duration of labor may be shortened. Because of maternal hypoxemia and lactic acidemia caused by convulsions, it is not unusual for fetal bradycardia to follow a seizure. Bradycardia usually recovers within 3 to 5 minutes. If it persists more than about 10 minutes, however, then another cause such as placental abruption or imminent delivery must be considered. Pulmonary edema may follow shortly after eclamptic convulsions or up to several hours later. This usually is caused by aspiration pneumonitis from gastric-content inhalation during vomiting that frequently

accompanies convulsions. In some women, pulmonary edema may be caused by ventricular failure from increased afterload that may result from severe hypertension and further aggravated by vigorous intravenous fluid administration **(Dennis et al., 2012b).**

Such pulmonary edema from ventricular failure is more common in morbidly obese women and in those with previously unappreciated chronic hypertension. Occasionally, sudden death occurs synchronously with an eclamptic convulsion, or it follows shortly thereafter. Most often in these cases, death results from a massive cerebral hemorrhage **(Figure 11).** Hemiplegia may result from sublethal hemorrhage. Cerebral hemorrhages are more likely in older women with underlying chronic hypertension. Rarely, they may be due to a ruptured cerebral berry aneurysm or arteriovenous malformation **(Witlin et al., 1997a).**

In approximately 10 percent of women, some degree of blindness follows a seizure. Blindness with severe preeclampsia without convulsions is usually due to retinal detachment **(Vigil-De Gracia et al., 2011).**

Conversely, blindness with eclampsia is almost always due to occipital lobe edema **(Cunningham et al., 1995).** In both instances, however, the prognosis for return to normal function is good and is usually complete within 1 to 2 weeks postpartum. Up to 5 percent of women with eclampsia have substantively altered consciousness, including persistent coma, following a seizure. This is due to extensive cerebral edema, and transtentorial herniation may cause death. Rarely, eclampsia is followed by psychosis, and the woman becomes violent. This may last for several days to 2 weeks, but the prognosis for return to normal function is good, provided there was no preexisting mental illness. It is presumed to be similar to postpartum psychosis. Antipsychotic medications have proved effective in the few cases of posteclampsia psychosis **(Cunningham et al., 2000).**

Differential Diagnosis

Generally, eclampsia is more likely to be diagnosed too frequently rather than overlooked. Epilepsy, encephalitis, meningitis, brain tumor, neurocysticercosis, amnionic

fluid embolism, postdural puncture cephalgia, and ruptured cerebral aneurysm during late pregnancy and the puerperium may simulate eclampsia. Until other such causes are excluded, however, all pregnant women with convulsions should be considered to have eclampsia **(Cunningham et al., 2000).**

Management of Eclampsia

It has been long recognized that magnesium sulfate is highly effective in preventing convulsions in women with preeclampsia and in stopping them in those with eclampsia. Most eclampsia old regimens used in the United States adhered to a similar philosophy still in use today, the tenets of which include the following **(Jana et al., 2013):**

1. Control of convulsions using an intravenously administered loading dose of magnesium sulfate that is followed by a maintenance dose, usually intravenous, of magnesium sulfate
2. Intermittent administration of an antihypertensive medication to lower blood pressure whenever it is considered dangerously high
3. Avoidance of diuretics unless there is obvious pulmonary edema, limitation of intravenous fluid administration unless fluid loss is excessive, and avoidance of hyperosmotic agents
4. Delivery of the fetus to achieve a remission of preeclampsia.

Magnesium Sulfate to Control Convulsions

In more severe cases of preeclampsia and in eclampsia, magnesium sulfate administered parenterally is an effective anticonvulsant that avoids producing central nervous system depression in either the mother or the infant. It may be given intravenously by continuous infusion or intramuscularly by intermittent injection **(Table XII).** The dosages for severe preeclampsia are the same as for eclampsia. Because labor and delivery is a more likely time for convulsions to develop, women with preeclampsia-eclampsia usually are given magnesium sulfate during labor and for 24 hours postpartum **(Salinger et al., 2013).**

Magnesium sulfate is almost universally administered intravenously. In most units, the intramuscular route has been abandoned. Of concern, magnesium sulfate solutions, although inexpensive to prepare, are not readily available in all parts of the developing world. And even when the solutions are available, the technology to infuse them may not be. It should not be overlooked that the drug can be administered intramuscularly and that this route is as effective as intravenous administration. In two reports from India, intramuscular regimens were nearly equivalent in preventing recurrent convulsions and maternal deaths in women with eclampsia **(Chowdhury et al., 2009).**

TABLE XII. Magnesium Sulfate Dosage Schedule for Severe Preeclampsia and Eclampsia:

Continuous Intravenous (IV) Infusion

Give 4- to 6-g loading dose of magnesium sulfate diluted in 100 mL of IV fluid administered over 15–20 min

Begin 2 g/hr in 100 mL of IV maintenance infusion. Some recommend 1 g/hr

Monitor for magnesium toxicity:

Assess deep tendon reflexes periodically

Some measure serum magnesium level at 4–6 hr and adjust infusion to maintain levels between 4 and 7 mEq/L (4.8 to 8.4 mg/dL)

Measure serum magnesium levels if serum creatinine ≥ 1.0 mg/dL

Magnesium sulfate is discontinued 24 hr after delivery

Intermittent Intramuscular Injections

Give 4 g of magnesium sulfate ($MgSO_4 \cdot 7H_2O$ USP) as a 20% solution intravenously at a rate not to exceed 1 g/min

Follow promptly with 10 g of 50% magnesium sulfate solution, one half (5 g) injected deeply in the upper outer quadrant of each buttock through a 3-inch-long 20-gauge needle. (Addition of 1.0 mL of 2% lidocaine minimizes discomfort.) If convulsions persist after 15 min, give up to 2 g more intravenously as a 20% solution at a rate not to exceed 1 g/min. If the woman is large, up to 4 g may be given slowly

Every 4 hr thereafter, give 5 g of a 50% solution of magnesium sulfate injected deeply in

the upper outer quadrant of alternate buttocks, but only after ensuring that:

The patellar reflex is present,

Respirations are not depressed, and

Urine output the previous 4 hr exceeded 100 mL

Magnesium sulfate is not given to treat hypertension. Based on several studies cited subsequently and extensive clinical observations, magnesium most likely exerts a specific anticonvulsant action on the cerebral cortex. Typically, the mother stops convulsing after the initial 4-g loading dose. By an hour or two, she regains consciousness sufficiently to be oriented to place and time. The magnesium sulfate dosages presented in **Table XII** usually result in plasma magnesium levels illustrated in **Figure 19.** When magnesium sulfate is given to arrest eclamptic seizures, 10 to 15 percent of women will have a subsequent convulsion. If so, an additional 2-g dose of magnesium sulfate in a 20-percent solution is slowly administered intravenously. In a small woman, this additional 2-g dose may be used once, but it can be given twice if needed in a larger woman. In only 5 of 245 women with eclampsia at Parkland Hospital was it necessary to use supplementary anticonvulsant medication to control convulsions **(Pritchard et al., 1984).** For these, an intravenous barbiturate is given slowly. Midazolam or lorazepam may be given in a small single dose, but prolonged use is avoided because it is associated with a higher mortality rate **(Royal College of Obstetricians and Gynecologists, 2006).**

Maintenance magnesium sulfate therapy is continued for 24 hours after delivery. For eclampsia that develops postpartum, magnesium sulfate is administered for 24 hours after the onset of convulsions. **Ehrenberg and Mercer (2006)** studied abbreviated postpartum magnesium administration in 200 women with mild preeclampsia. Of 101 women randomized to 12-hour treatment, seven had worsening preeclampsia, and treatment was extended to 24 hours. None of these 101 women and none of the other cohort of 95 given the 24-hour magnesium infusion developed eclampsia. This abbreviated regimen needs further study before being routinely administered for severe preeclampsia or eclampsia.

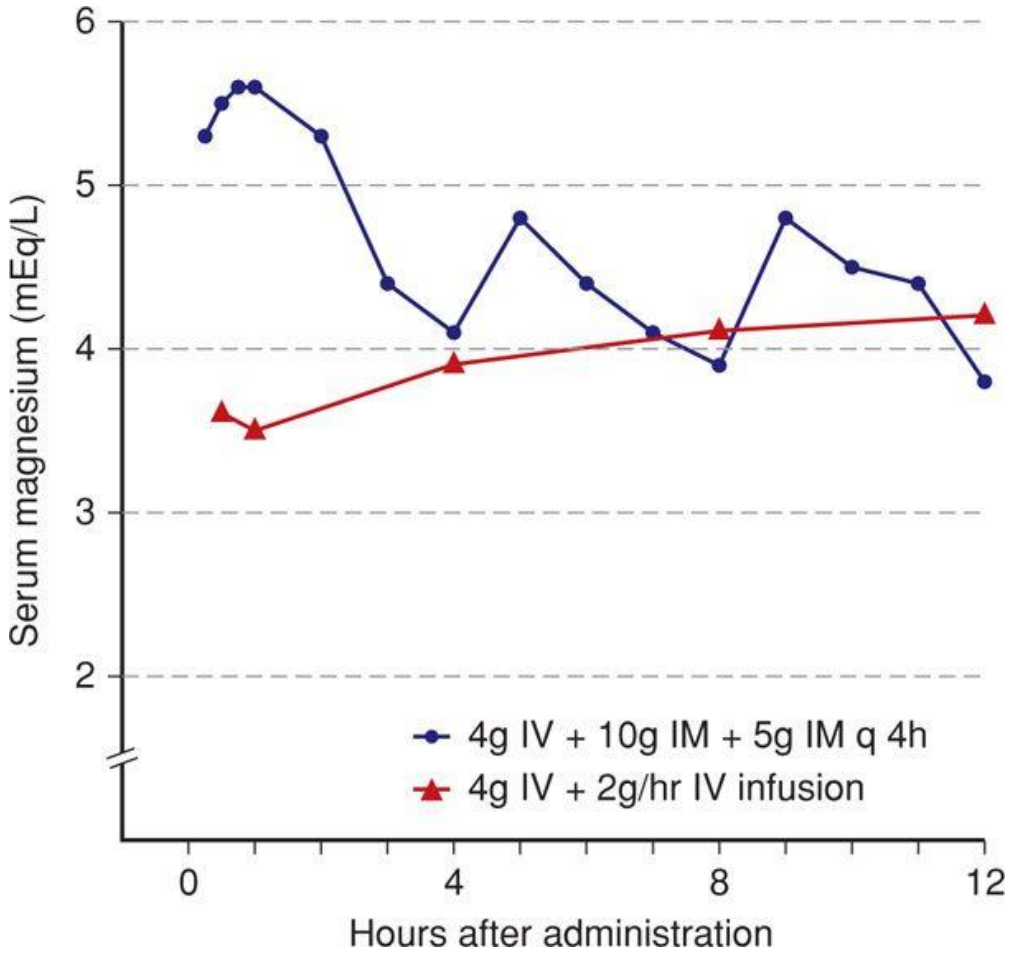

FIGURE 19. Comparison of serum magnesium levels in mEq/L following a 4-g intravenous loading dose of magnesium sulfate and then maintained by either an intramuscular or continuing infusion. Multiply by 1.2 to convert mEq/L to mg/dL **(Data from Sibai et al., 1984).**

Pharmacology and Toxicology

Magnesium sulfate USP is $MgSO_4 \cdot 7H_2O$ and not simple $MgSO_4$. It contains 8.12 mEq per 1 g. Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is unusual when the glomerular filtration rate is normal or only slightly decreased.

Adequate urine output usually correlates with preserved glomerular filtration rates. That said, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not, per se, predict renal function. Thus, serum creatinine levels must be measured to detect a decreased glomerular filtration rate. Eclamptic convulsions are almost always prevented or arrested by plasma magnesium levels maintained at 4 to 7 mEq/L, 4.8 to 8.4 mg/dL, or 2.0 to 3.5 mmol/L. Although laboratories typically report total magnesium levels, free or ionized magnesium is the active moiety for suppressing neuronal excitability. **Taber and associates (2002)** found poor correlation between total and ionized levels. Further studies are necessary to determine if either measurement provides a superior method for surveillance.

After a 4-g intravenous loading dose in nonobese women, magnesium levels observed with the intramuscular regimen and those observed with the maintenance infusion of 2 g/hr are similar **(Figure 19).** The obesity epidemic has affected these observations. **Tudela and colleagues (2013)** reported observations from Parkland Hospital with magnesium administration to obese women. More than 60 percent of women whose body mass index (BMI) exceeded 30 kg/m2 and who were receiving the 2-g/hr dose had subtherapeutic levels at 4 hours. Thus, 40 percent of obese women would require 3 g/hr to maintain effective plasma levels. That said, currently most do not recommend routine magnesium level measurements **(American College of Obstetricians and Gynecologists, 2013b).**

Patellar reflexes disappear when the plasma magnesium level reaches 10 mEq/L—about 12 mg/dL—presumably because of a curariform action. This sign serves to warn of impending magnesium toxicity. When plasma levels rise above 10 mEq/L, breathing becomes weakened. At 12 mEq/L or higher levels, respiratory paralysis and respiratory arrest follow (**Royal College of Obstetricians and Gynaecologists, 2006).**

Somjen and coworkers (1966) induced marked hypermagnesemia in themselves by intravenous infusion and achieved plasma levels up to 15 mEq/L. Predictably, at such high plasma levels, respiratory depression developed that necessitated mechanical

ventilation, but depression of the sensorium was not dramatic as long as hypoxia was prevented.

Treatment with calcium gluconate or calcium chloride, 1 g intravenously, along with withholding further magnesium sulfate, usually reverses mild to moderate respiratory depression. One of these agents should be readily available whenever magnesium is being infused. Unfortunately, the effects of intravenously administered calcium may be short-lived if there is a steady-state toxic level. For severe respiratory depression and arrest, prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium from high levels of magnesium are uncommon. It appears that cardiac dysfunction associated with magnesium is due to respiratory arrest and hypoxia. With appropriate ventilation, cardiac action is satisfactory even when plasma magnesium levels are exceedingly high **(Morisaki et al., 2000).**

Because magnesium is cleared almost exclusively by renal excretion, the dosages described will become excessive if glomerular filtration is substantially decreased. The initial 4-g loading dose of magnesium sulfate can be safely administered regardless of renal function. It is important to administer the standard loading dose and not to reduce it under the mistaken conception that diminished renal function requires it. This is because after distribution, a loading dose achieves the desired therapeutic level, and the infusion maintains the steady-state level. Thus, only the maintenance infusion rate should be altered with diminished glomerular filtration rate. Renal function is estimated by measuring plasma creatinine. Whenever plasma creatinine levels are > 1.0 mg/mL, serum magnesium levels are measured to guide the infusion rate. With severe renal dysfunction, only the loading dose of magnesium sulfate is required to produce a steady-state therapeutic level **(Arango et al., 2006).**

Acute cardiovascular effects of parenteral magnesium in women with severe preeclampsia have been studied using data obtained by pulmonary and radial artery catheterization. After a 4-g intravenous dose administered over 15 minutes, mean arterial pressure fell slightly, accompanied by a 13-percent increase in cardiac index **(Cotton et al., 1986b).**

Thus, magnesium decreased systemic vascular resistance and mean arterial pressure. At the same time, it increased cardiac output without evidence of myocardial depression. These findings were coincidental with transient nausea and flushing, and the cardiovascular effects persisted for only 15 minutes despite continued magnesium infusion. **Thurnau and associates (1987)** showed that there was a small but highly significant increase in total magnesium concentration in the cerebrospinal fluid with magnesium therapy. The magnitude of the increase was directly proportional to the corresponding serum concentration.

Magnesium is anticonvulsant and neuroprotective in several animal models. Some proposed mechanisms of action include: (1) reduced presynaptic release of the neurotransmitter glutamate, (2) blockade of glutamatergic N-methyl-D-aspartate (NMDA) receptors, (3) potentiation of adenosine action, (4) improved calcium buffering by mitochondria, and (5) blockage of calcium entry via voltage-gated channels **(Wang et al., 2012a).**

Uterine Effects

Relatively high serum magnesium concentrations depress myometrial contractility both in vivo and in vitro. With the regimen described and the plasma levels that result, no evidence of myometrial depression has been observed beyond a transient decrease in activity during and immediately after the initial intravenous loading dose **(Atkinson et al., 1995).**

Leveno and associates (1998) compared outcomes in 480 nulliparous women given phenytoin for preeclampsia with outcomes in 425 preeclamptic women given magnesium sulfate. Magnesium did not significantly alter the need for oxytocin stimulation of labor, admission-to-delivery intervals, or route of delivery. Similar results have been reported by others **(Witlin et al., 1997b; Szal et al., 1999).**

The mechanisms by which magnesium might inhibit uterine contractility are not established. It is generally assumed, however, that these depend on its effects on intracellular calcium. Inhibition of uterine contractility is magnesium dose dependent,

and serum levels of at least 8 to 10 mEq/L are necessary to inhibit uterine contractions. This likely explains why there are few if any uterine effects seen clinically when magnesium sulfate is given for preeclampsia. Magnesium is also not considered to be an effective tocolytic agent **(Watt-Morse et al., 1995).**

Fetal and Neonatal Effects

Magnesium administered parenterally promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amnionic fluid **(Hallak et al., 1993).** Levels in amnionic fluid increase with duration of maternal infusion **(Gortzak-Uzen et al., 2005).** Current evidence supports the view that magnesium sulfate has small but significant effects on the fetal heart rate pattern—specifically beat-to-beat variability. **Hallak and coworkers (1999)** compared an infusion of magnesium sulfate with a saline infusion. These investigators reported that magnesium was associated with a small and clinically insignificant decrease in variability.

Similarly, in a retrospective study, **Duffy and associates (2012)** reported a lower heart rate baseline that was within the normal range; decreased variability; and fewer prolonged decelerations. They noted no adverse outcomes.

Overall, maternal magnesium therapy appears safe for perinates. For example, a recent MFMU Network study of more than 1500 exposed preterm neonates found no association between the need for neonatal resuscitation and cord blood magnesium levels **(Johnson et al., 2012).** Still, there are a few neonatal adverse events associated with its use. In a Parkland Hospital study of 6654 mostly term exposed newborns, 6 percent had hypotonia **(Abbassi-Ghanavati et al., 2012).** In addition, exposed neonates had lower 1- and 5-minute Apgar scores, a higher intubation rate, and more admissions to the special care nursery. The study showed that neonatal depression occurs only if there is severe hypermagnesemia at delivery.

Observational studies have suggested a protective effect of magnesium against the development of cerebral palsy in very-low-birthweight infants **(Nelson et al., 1995; Schendel et al., 1996).** At least five randomized trials have also assessed neuroprotective

effects in preterm newborns. **Nguyen and colleagues (2013)** expanded this possibility to include term newborn neuroprotection. They performed a Cochrane Database review to compare term neonatal outcomes with and without exposure to peripartum magnesium therapy and reported that there were insufficient data to draw conclusions.

Finally, long-term use of magnesium, given for several days for tocolysis, has been associated with neonatal osteopenia **(American College of Obstetricians and Gynecologists, 2013c).**

Maternal Safety and Efficacy of Magnesium Sulfate

The multinational Eclampsia Trial Collaborative Group study (1995) involved 1687 women with eclampsia randomly allocated to different anticonvulsant regimens. In one cohort, 453 women were randomly assigned to be given magnesium sulfate and compared with 452 given diazepam.

In a second cohort, 388 eclamptic women were randomly assigned to be given magnesium sulfate and compared with 387 women given phenytoin. The results of these and other comparative studies that each enrolled at least 50 women are summarized in **Table XIII.** In aggregate, magnesium sulfate therapy was associated with a significantly lower incidence of recurrent seizures compared with women given an alternative anticonvulsant—9.7 versus 23 percent. Importantly, the maternal death rate of 3.1 percent with magnesium sulfate was significantly lower than that of 4.9 percent for the other regimens.

TABLE XIII. Randomized Comparative Trials of Magnesium Sulfate with Another Anticonvulsant to Prevent Recurrent Eclamptic Convulsions:

		Recurrent Seizures			Maternal Deaths		
Study	Comparison Drug	$MgSO_4$ (%)	Other Drug (%)	RR (95% CI)	$MgSO_4$ (%)	Other Drug (%)	RR (95% CI)
Crowther (1990)	Diazepam	5/24	7/27	0.80 (0.29–2.2)	1/24	0/27	
Bhalla (1994)	Lytic cocktail	1/45	11/45	0.09 (0.1–0.68)	0/45	2/45	
Eclampsia Trial Collaborative Group (1995)	Phenytoin	60/453	126/452	0.48 (0.36–0.63)	10/388	20/387	0.5 (0.24–1.00)
	Diazepam	22/388	66/387	0.33 (0.21–0.53)	17/453	24/452	0.74 (0.40–1.36)
Totals		88/910 (9.7)	210/911 (23)	0.41 (0.32–0.51)	28/910 (3.1)	45/911 (4.9)	0.62 (0.39–0.99)

Magnesium safety and toxicity was recently reviewed by **Smith and coworkers (2013).** In more than 9500 treated women, the overall rate of absent patellar tendon reflexes was 1.6 percent; respiratory depression 1.3 percent; and calcium gluconate administration 0.2 percent. They reported only one maternal death due to magnesium toxicity **(Pritchard et al., 1984).**

Management of Severe Hypertension

Dangerous hypertension can cause cerebrovascular hemorrhage and hypertensive encephalopathy, and it can trigger eclamptic convulsions in women with preeclampsia. Other complications include hypertensive afterload congestive heart failure and placental abruption **(Clark et al., 2012).**

Because of these sequelae, the **National High Blood Pressure Education Program Working Group (2000)** and the **2013 Task Force** recommend treatment to lower systolic pressures to or below 160 mm Hg and diastolic pressures to or below 110 mm Hg.

Martin and associates (2005) reported provocative observations that highlight the importance of treating systolic hypertension. They described 28 selected women with severe preeclampsia who suffered an associated stroke. Most of these were hemorrhagic strokes—93 percent—and all women had systolic pressures > 160 mm Hg before suffering their stroke.

By contrast, only 20 percent of these same women had diastolic pressures > 110 mm Hg. It seems likely that at least half of serious hemorrhagic strokes associated with

preeclampsia are in women with chronic hypertension. Long-standing hypertension results in development of Charcot-Bouchard aneurysms in the deep penetrating arteries of the lenticulostriate branch of the middle cerebral arteries. These vessels supply the basal ganglia, putamen, thalamus, and adjacent deep white matter, as well as the pons and deep cerebellum. These unique aneurysmal weakening predisposes these small arteries to rupture during sudden hypertensive episodes **(Cunningham et al., 2005).**

Anti-hypertensive Agents

Several drugs are available to rapidly lower dangerously elevated blood pressure in women with the gestational hypertensive disorders. The three most commonly employed are hydralazine, labetalol, and nifedipine. For years, parenteral hydralazine was the only one of these three available. But when parenteral labetalol was later introduced, it was considered to be equally effective for obstetrical use. Orally administered nifedipine has since then gained some popularity as first-line treatment for severe gestational hypertension.

Hydralazine

This is probably still the most commonly used antihypertensive agent in the United States for treatment of women with severe gestational hypertension. Hydralazine is administered intravenously with a 5-mg initial dose, and this is followed by 5- to 10-mg doses at 15- to 20-minute intervals until a satisfactory response is achieved **(American College of Obstetricians and Gynecologists, 2012b).** Some limit the total dose to 30 mg per treatment cycle **(Sibai et al., 2003).**

The target response antepartum or intrapartum is a decrease in diastolic blood pressure to 90 to 110 mm Hg. Lower diastolic pressures risk compromised placental perfusion. Hydralazine has proven remarkably effective to prevent cerebral hemorrhage.

Its onset of action can be as rapid as 10 minutes. Although repeated administration every 15 to 20 minutes may theoretically lead to undesirable hypotension, this has not been occurred when given in these 5- to 10-mg increments. Between 5 and 10 percent of all women with intrapartum hypertensive disorders are given a parenteral antihypertensive agent. The total dose is not limited and seldom has a second antihypertensive agent been needed. Although less popular in Europe, hydralazine is used in some centers, according to the **Royal College of Obstetricians and Gynaecologists (2006).**

A dissenting opinion for first-line intrapartum use of hydralazine was voiced by the Vancouver group after a systematic review **(Magee et al., 2009).** At the same time, however, **Umans and coworkers (2014)** concluded that objective outcome data did not support the use of one drug over another. As with any antihypertensive agent, the tendency to give a larger initial dose of hydralazine if the blood pressure is higher must be avoided. The response to even 5- to 10-mg doses cannot be predicted by hypertension severity. Thus, the protocol is to always administer 5 mg as the initial dose. An adverse response to exceeding this initial dose is shown in **Figure 20.**

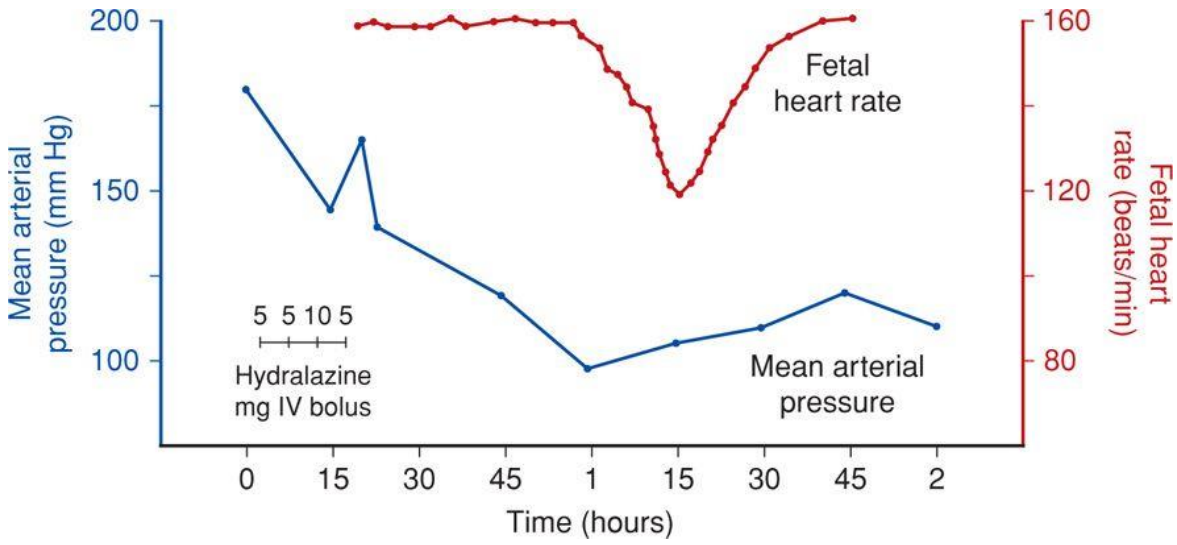

FIGURE 20. Woman with chronic hypertension complicated by severe superimposed preeclampsia, and hydralazine was injected more frequently than recommended. Her mean arterial pressure (MAP) decreased in less than 1 hour from 240–270/130–150 mm Hg to 110/80 mm Hg, and fetal heart rate decelerations

characteristic of uteroplacental insufficiency. Decelerations persisted until her blood pressure was increased with rapid crystalloid infusion. Hydralazine was given at 5-minute instead of 15-minute intervals. MAP decreased from 180 to 90 mm Hg within 1 hour and was associated with fetal bradycardia. Rapid crystalloid infusion raised MAP to 115 mm Hg, and the fetus recovered.

In some cases, this fetal response to diminished uterine perfusion may be confused with placental abruption and may result in unnecessary and potentially dangerous emergent cesarean delivery **(Umans et al., 2014).**

Labetalol

This effective intravenous antihypertensive agent is an α1- and nonselective β-blocker. Some prefer its use over hydralazine because of fewer side effects **(Sibai, 2003).** At Parkland Hospital, we give 10 mg intravenously initially. If the blood pressure has not decreased to the desirable level in 10 minutes, then 20 mg is given. The next 10-minute incremental dose is 40 mg and is followed by another 40 mg if needed. If a salutary response is not achieved, then an 80-mg dose is given. **Sibai (2003)** recommends 20 to 40 mg every 10 to 15 minutes as needed and a maximum dose of 220 mg per treatment cycle. **The American College of Obstetricians and Gynecologists (2012b)** recommends starting with a 20-mg intravenous bolus. If not effective within 10 minutes, this is followed by 40 mg, then 80 mg every 10 minutes. Administration should not exceed a 220-mg total dose per treatment cycle.

Hydralazine versus Labetalol

Comparative studies of these two antihypertensive agents show equivalent results **(Umans et al., 2014).** In an older trial, **Mabie and colleagues (1987)** compared intravenous hydralazine with labetalol for blood pressure control in 60 peripartum women. Labetalol lowered blood pressure more rapidly, and associated tachycardia was minimal. However, hydralazine lowered mean arterial pressures to safe levels more effectively.

In a later trial, **Vigil-De Gracia and associates (2007)** randomly assigned 200 severely hypertensive women intrapartum to be given either: (1) intravenous hydralazine—5 mg, which could be given every 20 minutes and repeated to a maximum of five doses, or (2) intravenous labetalol—20 mg initially, followed by 40 mg in 20 minutes and then 80 mg every 20 minutes if needed up to a maximum 300-mg dose. Maternal and neonatal outcomes were similar. Hydralazine caused significantly more maternal tachycardia and palpitations, whereas labetalol more frequently caused maternal hypotension and bradycardia. Both drugs have been associated with a reduced frequency of fetal heart rate accelerations **(Cahill et al., 2013).**

Nifedipine

This calcium-channel blocking agent has become popular because of its efficacy for control of acute pregnancy-related hypertension. **The NHBPEP Working Group (2000)** and **the Royal College of Obstetricians and Gynaecologists (2006)** recommend a 10-mg initial oral dose to be repeated in 30 minutes if necessary. Nifedipine given sublingually is no longer recommended. Randomized trials that compared nifedipine with labetalol found neither drug definitively superior to the other. However, nifedipine lowered blood pressure more quickly **(Scardo et al., 1999; Vermillion et al., 1999; Shekhar et al., 2013).**

Other Antihypertensive Agents

A few other generally available antihypertensive agents have been tested in clinical trials but are not widely used **(Umans et al., 2014). Belfort and associates (1990)** administered the calcium antagonist verapamil by intravenous infusion at 5 to 10 mg per hour. Mean arterial pressure was lowered by 20 percent. **Belfort and coworkers (1996, 2003)** reported that nimodipine given either by continuous infusion or orally was effective to lower blood pressure in women with severe preeclampsia.

Bolte and colleagues (1998, 2001) reported good results in preeclamptic women given intravenous ketanserin, a selective serotonergic (5HT2A) receptor blocker. Nitroprusside or nitroglycerine is recommended by some if there is not optimal response to first-line agents. With these latter two agents, fetal cyanide toxicity may develop after 4 hours.

There are experimental antihypertensive drugs that may become useful for preeclampsia treatment. One is calcitonin gene related peptide (CGRP), a 37-amino acid potent vasodilator. Another is antidigoxin antibody Fab (DIF) directed against endogenous digitalis-like factors, also called cardiotonic steroids **(Bagrov, 2008; Lam, 2013).**

Diuretics

Potent loop diuretics can further compromise placental perfusion. Immediate effects include depletion of intravascular volume, which most often is already reduced compared with that of normal pregnancy. Therefore, before delivery, diuretics are not used to lower blood pressure **(Zeeman, 2009).**

FLUID THERAPY

Lactated Ringer solution is administered routinely at the rate of 60 mL to no more than 125 mL per hour unless there is unusual fluid loss from vomiting, diarrhea, or diaphoresis, or, more likely, excessive blood loss with delivery. Oliguria is common with severe preeclampsia. Thus, coupled with the knowledge that maternal blood volume is likely constricted compared with that of normal pregnancy, it is tempting to administer intravenous fluids more vigorously. But controlled, conservative fluid administration is preferred for the typical woman with severe preeclampsia who already has excessive extracellular fluid that is inappropriately distributed between intravascular and extravascular spaces **(Sciscione et al., 2003).**

Infusion of large fluid volumes enhances the mal-distribution of extravascular fluid and thereby appreciably increases the risk of pulmonary and cerebral edema. For

labor analgesia with neuraxial analgesia, crystalloid solutions are infused slowly in graded amounts **(Dennis et al., 2012a).**

PULMONARY EDEMA

Women with severe preeclampsia-eclampsia who develop pulmonary edema most often do so postpartum. With pulmonary edema in the eclamptic woman, aspiration of gastric contents, which may be the result of convulsions, anesthesia, or oversedation, should be excluded. There are three common causes of pulmonary edema in women with severe preeclampsia syndrome—pulmonary capillary permeability edema, cardiogenic edema, or a combination of the two **(Cunningham et al., 2012).**

Some women with severe preeclampsia—especially if given vigorous fluid replacement—will have mild pulmonary congestion from permeability edema. This is caused by normal pregnancy changes magnified by the preeclampsia syndrome. Importantly, plasma oncotic pressure decreases appreciably in normal term pregnancy because of decreased serum albumin concentration, and oncotic pressure falls even more with preeclampsia. And both increased extravascular fluid oncotic pressure and increased capillary permeability have been described in women with preeclampsia **(Brown et al., 1989).**

Invasive Hemodynamic Monitoring

Knowledge concerning cardiovascular and hemodynamic pathophysiological alterations associated with severe preeclampsia-eclampsia has accrued from studies done using invasive monitoring and a flow-directed pulmonary artery catheter **(Clark and Dildy, 2010).**

Two conditions frequently cited as indications are preeclampsia associated with either oliguria or pulmonary edema. Somewhat ironically, it is usually vigorous treatment of the former that results in most cases of the latter. **The American College of Obstetricians and Gynecologists (2013a)** recommends against routine invasive monitoring. The College notes that such monitoring should be reserved for severely

preeclamptic women with accompanying severe cardiac disease, renal disease, or both or in cases of refractory hypertension, oliguria, and pulmonary edema. An alternative noninvasive hemodynamic monitoring strategy has been evaluated in preliminary studies **(Moroz et al., 2013).**

PLASMA VOLUME EXPANSION

Because the preeclampsia syndrome is associated with hemoconcentration, attempts to expand blood volume seem intuitively reasonable **(Ganzevoort et al., 2004).** This has led some to infuse various fluids, starch polymers, albumin concentrates, or combinations thereof to expand blood volume. There are, however, older observational studies that describe serious complications—especially pulmonary edema—with volume expansion. In general, these studies were not controlled or even comparative **(Habek et al., 2006).**

The Amsterdam randomized study reported by **Ganzevoort and coworkers (2005a; 2005b)** was a well-designed investigation done to evaluate volume expansion. A total of 216 women with severe preeclampsia were enrolled between 24 and 34 weeks' gestation. The study included women whose preeclampsia was complicated by HELLP syndrome, eclampsia, or fetal-growth restriction. All women were given magnesium sulfate to prevent eclampsia, betamethasone to promote fetal pulmonary maturity, ketanserine to control dangerous hypertension, and normal saline infusions restricted only to deliver medications.

In the group randomly assigned to volume expansion, each woman was given 250 mL of 6-percent hydroxyethyl starch infused over 4 hours twice daily. Their maternal and perinatal outcomes were compared with a control group and are shown in **Table XIV.** None of these outcomes was significantly different between the two groups. Importantly, serious maternal morbidity and a substantive perinatal mortality rate accompanied their "expectant" management **(Ganzevoort et al., 2005a; 2005b).**

TABLE XIV. Maternal and Perinatal Outcomes in a Randomized Trial of Plasma Volume Expansion versus Saline Infusion in 216 Women with Severe Preeclampsia between 24 and 34 Weeks:

Outcomes	Control Group[a] (n = 105)	Treatment Group[a] (n = 111)
Maternal Outcomes (%)		
Eclampsia (after enrollment)	1.9	1.8
HELLP (after enrollment)	19.0	17.0
Pulmonary edema	2.9	4.5
Placental abruption	3.8	1.0
Perinatal Outcomes		
Fetal deaths (%)	7	12
Prolongation of pregnancy (mean)	11.6 d	6.7 d
EGA at death (mean)	26.7 wk	26.3 wk
Birthweight (mean)	625 g	640 g
Live births (%)	93	88
Prolongation of pregnancy (mean)	10.5 d	7.4 d
EGA at delivery (mean)	31.6 wk	31.4 wk
RDS (%)	30	35
Neonatal death (%)	7.6	8.1
Perinatal mortality rate (n per 1000)	142/1000	207/1000

[a]All comparisons $p > 0.05$.
EGA = estimated gestational age; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; RDS = respiratory distress syndrome.
Data from Ganzevoort, 2005a, b.

Neuro-prophylaxis—Prevention of Seizures

There have been several randomized trials designed to test the efficacy of seizure prophylaxis for women with gestational hypertension, with or without proteinuria. In most of these, magnesium sulfate was compared with another anticonvulsant or with a placebo. In all studies, magnesium sulfate was reported to be superior to the comparator agent to prevent eclampsia. Four of the larger studies are summarized in **Table XV. Lucas and colleagues (1995)** reported that magnesium sulfate therapy was superior to phenytoin to prevent eclamptic seizures in women with gestational hypertension and preeclampsia. **Belfort and coworkers (2003)** compared magnesium sulfate and

nimodipine—a calcium-channel blocker with specific cerebral vasodilator activity—for eclampsia prevention. In this unblinded randomized trial involving 1650 women with severe preeclampsia, the rate of eclampsia was more than threefold higher for women allocated to the nimodipine group—2.6 versus 0.8 percent.

TABLE XV. Randomized Trials of Prophylaxis with Magnesium Sulfate and Placebo or Another Anticonvulsant in Women with Gestational Hypertension:

	No.with Seizures/Total No. Treated (%)		
Study/Inclusions	Magnesium Sulfate	Control	Comparison[a]
Lucas et al (1995) Gestational hypertension[b]	0/1049 (0)	Phenytoin 10/1089 (0.9)	$p < 0.001$
Coetzee et al (1998) Severe preeclampsia	1/345 (0.3)	Placebo 11/340 (3.2)	RR = 0.09 (0.1–0.69)
Magpie Trial (2002)[c] Severe preeclampsia	40/5055 (0.8)	Placebo 96/5055 (1.9)	RR = 0.42 (0.26–0.60)
Belfort et al (2003) Severe preeclampsia	7/831 (0.8)	Nimodipine 21/819 (2.6)	RR = 0.33 (0.14–0.77)

[a]All comparisons significant $p < 0.05$.
[b]Included women with and without proteinuria and those with all severities of preeclampsia.
[c]Magpie Trial Collaboration Group, 2002.

The largest comparative study was the entitled MAGnesium Sulfate for Prevention of Eclampsia and reported by the **Magpie Trial Collaboration Group (2002).** More than 10,000 women with severe preeclampsia from 33 countries were randomly allocated to treatment with magnesium sulfate or placebo. Women given magnesium had a 58-percent significantly lower risk of eclampsia than those given placebo. **Smyth and associates (2009)** provided follow-up data of infants born to these mothers given magnesium sulfate. At approximately 18 months, child behavior did not differ in those exposed compared with those not exposed to magnesium sulfate.

Who Should Be Given Magnesium Sulfate?

Magnesium will prevent proportionately more seizures in women with correspondingly worse disease. However, severity is difficult to quantify, and thus it is difficult to decide which individual woman might benefit most from neuro-prophylaxis. **The 2013 Task Force** recommends that women with either eclampsia or severe preeclampsia should be given magnesium sulfate prophylaxis. Again, criteria that establish "severity" are not totally uniform. At the same time, however, **the 2013 Task Force** suggests that all women with "mild" preeclampsia do not need magnesium sulfate neuro-prophylaxis. The conundrum is whether or not to give neuro-prophylaxis to any of these women with "non-severe" gestational hypertension or preeclampsia **(Alexander et al., 2006).**

In many other countries, and principally following dissemination of the **Magpie Trial Collaboration Group (2002)** study results, magnesium sulfate is now recommended for women with severe preeclampsia. In some, however, debate continues concerning whether therapy should be reserved for women who have an eclamptic seizure. Eclamptic seizures are dangerous. Maternal mortality rates of up to 5 percent have been reported even in recent studies **(Andersgaard et al., 2006; Schutte et al., 2008; Zwart et al., 2008; Benhamou et al., 2009; Moodley et al., 2010).**

Moreover, there are substantially increased perinatal mortality rates in both industrialized countries and underdeveloped ones **(Knight et al., 2007; Schutte et al., 2008; Abd El Aal et al., 2012; Ndaboine et al., 2012; von Dadelszen et al., 2012).** Finally, the possibility of adverse long-term neuropsychological and vision-related sequelae of eclampsia described by **Aukes et al. (2009; 2012), Postma et al. (2009), Wiegman et al. (2012),** and their coworkers, have raised additional concerns that eclamptic seizures are not "benign."

Selective versus Universal Magnesium Sulfate Prophylaxis

There is uncertainty around which women with non-severe gestational hypertension should be given magnesium sulfate neuro-prophylaxis. **Lucas and associates (1995)** had found that the risk of eclampsia without magnesium prophylaxis

was approximately 1 in 100 for women with mild preeclampsia. Up until 2000, all women with gestational hypertension were given magnesium prophylaxis intramuscularly as first described by Pritchard in 1955. After 2000, a standardized protocol for intravenously administered magnesium sulfate was instituted **(Alexander et al., 2006).**

At the same time, practice of universal seizure prophylaxis for all women with gestational hypertension has changed to one of selective prophylaxis given only to women who met Parkland Hospital Criteria for severe gestational hypertension. These criteria, shown in **Table XVI**, included women with ≥ 2+ proteinuria measured by dipstick in a catheterized urine specimen. Following this protocol change, 60 percent of 6518 women with gestational hypertension during a 4½-year period were given magnesium sulfate neuro-prophylaxis **(Table XVII).** The remaining 40 percent with non-severe hypertension were not treated, and of these, 27 women developed eclamptic seizures—1 in 92 **(American College of Obstetricians and Gynecologists, 2013d).**

TABLE XVI. Selective versus Universal Magnesium Sulfate Prophylaxis: Parkland Hospital Criteria to Define Severity of Gestational Hypertension:

In a woman with new-onset proteinuric hypertension, at least one of the following criteria is required:

- Systolic BP ≥ 160 or diastolic BP ≥ 110 mm Hg
- Proteinuria ≥ 2+ by dipstick in a catheterized urine specimen
- Serum creatinine > 1.2 mg/dL
- Platelet count < 100,000/μL
- Aspartate aminotransferase (AST) elevated two times above upper limit of normal range
- Persistent headache or scotomata
- Persistent midepigastric or right-upper quadrant pain

BP = blood pressure. **(Criteria based on those from National High Blood Pressure Education Program Working Group, 2000; American College of Obstetricians and Gynecologists, 2012b; cited by Alexander et al., 2006).**

The seizure rate was only 1 in 358 for 3935 women with criteria for severe disease who were given magnesium sulfate, and thus these cases were treatment failures. To assess morbidity, outcomes in 87 eclamptic women were compared with outcomes in all 6431 non-eclamptic hypertensive women. Although most maternal outcomes were similar, almost a fourth of women with eclampsia who underwent emergent cesarean delivery required general anesthesia. This is a great concern because eclamptic women have laryngo-tracheal edema and are at a higher risk for failed intubation, gastric acid aspiration, and death **(American College of Obstetricians and Gynecologists, 2013d).**

Neonatal outcomes were also a concern because the composite morbidity defined in **Table XVII** was significantly increased tenfold in eclamptic compared with non-eclamptic women—12 versus 1 percent, respectively.

TABLE XVII. Selected Pregnancy Outcomes in 6518 Women with Gestational Hypertension According to Whether They Developed Eclampsia:

Pregnancy Outcomes	Eclampsia No. (%)	Gest. HTN[a] No. (%)	*p* value
Number	87	6431	
Maternal			
Cesarean delivery	32 (37)	2423 (38)	0.86
Placental abruption	1 (1)	72 (1)	0.98
General anesthesia[b]	20 (23)	270 (4)	< 0.001
Neonatal			
Composite morbidity[c]	10 (12)	240 (1)	0.04

[a]Includes women who had preeclampsia.
[b]Emergent cesarean delivery.
[c]One or more: cord artery pH < 7.0; 5-minute Apgar score < 4; perinatal death; or unanticipated admission of term infant to an intensive care nursery.
Gest. HTN = gestational hypertension.
Data from Alexander, 2006.

Thus, if one uses the Parkland criteria for non-severe gestational hypertension, about 1 of 100 such women who are not given magnesium sulfate prophylaxis can be expected to have an eclamptic seizure. A fourth of these women likely will require emergent cesarean delivery with attendant maternal and perinatal morbidity and mortality from general anesthesia. From this, the major question regarding management of non-severe gestational hypertension remains—whether it is acceptable to avoid unnecessary treatment of 99 women to risk eclampsia in one? The answer appears to be yes as suggested by **the 2013 Task Force.**

DELIVERY

To avoid maternal risks from cesarean delivery, steps to effect vaginal delivery are used initially in women with eclampsia. Following a seizure, labor often ensues spontaneously or can be induced successfully even in women remote from term. An immediate cure does not promptly follow delivery by any route, but serious morbidity is less common during the puerperium in women delivered vaginally **(Alanis et al., 2008).**

Blood Loss at Delivery

Hemoconcentration or lack of normal pregnancy-induced hypervolemia is an almost predictable feature of severe preeclampsia-eclampsia as quantified by **Zeeman and associates (2009).** These women, who consequently lack normal pregnancy hypervolemia, are much less tolerant of even normal blood loss than are normotensive pregnant women. It is of great importance to recognize that an appreciable fall in blood pressure soon after delivery most often means excessive blood loss and not sudden resolution of vasospasm and endothelial damage. When oliguria follows delivery, the hematocrit should be evaluated frequently to help detect excessive blood loss. If identified, hemorrhage should be treated appropriately by careful crystalloid and blood transfusion.

Analgesia and Anesthesia

During the past 20 years, the use of conduction analgesia for women with preeclampsia syndrome has proven ideal. Initial problems with this method included hypotension and diminished uterine perfusion caused by sympathetic blockade in these women with attenuated hypervolemia. But pulmonary edema was mitigated by techniques that used slow induction of epidural analgesia with dilute solutions of anesthetic agents to counter the need for rapid infusion of large volumes of crystalloid or colloid to correct maternal hypotension **(Wallace et al., 1995; Hogg et al., 1999).**

Moreover, epidural blockade avoids general anesthesia, in which the stimulation of tracheal intubation may cause sudden severe hypertension. Such blood pressure increases, in turn, can cause pulmonary edema, cerebral edema, or intracranial hemorrhage. Finally, tracheal intubation may be particularly difficult and thus hazardous in women with airway edema due to preeclampsia **(American College of Obstetricians and Gynecologists, 2013d).**

At least three randomized studies have been performed to evaluate these methods of analgesia and anesthesia. **Wallace and colleagues (1995)** studied 80 women at Parkland Hospital with severe preeclampsia who were to undergo cesarean delivery. They had not been given labor epidural analgesia and were randomized to receive general

anesthesia, epidural analgesia, or combined spinal-epidural analgesia. Their average preoperative blood pressures approximated 170/110 mm Hg, and all had proteinuria. Anesthetic and obstetrical management included antihypertensive drug therapy and limited intravenous fluids as previously described. Perinatal outcomes in each group were similar. Maternal hypotension resulting from regional analgesia was managed with judicious intravenous fluid administration. In women undergoing general anesthesia, maternal blood pressure was managed to avoid severe hypertension **(Figure 21).** There were no serious maternal or fetal complications attributable to any of the three anesthetic methods. It was concluded that all three are acceptable for use in women with pregnancies complicated by severe preeclampsia if steps are taken to ensure a careful approach to the selected method.

Another randomized study included 70 women with severe preeclampsia receiving spinal analgesia versus general anesthesia **(Dyer et al., 2003).** All had a nonreassuring fetal heart rate tracing as the indication for cesarean delivery, and outcomes were equivalent. **Dyer and coworkers (2008)** later showed that decreased mean arterial blood pressure induced by epidural blockade could be effectively counteracted by phenylephrine infusion to maintain cardiac output.

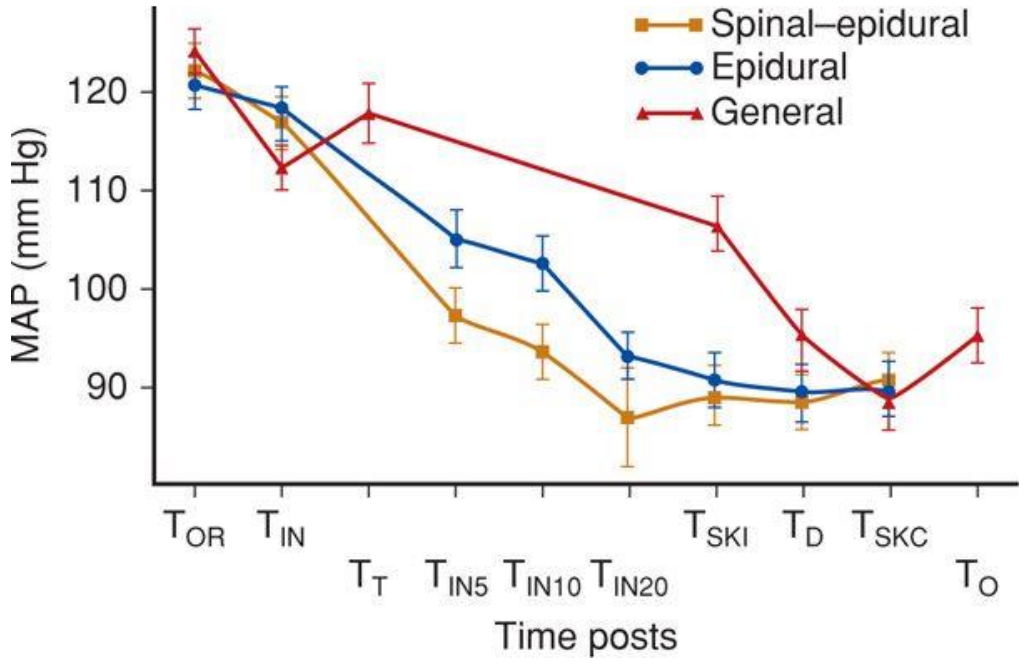

FIGURE 21. Blood pressure effects of general anesthesia versus epidural or spinal–epidural analgesia for cesarean delivery in 80 women with severe preeclampsia. MAP = mean arterial pressure. Time posts (T): OR = operating room; IN = induction of anesthesia; T = tracheal intubation; IN5 = induction + 5 min; IN10 = induction + 10 min; IN20 = induction + 20 min; SKI = skin incision; D = delivery; SKC = skin closure; O = extubation **(From Wallace et al., 1995).**

In a study from the University of Alabama at Birmingham, **Head and colleagues (2002)** randomly assigned 116 women with severe preeclampsia to receive either epidural or patient-controlled intravenous meperidine analgesia during labor. A standardized protocol limited intravenous fluids to 100 mL/hr. More women—9 percent—from the group assigned to epidural analgesia required ephedrine for hypotension. As expected, pain relief was superior in the epidural group, but maternal and neonatal complications were similar between groups. One woman in each group developed pulmonary edema.

It is important to emphasize that epidural analgesia is not to be considered treatment of preeclampsia. **Lucas and associates (2001)** studied 738 laboring women at Parkland Hospital who were 36 weeks or more and who had gestational hypertension of varying severity. Patients were randomly assigned to receive either epidural analgesia or patient-controlled intravenous meperidine analgesia. Maternal and neonatal outcomes were similar in the two study groups. However, as shown in **Table XVIII,** epidural analgesia resulted in a greater decrement of mean maternal arterial pressure compared with meperidine, but it was not superior in preventing recurrent severe hypertension later in labor.

TABLE XVIII. Comparison of Cardiovascular Effects of Epidural versus Patient-Controlled Meperidine Analgesia During Labor in Women with Gestational Hypertension:

Hemodynamic Change	Labor Analgesia		
	Epidural (n = 372)	Meperidine (n = 366)	*p* value
Mean arterial pressure change (mean)	−25 mm Hg	−15 mm Hg	< 0.001
Ephedrine for hypotension (%)	11%	0	< 0.001
Severe hypertension after analgesia (%) (BP ≥ 160/110 mm Hg)	< 1%	1%	NS

NS = not significant.
Data from Lucas, 2001.

For these reasons, judicious fluid administration is essential in severely preeclamptic women who receive regional analgesia. **Newsome and coworkers (1986)** showed that vigorous crystalloid infusion with epidural blockade in women with severe preeclampsia caused elevation of pulmonary capillary wedge pressures.

Aggressive volume replacement in these women increases their risk for pulmonary edema, especially in the first 72 hours postpartum **(Clark et al., 1985; Cotton et al., 1986a). When** pulmonary edema develops, there is also concern for development of cerebral edema. Finally, **Heller and associates (1983)** demonstrated that most cases of pharyngo-laryngeal edema were related to aggressive volume therapy.

Persistent Severe Postpartum Hypertension

The potential problem of antihypertensive agents causing serious compromise of uteroplacental perfusion and thus of fetal well-being is obviated by delivery. Postpartum, if difficulty arises in controlling severe hypertension or if intravenous hydralazine or labetalol are being used repeatedly, then oral regimens can be given. Examples include labetalol or another β-blocker, nifedipine or another calcium-channel blocker, and possible addition of a thiazide diuretic. Persistent or refractory hypertension is likely due to mobilization of pathological interstitial fluid and redistribution into the intravenous compartment, underlying chronic hypertension, or usually both **(Tan et al., 2002; Sibai, 2012).** In women with chronic hypertension and left-ventricular hypertrophy, severe

postpartum hypertension can cause pulmonary edema from cardiac failure **(Cunningham et al., 2012).**

Furosemide

Because persistence of severe hypertension corresponds to the onset and length of diuresis and extracellular fluid mobilization, it seems logical that furosemide-augmented diuresis might serve to hasten blood pressure control. To study this, **Ascarelli and coworkers (2005)** designed a randomized trial that included 264 postpartum preeclamptic women. After onset of spontaneous diuresis, patients were assigned to 20-mg oral furosemide given daily or no therapy. Women with mild disease had similar blood pressure control regardless of whether they received treatment or placebo.

However, women with severe preeclampsia who were treated, compared with those receiving placebo, had a lower mean systolic blood pressure at 2 days—142 versus 153 mm Hg. They also required less frequently administered antihypertensive therapy during the remainder of hospitalization—14 versus 26 percent, respectively. A simple method to estimate excessive extracellular/interstitial fluid was used. The postpartum weight is compared with the most recent prenatal weight, either from the last clinic visit or on admission for delivery. On average, soon after delivery, maternal weight should be reduced by at least 10 to 15 pounds depending on infant and placental weight, amnionic fluid volume, and blood loss. Because of various interventions, especially intravenous crystalloid infusions given during operative vaginal or cesarean delivery, women with severe preeclampsia often have an immediate postpartum weight in excess of their last prenatal weight. If this weight increase is associated with severe persistent postpartum hypertension, then diuresis with intravenous furosemide is usually helpful in controlling blood pressure.

Plasma Exchange

Martin and colleagues (1995) have described an atypical syndrome in which severe preeclampsia-eclampsia persists despite delivery. These investigators described 18 such women whom they encountered during a 10-year period. They advocate single or

multiple plasma exchange for these women. In some cases, 3 L of plasma was exchanged three times—a 36- to 45-donor unit exposure for each patient—before a response was forthcoming. Others have described plasma exchange performed in postpartum women with HELLP syndrome. In all of these cases, however, the distinction between HELLP syndrome and thrombotic thrombocytopenic purpura or hemolytic uremic syndrome was not clear **(Förster et al., 2002; Obeidat et al., 2002).**

Experiences with more than 50,000 women with gestational hypertension among nearly 450,000 pregnancies cared for**,** it has been encountered very few women with persistent postpartum hypertension, thrombocytopenia, and renal dysfunction who were diagnosed as having a thrombotic microangiopathy **(Dashe et al., 1998).** These latter syndromes complicating pregnancy were reviewed by **Martin et al. (2008) and George et al. (2013)** and their colleagues, who conclude that a rapid diagnostic test for ADAMTS-13 enzyme activity might be helpful to differentiate most of these syndromes.

Reversible Cerebral Vasoconstriction Syndrome

This is another cause of persistent hypertension, "thunderclap" headaches, seizures, and central nervous system findings. It is a form of postpartum angiopathy. As shown in **Figure 22,** it is characterized by diffuse segmental constriction of cerebral arteries and may be associated with ischemic and hemorrhagic strokes. The reversible cerebral vasoconstriction syndrome has several inciting causes that include pregnancy, and particularly preeclampsia **(Ducros et al., 2012).** It is more common in women, and in some cases, vasoconstriction may be so severe as to cause cerebral ischemia and infarction. The appropriate management is not known at this time **(Edlow et al., 2013).**

COUNSELING FOR FUTURE PREGNANCIES

Defective remodeling of the spiral arteries in some placentations has been posited as the cause of at least one preeclampsia phenotype. Lack of deep placentation has been associated with preeclampsia, placental abruption, fetal-growth restriction, and preterm

birth **(Wikström et al., 2011).** With this type of "overlap syndrome," hypertensive disorders may serve as markers for subsequent preterm labor and fetal-growth restriction. For example, even in subsequent non-hypertensive pregnancies, women who had preterm preeclampsia are at increased risk for preterm birth **(Connealy et al., 2013).**

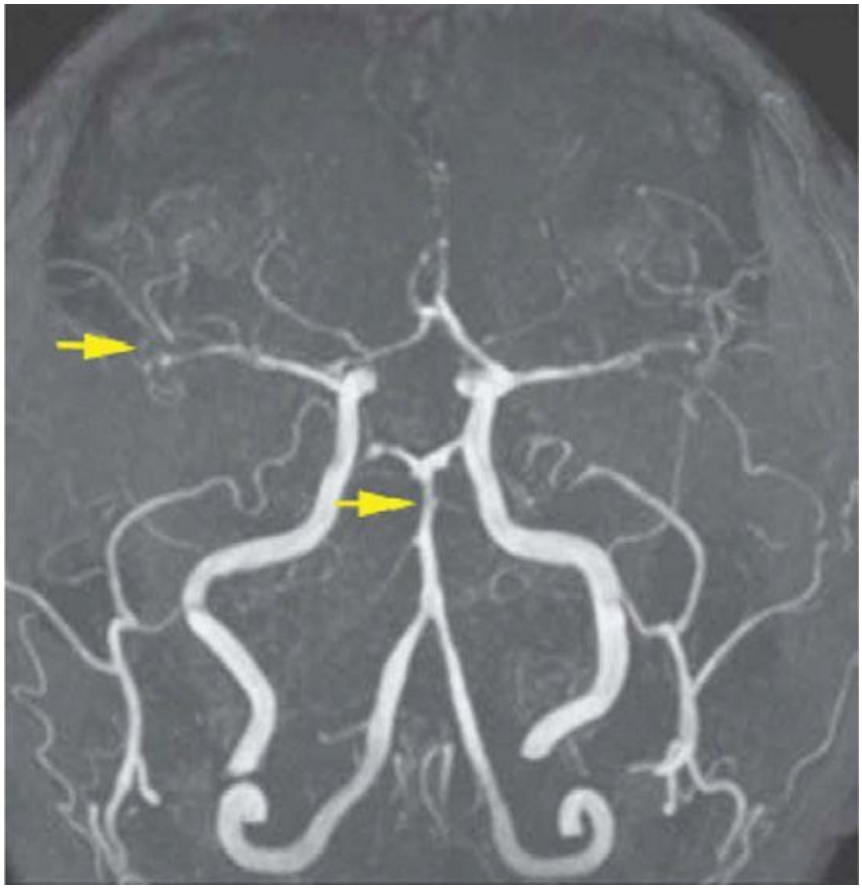

FIGURE 22. Reversible cerebral vasoconstriction syndrome. Magnetic resonance angiography shows generalized vasoconstriction of the anterior and posterior cerebral circulation (arrows) **(From Garcia-Reitboeck et al., 2013).**

In addition, women who have had either gestational hypertension or preeclampsia are at higher risk to develop hypertension in future pregnancies. Generally, the earlier preeclampsia is diagnosed during the index pregnancy, the greater the likelihood of recurrence. **Sibai and colleagues (1986, 1991)** found that nulliparas diagnosed with

preeclampsia before 30 weeks have a recurrence risk as high as 40 percent during a subsequent pregnancy.

In a prospective study of 500 women previously delivered for preeclampsia at 37 weeks, the recurrence rate in a subsequent gestation was 23 percent. These investigators found an increased risk during subsequent pregnancies for preterm delivery and fetal-growth restriction even if these women remained normotensive **(Bramham et al., 2011).**

In a study from the Denmark Birth Registry, **Lykke and coworkers (2009b)** analyzed singleton births in more than 535,000 women who had a first and second delivery. Women whose first pregnancy was complicated by preeclampsia between 32 and 36 weeks had a significant twofold increased incidence of preeclampsia in their second pregnancy—25 versus 14 percent—compared with women who were normotensive during the first pregnancy. Analyzed from another view, they also found that preterm delivery and fetal-growth restriction in the first pregnancy significantly increased the risk for preeclampsia in the second pregnancy.

As probably expected, women with HELLP syndrome have a substantive risk for recurrence in subsequent pregnancies. In two studies the risk ranged from 5 to 26 percent, but the true recurrence risk likely lies between these two extremes **(Habli et al., 2009).** Even if HELLP syndrome does not recur with subsequent pregnancies, there is a high incidence of preterm delivery, fetal-growth restriction, placental abruption, and cesarean delivery **(Hnat et al., 2002; Habli et al., 2009).**

LONG-TERM CONSEQUENCES

Over the past 20 years, evidence has accrued that preeclampsia, like fetal-growth disorders and preterm birth, is a marker for subsequent cardiovascular morbidity and mortality. Women with hypertension identified during pregnancy should be evaluated during the first several months postpartum and counseled regarding long-term risks. The Working Group concluded that hypertension attributable to pregnancy should resolve within 12 weeks of delivery **(National High Blood Pressure Education Program, 2000).**

Persistence beyond this time is considered to be chronic hypertension. **The Magpie Trial Follow-Up Collaborative Group (2007)** reported that 20 percent of 3375 preeclamptic women seen at a median of 26 months postpartum had hypertension. Importantly, even if hypertension does not persist in the short term, convincing evidence suggests that the risk for long-term cardiovascular morbidity is significantly increased in preeclamptic women.

Cardiovascular and Neurovascular Morbidity

With the advent of national databases, several studies confirm that any hypertension during pregnancy is a marker for an increased risk for morbidity and mortality in later life **(American College of Obstetricians and Gynecologists, 2013c).**

In a case-control study from Iceland, **Arnadottir and associates (2005)** analyzed outcomes for 325 women who had hypertension complicating pregnancy and who were delivered from 1931 through 1947. At a median follow-up of 50 years, 60 percent of women with pregnancy-related hypertension compared with only 53 percent of controls had died. Compared with 629 normotensive pregnant controls, the prevalences of ischemic heart disease—24 versus 15 percent, and stroke—9.5 versus 6.5 percent, were significantly increased in the women who had gestational hypertension.

In a Swedish population study of more than 400,000 nulliparas delivered between 1973 and 1982, **Wikström and coworkers (2005)** also found an increased incidence of ischemic heart disease in women with prior pregnancy-associated hypertension.

Lykke and associates (2009a) cited findings from a Danish registry of more than 780,000 nulliparous women. After a mean follow-up of almost 15 years, the incidence of chronic hypertension was significantly increased 5.2-fold in those who had gestational hypertension, 3.5-fold after mild preeclampsia, and 6.4-fold after severe preeclampsia.

After two hypertensive pregnancies, there was a 5.9-fold increase in the incidence. Importantly, these investigators also reported a significant 3.5-fold increased risk for type 2 diabetes **(Lykke et al., 2009a).**

Bellamy and coworkers (2007) performed a systematic review and meta-analysis of long-term risks for cardiovascular disease in women with preeclampsia. As shown in **Figure 23,** the risks in later life were increased for hypertension, ischemic heart disease, stroke, venous thromboembolism, and all-cause mortality.

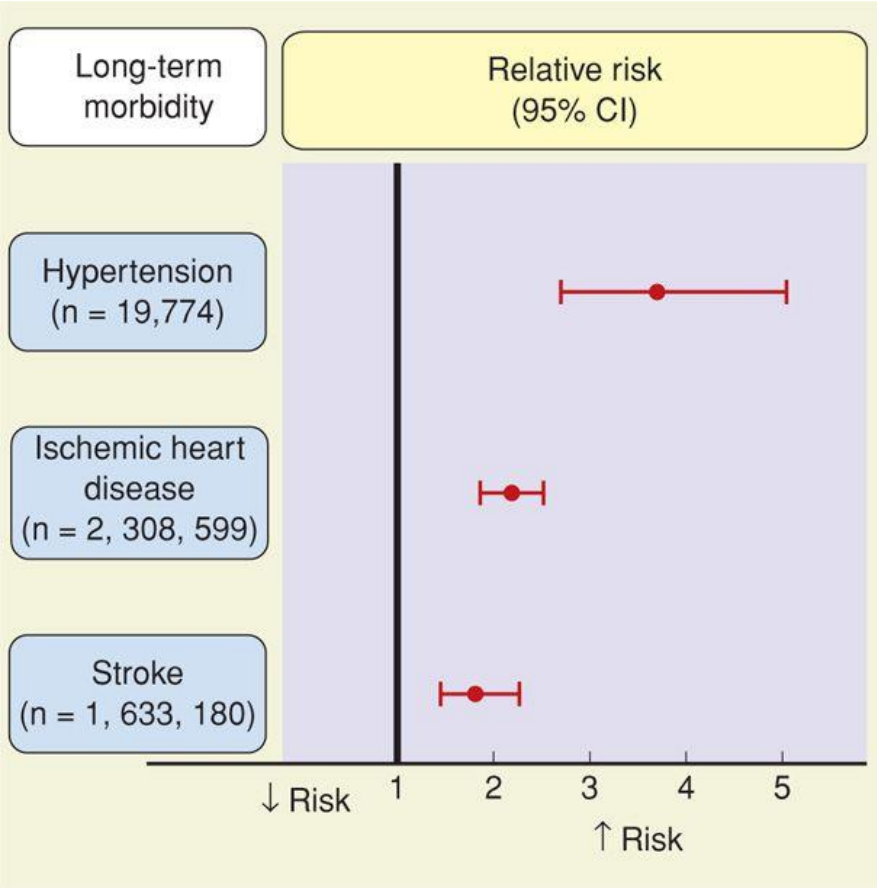

FIGURE 23. Long-term cardiovascular consequences of preeclampsia. All differences $p \leq .001$ **(Data from Bellamy et al., 2007).**

As emphasized by several investigators, other cofactors or comorbidities are related to acquisition of these long-term adverse outcomes **(Harskamp et al., 2007; Gastrich et al., 2012; Hermes et al., 2012; Spaan et al., 2012b).**

These include but are not limited to the metabolic syndrome, diabetes, obesity, dyslipidemia, and atherosclerosis. These conclusions are underscored by the findings of **Berends and colleagues (2008),** who confirmed shared constitutional risks for long-term

vascular-related disorders in preeclamptic women and in their parents. Similar preliminary observations were reported by **Smith (2009; 2012) and Stekkinger (2013) and their associates.**

At least in some of these women, their hypertensive cardiovascular pathologies appear to have begun near the time of their own births. For example, individuals who are born preterm have increased ventricular mass later in life **(Lewandowski et al., 2013).**

Women who have preeclampsia and who develop chronic hypertension later in life have an increased ventricular mass index before they become hypertensive. A similar phenomenon is associated with preterm birth and with fetal-growth disorders **(Ghossein-Doha et al., 2013).**

RENAL SEQUELAE

Preeclampsia appears to also be a marker for subsequent renal disease. In a preliminary study, the possibility was raised that persistent podocyturia might be a marker for such disease **(Garrett et al., 2013).** In a 40-year study of Norwegian birth and end-stage renal disease linked registries, although the absolute risk of renal failure was small, preeclampsia was associated with a fourfold increased risk **(Vikse et al., 2008).** Women with recurrent preeclampsia had an even greater risk. These data need to be considered in light of the findings that 15 to 20 percent of women with preeclampsia who undergo renal biopsy have evidence of chronic renal disease **(Chesley et al., 1978).**

In another long-term follow-up study, **Spaan and coworkers (2009)** compared formerly preeclamptic women with a cohort of women who were normotensive at delivery. At 20 years following delivery, preeclamptic women were significantly more likely to be chronically hypertensive—55 versus 7 percent—compared with control women. They also had higher peripheral vascular and renovascular resistance and decreased renal blood flow. These data do not permit conclusions as to cause versus effect.

NEUROLOGICAL SEQUELAE

Until recently, eclamptic seizures were believed to have no significant long-term sequelae. Findings have now accrued, however, that this is not always the case. Recall that almost all eclamptic women have multifocal areas of perivascular edema, and about a fourth also have areas of cerebral infarction **(Zeeman et al., 2004a).**

A Dutch group has reported several long-term follow-up studies in women with severe preeclampsia and eclampsia **(Aukes et al., 2007; 2009; 2012).** These investigators found long-term persistence of brain white-matter lesions that were incurred during eclamptic convulsions **(Aukes et al., 2009).** When studied with MR imaging at a mean of 7 years, 40 percent of formerly eclamptic women had more numerous and larger aggregate white matter lesions compared with 17 percent of normotensive control women. These investigators later also observed these white-matter lesions in preeclamptic women without convulsions **(Aukes et al., 2012).**

In studies designed to assess clinical relevance, **Aukes and colleagues (2007)** reported that formerly eclamptic women had subjectively impaired cognitive functioning. They also reported that women with multiple seizures had impaired sustained attention compared with normotensive controls **(Postma et al., 2009).**

Recently, **Wiegman and associates (2012)** described that formerly eclamptic women at approximately 10 years had lower vision-related quality of life compared with control subjects. Because there were no studies done before these women suffered from preeclampsia or eclampsia, the investigators appropriately concluded that cause versus effect of these white-matter lesions remains unknown.

PRENATAL CARE

Introduction

Organized prenatal care in the United States was introduced largely by social reformers and nurses. In 1901, Mrs. William Lowell Putnam of the Boston Infant Social Service Department began a program of nurse visits to women enrolled in the home delivery service of the Boston Lying-in Hospital **(Merkatz et al., 1990).**

It was so successful that a prenatal clinic was established in 1911. In 1915, J. Whit ridge Williams reviewed 10,000 consecutive deliveries at Johns Hopkins Hospital and concluded that 40 percent of 705 perinatal deaths could have been prevented by prenatal care. In 1954, Nicholas J. Eastman credited organized prenatal care with having "done more to save mothers' lives in our time than any other single factor." In the 1960s, Dr. Jack Pritchard established a network of university-operated prenatal clinics located in the most underserved communities in Dallas County. In large part because of increased accessibility, currently more than 95 percent of medically indigent women delivering at Parkland Hospital receive prenatal care. Importantly and related, the perinatal mortality rate of women in this system is less than that of the United States overall. Antenatal care is the clinical assessment of mother and fetus during pregnancy, for the purpose of obtaining the best possible outcome for the mother and child **(Duckitt and Harrington, 2011).**

The concept of the unbooked mothers has traditionally associated with women in developing countries who are unable or unwilling to access healthcare facilities. In studies of unbooked deliveries in African countries, older women of lower socioeconomic status and high parity have been identified as the groups most likely not to book for antenatal care and therefore more likely to have preterm babies and incur maternal mortality **(Filmer and Pritchett, 2001).**

Experiences from different countries have shown that reducing maternal mortality may depend in part on the availability and use of a professional attendant at labor and a referral mechanism for obstetric care for managing complications, or use of basic essential obstetric care facilities for all deliveries **(Ronsmans and Graham, 2006).**

In many developing countries however, the majority of births occur at home, frequently without the help of a skilled assistant (midwife, nurse trained as midwife or a doctor) **(Abou Zahr and Wardlaw, 2001).** The effect of antenatal care on maternal mortality is unclear **(Bullough et al., 2005).** However, there is broad agreement that antenatal care interventions can lead to improved maternal and newborn health, which can also impact on the survival and health of the infant **(World Health Organization-United Nations Children's Fund [WHO-UNICEF], 2003).**

A global evaluation of antenatal care has resulted in the recommendation to deliver antenatal services in 4 focused visits (Focused antenatal care; FANC), one within the first trimester and 3 after quickening, and this schedule is now endorsed by WHO **(van Eijk et al., 2008).** Proven effective antenatal interventions include serologic screening for syphilis, provision of malaria prevention, anti-tetanus immunization, and prevention of mother-to-child transmission of Human Immunodeficiency Virus (HIV) **(Khan et al., 2006).** To fully benefit from these interventions, it is important that women start visiting the antenatal clinic (ANC) early in pregnancy **(Freedman et al., 2005).**

MATERNAL HEALTH

Maternal health refers to the health of women during pregnancy, childbirth and the postpartum period. While motherhood is often a positive and fulfilling experience, it is associated with suffering, ill-health and even death for to many women. There is little information about maternal health and morbidity in many countries and, therefore, maternal mortality is often used as a proxy indicator for maternal health **(Filippi et al., 2005).**

Every minute, at least one woman dies from complications related to pregnancy or childbirth i.e. 529,000 women per year. In addition, for every woman who dies in childbirth, around 20 more suffer injury, infection or disease – approximately10 million women each year **(WHO, 2009)**. Five direct complications that account for more than 70% of maternal deaths are: hemorrhage, infection, unsafe abortion, eclampsia and obstructed labor. This did not change during the 12 year period from 1988 to 2000 **(Khan et al, 2006)** and even during the last decade **(WHO, 2009).**

Unavailable, inaccessible, unaffordable, and/or poor quality care are fundamentally responsible for maternal deaths worldwide. These deaths are detrimental to social development and well-being, as some one million children are left motherless each year. These children are 10 times more likely to die within two years of their mothers' death **(WHO, 2005).**

Importance of Antenatal Care in reduction of Maternal Morbidity and Mortality

In developing countries, the major causes of maternal mortality remain hemorrhage(21%), eclampsia (18.6%), sepsis (13.3%), abortion (11%), obstructed labor (8.7%) and others(27.4%) **(Society of Obstetricians and Gynecologists, 1990).**

Good antenatal care, its provision and accessibility can mostly prevent all the above causes that require emergency obstetrical care. In 1994, the International Conference on Population and development (ICPD) held in Cairo, emphasized the importance and need for maternal health care services that will enable women to go safely through pregnancy and childbirth to produce a healthy baby. One of the cornerstone of provision of good maternal health service is antenatal care that not only identifies risks and detects complications like hypertension and mal-presentations, but also provides information on: i-recognition of danger signs and symptoms, ii- where to going case of emergency and iii- transportation to referral site **(Matthews et al., 2001).**

Antenatal visits can play a critical role in establishing confidence between the woman, the family and the health care provider. In developing countries only 65% women receive antenatal care compared to 97% in developed countries. In urban Sindh

63% women avail antenatal care as opposed to only 15% in the rural areas. According to the Maternal and Infant Mortality Survey (MIMS)- Sindh of 3998 women, the three main reasons cited for not availing antenatal care were women's perception of no complaints (44%), services not available (21.4%) and costs too much (14%). The article published in this issue indicates that social status and economic conditions were important determinants of utilization of antenatal services **(MIMS- Sindh, 1994).**

A study from Rajasthan, India also observed that socio-economic status and literacy levels influenced utilization of antenatal service **(Mondal, 1997).** The importance of quality antenatal care cannot be questioned. But without availability of transport and efficient round the clock Emergency Obstetric Care (EmOC) facilities, it is not possible to reduce maternal morbidity and mortality. It is estimated that in Pakistan 1 in 20 women who suffer from complications of pregnancy reach a health facility where EmOC is available. This is due to three types of delays: delay in seeking care, delay in reaching to an EmOC and delay in starting treatment due to non-availability of trained health care personnel, blood, life saving drugs and equipment. In a survey of 48 health facility in 4 districts of Sindh almost none were providing quality EmOC **(Women's Health in Pakistan, 1997).**

MATERNAL HEALTH SERVICES IN DEVELOPED COUNTRIES

The importance of maternal health care is acknowledged nationally and internationally and listed among one of the Millennium development goals **(WHO, 2004).**

For last few decades, maternal health care became one of the key points in the health care service delivered in developed countries and because of that, these countries achieved significant results in terms of reduction of maternal mortality and morbidity. For example in Australia, the Western Australian Department of Health developed integrated and responsive maternal health care services that can be adapted according to the individual need of the patients in their own settings **(Western-Australian Department**

of Health, 2007). In the United Kingdom, maternal care is available to all women **(The House of Commons, 2003).**

MATERNAL HEALTH SERVICES IN DEVELOPING COUNTRIES

The situation is different in developing countries. In these countries, maternal mortality and morbidity remain high. However, many countries have taken important steps to address this problem. In Tanzania, **Jahn et al. (1996)** reported that despite pursuing the risk approach and good antenatal coverage, antenatal care in Tanzania has only limited effect on extending obstetric care to high-risk mothers.

In Zambia, the Department of Health has taken necessary steps to provide a patient-centered family orientated maternal health care services based on "Making pregnancy safer initiative' of WHO **(Maimbolwa, 2004).**

In Mozambique, the Department of Health introduced a patient friendly community participation approach by involving the patients, their families and communities **(Sundby et al., 2002).**

Although the effect of these newer initiatives on maternal mortality and morbidity is yet to be seen, there are some evidences emerging. For example, in Ghana, utilization of maternal health services was found to be directly associated with reduction in maternal and neonatal mortality **(Ansong-Tomui et al., 2007).**

In Botswana, the numbers of syphilis cases were declining because of compulsory checking of Rapid Plasma Reagin (RPR) test during antenatal attendance **(Creek et al., 2005).**

MATERNAL HEALTH SERVICES IN SOUTH AFRICA

In South Africa, maternal and child care always remained as key priority areas for the Government. The South African government also introduced free maternal care in 1994 **(Republic of South Africa, 1994).** The Maternal, child and women's health is currently one of the strategic goals for the current strategic plan **(Department of Health,**

2009). As a part of that process, the Minister of Health established National Committee for Confidential Enquiries into Maternal Deaths. This Committee has produced four reports till date. These reports critically analyze the maternal mortality in South Africa and provide valuable recommendations. However, most of these recommendations remained same for the last decade and not much progress has been made for implementation of these recommendations at the facility level. Poor record-keeping, inadequate supervision, poor levels of clinical knowledge and under-utilisation of midwife obstetric units were some of the challenges identified for maternal health services in South Africa **(Thomas et al., 2007).**

Maternity cases in South Africa are managed in different levels of health care (primary, secondary or tertiary) according to the risk category of patients. Patients are classified into no risk, low risk, medium risk and high risk. Based on the classifications, the cases are managed at appropriate level of care. This risk classification is expected to guide the management of cases at the health facilities. This arrangement is expected to improve maternal services and maternal and perinatal outcomes **(Farrell and Pattinson, 2005).** However, a similar study done in Zimbabwe did not find the usefulness of risk scores **(Majoko et al. 2002).**

Recently, the Perinatal Mother to Child Transmission (PMTCT) Programme became an integral part of maternal health services. Adequate management of HIV in pregnancy is key to the successful implementation of maternal health services due to a high prevalence of HIV in this country **(Hoque et al., 2008).**

ANTENATAL CARE

Antenatal care is identified as one of the key programmes for improvement of maternal health not only in South Africa but also rest of the world. Antenatal care is an intervention aimed at pregnant women to ensure the best possible outcome for both the mother and the baby. The WHO recommends antenatal care to be one of the interventions aimed at decreasing maternal and perinatal mortality and it recommends at least four visits for an adequate level of antenatal care **(WHO, 2009).**

Women should book as soon as pregnancy is detected which could be as early as six weeks of gestation in order to be screened for any pregnancy related problems, to review the risk of the pregnancy and to make provision for medications that may improve the pregnancy outcome. A woman is generally considered to be booked if she has had at least two clinic visits at least two weeks before giving birth and had booking bloods taken at the first visit **(Cronje and Grobler, 2003; WHO, 2009).**

Despite all the advantages of regular antenatal care, late bookings and missed visits still occur in South Africa. There are still some pregnant women who present to the health facility to deliver without ever attending any antenatal care. Some of the reasons for late bookings include the following: young age, primigravidae, multigravidae, being a single parent, low socio-economic status, unemployment, and time constraints and for some women, the distance away from the health care facility contributes to being un-booked **(Blondel et al, 1993; Mutihir and Nyiputen, 2007).**

Booked women are found to get early, ongoing monitoring and a continuous risk assessment **(Fiscella, 1995).** This includes health education, information about self-care in pregnancy, danger signs and symptoms of pregnancy. The antenatal care could address a delivery plan with an estimated date, place and mode of delivery for the current pregnancy and allow for planning of future pregnancies and contraception use. If indicated, additional tests, nutritional supplements and treatment of medical problems could be commenced. Antenatal care also has the additional advantage of ensuring that a woman is attended to by a skilled healthcare professional during pregnancy and labor which is an important point of entry in the prevention of mother to child transmission of HIV **(Abou-Zahr and Wardlaw, 2003).** On the other hand, unbooked pregnant women were found to be twice at risk of operative delivery, four times more likely to suffer delivery complications and twice likely to have low birth weight babies when compared to booked patients **(Okunlola et al., 2008).**

With regards to universal access to reproductive health, the provision of antenatal care is used as an indicator of access. The 2003 South African Demographic Health Survey (SADHS) reported antenatal attendance to be in the region of 92% for the pregnant population, which was slightly lower (94%) than the 1998 survey. About 5.3% of pregnant women never attended antenatal care and the remaining 2.7% had no knowledge of any antenatal care service provision. The majority (60%) of first antenatal visits occurred within the first 6 months of pregnancy. Approximately one quarter of women attended for the first time at between 6 and 7 months and almost 3% attended for the first time in their 8th month of pregnancy **(Department of Health, 2007).**

The 2006 District Health Information System (DHIS) data reported antenatal coverage of 100% but some provinces (such as Gauteng, Kwa-Zulu Natal, Mpumalanga and Northern Cape) reported antenatal coverage of more than 100%, raising concerns about the quality of data. The same report described the average number of antenatal visits was 3.4 **(Health Systems Trust, 2009).**

Briggs (1988) studied a cohort of 10,665 deliveries in a hospital in Nigeria and found booking status was significantly associated with ante-partum and postpartum hemorrhage, severe anemia, and undiagnosed medical and surgical complications. The author stressed the importance of antenatal care as one of the key factors to a large-scale reduction in maternal mortality.

Subsequently, another Nigerian study in a different hospital found 29% unbooked mother among a cohort of 1,154 deliveries. The study also found a significant association between booking status and occurrence of maternal complications (such as anemia and ante-partum hemorrhage) and perinatal outcomes (such as preterm babies**) (Owalabi et al., 2008).**

However, a South African study found no difference in the perinatal mortality between booked and unbooked mothers, although there were higher rates of low birth weight and prematurity among the unbooked mothers **(Ndiweni and Buchmann, 1998).**

ANTENATAL CARE BOOKING AND PROFILE OF PATIENTS

It is important to identify profile of unbooked patients and develop an understanding of the factors that might influence their inability to book during pregnancy. Almost thirty years ago, **Larsen and van Middelkoop (1982)** conducted a study at the King Edward VIII Hospital, Durban and found that the unbooked mother was found to come more frequently from a background of unstable relationships, financial and emotional support and geographical inaccessibility. Unwanted babies and inadequate parenting arrangements were more frequent in this group. Previous operative deliveries were found to have no influence on booking status.

A recent study done in Azerbaijan found women's education, socio-economic status, gravidity and desirability of the current pregnancy have a significant effect on antenatal care utilization **(Habibov, 2010).**

This was similar to findings of a study done in Brussels, where researchers found women's education, higher socio-economic status, and low gravidity had a significant effect on higher antenatal care utilization. They also found ethnicity, and previous medical history played some role **(Beeckman et al., 2010).**

In addition to the patient related factors, assessing health care facilities may also play a role in antenatal care utilization. This is influenced by various factors such as transport from home, poor quality of services, and attitude of health care providers. Therefore, it is important to study both patient and health system related factors in a local setting to develop an understanding of antenatal care utilization in that area **(Gaunt, 2010).**

Overview of Prenatal Care

Almost a century after its introduction, prenatal care has become one of the most frequently used health services in the United States. In 2006, more than 4.2 million births were registered in the United States **(Martin et al., 2009).**

In 2001, there were approximately 50 million prenatal visits—the median was 12.3 visits per pregnancy—and as shown in **Figure 24,** many women had 17 or more visits.

Since the early 1990s, the largest gains in timely prenatal care have been among minority groups. As shown in **Figure 25,** however, disparity continues. In 2006, African American and Hispanic women were more than twice as likely as non-Hispanic white women to begin prenatal care after the first trimester **(Martin et al., 2009).**

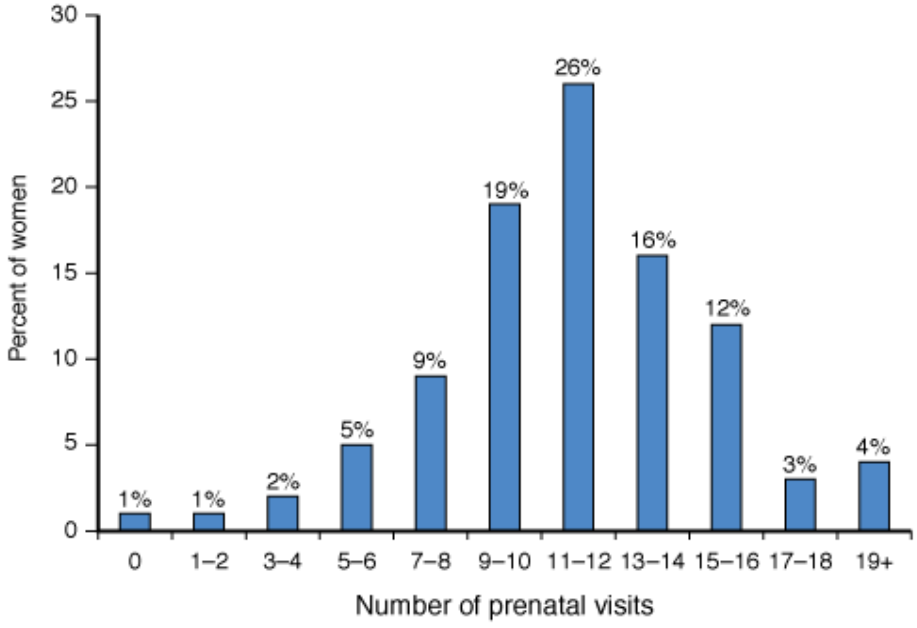

FIGURE 24. Frequency distribution of the number of prenatal visits for the United States in 2001 (Adapted from Martin et al., 2002b).

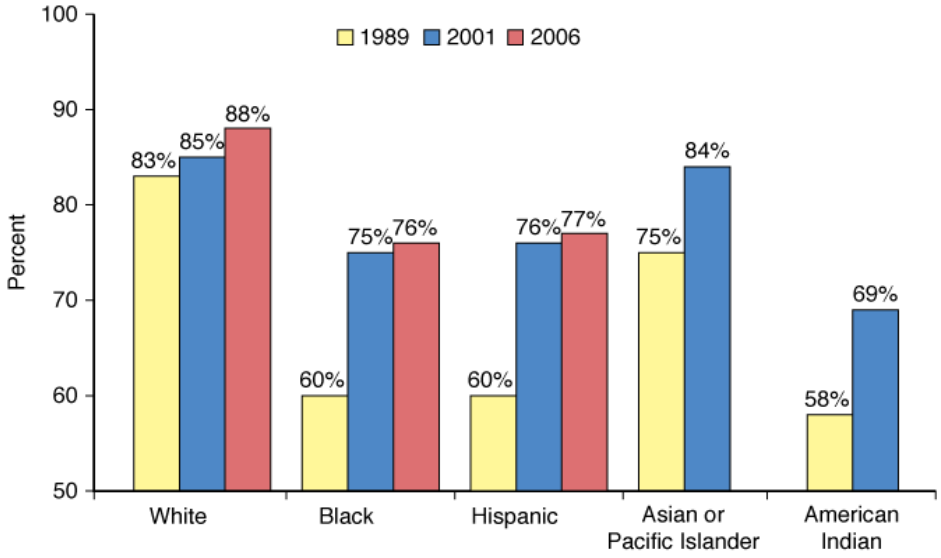

Figure 25. Percentage of women in the United States with prenatal care beginning in the first trimester by ethnicity in 1989, 2001, and 2006 (Adapted from Martin et al., 2002b; 2009.)

Obstetrical and medical risk factors or complications identifiable during prenatal care are summarized in **Table XIX.** Importantly, many of these complications are treatable

TABLE XIX. Obstetrical and Medical Risk Factors Detected during Prenatal Care in the United States in 2001 (Data from Martin et al., 2002b):

Risk Factor	**Births**	**Percent**
Total live births	4,025,933	100
Gestational hypertension	150,329	3.7
Diabetes	124,242	3.1
Anemia	99,558	2.5
Hydramnios/oligohydramnios	54,694	1.4
Lung disease	48,246	1.2
Genital herpes	33,560	0.8
Chronic hypertension	32,232	0.8
D (Rh) sensitization	26,933	0.7

Cardiac disease	20,698	0.5
Renal disease	12,045	0.3
Incompetent cervix	11,251	0.3
Hemoglobinopathy	3,141	0.1
Total	616,929	15.3

Assessing Adequacy of Prenatal Care

A commonly employed system for measuring prenatal care adequacy is the index of **Kessner et al. (1973).** As shown in **Table XX,** this Kessner Index incorporates three items from the birth certificate: length of gestation, timing of the first prenatal visit, and number of visits.

Table XX. Kessner Index Criteria:

Adequate Prenatal Care

Initial visit in first trimester and:

Weeks		**Attended Prenatal Visits**
17	and	2 or more
18–21	and	3 or more
22–25	and	4 or more
26–29	and	5 or more
30–31	and	6 or more
32–33	and	7 or more
34–35	and	8 or more
36 or more	and	9 or more

Inadequate Prenatal Care

Initial visit in third trimester or:

Weeks		**Attended Prenatal Visits**
17–21	and	None
22–29	and	1 or fewer
30–31	and	2 or fewer

32–33	and	3 or fewer
34 or more	and	4 or fewer

Intermediate Care

All other combinations

It does not, however, measure the quality of care, nor does it consider the relative risk of complications for the mother. Still, the index remains a useful measure of prenatal care adequacy. Using this index, the National Center for Health Statistics concluded that 12 percent of American women who were delivered in 2000 received inadequate prenatal care **(Martin et al., 2002a).**

The **Centers for Disease Control and Prevention (CDC) (2000)** analyzed birth certificate data for the years 1989 to 1997 and found that half of women with delayed or no prenatal care wanted to begin care earlier. Reasons for inadequate prenatal care are varied by social and ethnic group, age, and method of payment. The most common reason cited was late identification of pregnancy by the patient. The second most commonly cited barrier was lack of money or insurance for such care. The third was inability to obtain an appointment.

Effectiveness of Prenatal Care

Prenatal care designed during the early 1900s was focused on lowering the extremely high maternal mortality rates. Such care undoubtedly contributed to the dramatic decline in maternal mortality rates from 690 per 100,000 births in 1920 to 50 per 100,000 by 1955 **(Loudon, 1992).** Maternal Mortality, the current low maternal mortality rate of approximately 8 per 100,000 is likely associated with the high utilization of prenatal care. Indeed, in a population-based study from North Carolina, **Harper et al. (2003)** found that the risk of pregnancy-related maternal death was decreased fivefold among recipients of prenatal care.

There are other studies that attest to the efficacy of prenatal care. **Herbst et al. (2003)** found that no prenatal care was associated with more than a twofold increased risk of preterm birth. **Schramm (1992)** compared the costs and benefits of prenatal care in

1988 for more than 12,000 Medicaid patients in Missouri. For each $1 spent for prenatal care, there were estimated savings of $1.49 in newborn and postpartum costs.

Vintzileos et al. (2002a) analyzed National Center for Health Statistics data for 1995 to 1997. They reported that women with prenatal care had an overall stillbirth rate of 2.7 per 1000 compared with 14.1 per 1000 for women without prenatal care—an adjusted relative risk of 3.3 for fetal death.

Vintzileos et al. (2002b; 2003) later reported that prenatal care was associated with significantly lower rates of preterm births as well as neonatal death associated with several high-risk conditions that included placenta previa, fetal-growth restriction, and post-term pregnancy.

Component of Prenatal Care

The essence of prenatal care is described by the **American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2007)** as: "A comprehensive antepartum care program involves a coordinated approach to medical care and psychosocial support that optimally begins before conception and extends throughout the antepartum period." This comprehensive program includes: (1) pre-conceptional care, (2) prompt diagnosis of pregnancy, (3) initial prenatal evaluation, and (4) follow-up prenatal visits.

Pre-conceptional Care

Because health during pregnancy depends on health before pregnancy, pre-conceptional care should logically be an integral prelude to prenatal care. A comprehensive pre-conceptional care program has the potential to assist women by reducing risks, promoting healthy lifestyles, and improving readiness for pregnancy.

Diagnosis of pregnancy

The diagnosis of pregnancy usually begins when a woman presents with symptoms, and possibly a positive home urine pregnancy test result. Typically, such

women receive confirmatory testing of urine or blood for human chorionic gonadotropin (hCG). There may be presumptive or diagnostic findings of pregnancy on examination. Sonography is often used, particularly in those cases in which there is question about pregnancy viability or location **(Cole et al., 2004).**

Initial Prenatal Evaluation

According to **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007),** prenatal care should be initiated as soon as there is a reasonable likelihood of pregnancy. The major goals are to:

1. Define the health status of the mother and fetus.
2. Estimate the gestational age.
3. Initiate a plan for continuing obstetrical care.

Typical components of the initial visit are summarized in **Table XXI.** Initial plan for subsequent care may range from relatively infrequent routine visits to prompt hospitalization because of serious maternal or fetal disease.

PRENATAL RECORD

Use of a standardized record within a perinatal healthcare system greatly aids antepartum and intrapartum management. Standardizing documentation may allow communication and continuity of care between providers and enable objective measures of care quality to be evaluated over time and across different clinical settings **(Gregory et al., 2006).** A prototype is provided by the **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007).**

TABLE XXI. Typical Components of Routine Prenatal Care (Data from Martin et al., 2008):

	Weeks			
	First Visit	**15–20**	**24–28**	**29–41**
History				
Complete	*			
Updated		*	*	*
Physical examination				
Complete	*			
Blood pressure	*	*	*	*
Maternal weight	*	*	*	*
Pelvic/cervical examination	*			
Fundal height	*	*	*	*
Fetal heart rate/position	*	*	*	*
Laboratory tests				
Hematocrit or hemoglobin	*		*	
Blood type and Rh factor	*			
Antibody screen	*		**A**	
Pap smear screening	*			
Glucose tolerance test				

Continue TABLE XXI. Typical Components of Routine Prenatal Care (Data from Martin et al., 2008):

	Weeks			
	First Visit	**15–20**	**24–28**	**29–41**
Fetal aneuploidy screening	**B**[a] and/or	**B**		
Neural-tube defect screening		**B**		
Cystic fibrosis screening	**B** or	**B**		
Urine protein assessment	*			
Urine culture	*			
Rubella serology	*			
Syphilis serology	*			**C**
Gonococcal culture	**D**			**D**
Chlamydial culture	*			**C**
Hepatitis B serology	*			
HIV serology	**B**			
Group B streptococcus culture				**E**

- [a] First-trimester aneuploidy screening may be offered between 11 and 14 weeks.
- HIV = human immunodeficiency virus.
- **A** Performed at 28 weeks, if indicated.
- **B** Test should be offered.
- **C** High-risk women should be retested at the beginning of the third trimester.
- **D** High-risk women should be screened at the first prenatal visit and again in the third trimester.
- **E** Rectovaginal culture should be obtained between 35 and 37 weeks.

DEFINITIONS

There are several definitions pertinent to establishment of an accurate prenatal record.

- *Nulligravida:* a woman who currently is not pregnant, nor has she ever been pregnant.
- *Gravida:* a woman who currently is pregnant or she has been in the past, irrespective of the pregnancy outcome. With the establishment of the first pregnancy, she becomes a primigravida, and with successive pregnancies, a multigravida.
- *Nullipara:* a woman who has never completed a pregnancy beyond 20 weeks' gestation. She may or may not have been pregnant or may have had a spontaneous or elective abortion(s) or an ectopic pregnancy.
- *Primipara:* a woman who has been delivered only once of a fetus or fetuses born alive or dead with an estimated length of gestation of 20 or more weeks.
- *Multipara:* a woman who has completed two or more pregnancies to 20 weeks or more. Parity is determined by the number of pregnancies reaching 20 weeks and not by the number of fetuses delivered. Parity is the same (para 1) for a singleton or multifetal delivery or delivery of a live or stillborn infant.

In the past, a 500-g birth weight threshold was used to define parity. This threshold is no longer as pertinent because of the survival of infants with birth weights less than 500 g.

In some locales, the obstetrical history is summarized by a series of digits connected by dashes. These refer to the number of term infants, preterm infants, abortuses less than 20 weeks, and children currently alive. For example, a woman who is para 2–1–0–3 has had two term deliveries, one preterm delivery, and no abortuses, and has three living children. Because these are non-conventional, it is helpful to specify the outcome of any pregnancy that did not end normally **(Merkatz et al., 1990).**

HISTORY

For the most part, the same essentials go into appropriate history-taking from the pregnant woman as elsewhere in medicine. Detailed information concerning past

obstetrical history is crucial because many prior pregnancy complications tend to recur in subsequent pregnancies. The menstrual history is extremely important. The woman who spontaneously menstruates regularly every 28 days or so is most likely to ovulate at midcycle. Thus, gestational or menstrual age is the number of weeks since the onset of the last menstrual period. If her menstrual cycles were significantly longer than 28 to 30 days, ovulation more likely occurred well beyond 14 days. If the intervals were much longer and irregular, chronic anovulation is likely to have preceded some of the episodes identified as menses. Without a history of regular, predictable, cyclic, spontaneous menses that suggest ovulatory cycles, accurate dating of pregnancy by history and physical examination is difficult. It is also important to be sure whether or not steroidal contraceptives were used before the pregnancy. Because ovulation may not have resumed 2 weeks after the onset of the last withdrawal bleeding and instead may have occurred at an appreciably later and highly variable date, using the time of ovulation for predicting the time of conception in this circumstance may be erroneous. Use of sonography in early pregnancy will clarify gestational age in these situations **(Merkatz et al., 1990).**

Psychosocial Screening

The **American College of Obstetricians and Gynecologists (2006)** defines psychosocial risk factors as non biomedical factors that affect mental and physical well-being. The College advocates psychosocial screening at least once each trimester to increase the likelihood of identifying important issues and reducing adverse pregnancy outcomes. Screening for barriers to care includes lack of transportation, child care, or family support; unstable housing; unintended pregnancy; communication barriers; nutritional problems; cigarette smoking; substance abuse; depression; and safety concerns that include domestic violence.

Such screening is performed regardless of social status, education level, or race and ethnicity, shown in **Table XXII** is one recommended screening tool.

TABLE XXII. Psychosocial Screening Tool (American College of Obstetricians and Gynecologists, 2006):

1. Do you have any problems (job, transportation, etc.) that prevent you from keeping your healthcare appointments? Yes No
2. Do you feel unsafe where you live? Yes No
3. In the past 2 months, have you used any form of tobacco? Yes No
4. In the past 2 months, have you used drugs or alcohol? Yes No
5. In the past year, have you been threatened, hit, slapped, or kicked by anyone you know? Yes No
6. Has anyone forced you to perform any sexual act that you did not want to do? Yes No
7. On a 1-to-5 scale, how do you rate your current stress level? 1 2 3 4 5
8. How many times have you moved in the past 12 months? _____ low high
9. If you could change the timing of this pregnancy, would you want it: __ earlier; __ later; __not at all; __ no change.

Cigarette Smoking

Smoking results in unequivocal adverse sequelae for pregnant women and their fetuses **(United States Department of Health and Human Services, 2000).** Maternal smoking data has been included on the birth certificate since 1989. The number of pregnant women who smoke continues to decline, and from 1990 to 2003, the reported rate decreased from 18 to 13 percent **(American College of Obstetricians and Gynecologists, 2005b; Martin et al., 2009).**

According to the **CDC (2007),** 13 percent of women admitted to smoking during the last 3 months of pregnancy. Those most likely to smoke were younger and had less education.

Numerous adverse outcomes have been linked to smoking during pregnancy. Tobacco had potential teratogenic effects. There is a twofold risk of placenta previa, placental abruption, and premature membrane rupture compared with nonsmokers. Further, babies born to women who smoke are approximately 30 percent more likely to

be born preterm, weigh on average a half pound less, and are up to three times more likely to die of sudden infant death syndrome (SIDS) than infants born to nonsmokers **(CDC, 2007).**

In 2001, the incidence of low-birthweight infants born to American women who smoked during pregnancy was 11.9 percent compared with 7.3 percent born to nonsmokers **(Martin et al., 2002b).** Finally, risks for spontaneous abortion, fetal death, and fetal digital anomalies are also increased **(Man and Chang, 2006).**

A number of pathophysiological mechanisms have been proposed to explain these adverse outcomes. They include fetal hypoxia from increased carboxyhemoglobin, reduced uteroplacental blood flow, and direct toxic effects of nicotine and other compounds in smoke **(ACOG, 2005b).**

Nicotine transfer is so efficient that fetal nicotine exposure is greater than that of the mother**.** Exposed fetuses have decreased heart rate variability, due to impaired autonomic regulation **(Luck et al., 1985).**

According to the **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007),** perinatal mortality rates would be reduced by 5 percent if maternal smoking was eliminated.

Smoking Cessation

The most successful efforts for smoking cessation during pregnancy involve interventions that emphasize how to stop. One example is a 5-step session lasting 15 minutes or less in which the provider: (1) Asks about smoking status; (2) Advises those who smoke to stop; (3) Assesses the willingness to quit within the next 30 days; (4) Assists interested patients by providing pregnancy-specific self-help materials; and (5) Arranges follow-up visits to track progress **(American College of Obstetricians and Gynecologists, 2005b).**

Nicotine replacement products have not been sufficiently evaluated to determine their effectiveness and safety in pregnancy. Interdiction is optimal-but not always pragmatic-before conception. Thus, the **American College of Obstetricians and Gynecologists (2005b)** has concluded that it is reasonable to use nicotine medications during pregnancy if prior non pharmacological attempts have failed.

Wisborg et al. (2000) randomly assigned 250 women who smoked at least 10 cigarettes per day to receive nicotine or a placebo patch beginning after the first trimester. Overall, 26 percent of these women stopped smoking, but there were no significant differences in smoking cessation, birth weight, or preterm delivery between the two groups. Importantly, no serious adverse effects from the patches were reported, but compliance with either treatment was low.

Alcohol Use during Pregnancy

Ethanol is a potent teratogen and can cause fetal alcohol syndrome characterized by growth restriction, facial abnormalities, and central nervous system dysfunction. Women who are pregnant or considering pregnancy should abstain from using any alcoholic beverages. Such use is substantively underreported on the birth certificate—less than 1 percent of women reported any alcohol use during pregnancy in 2001 **(Martin et al., 2002b).**

But, according to the **CDC, (2002a),** approximately 13 percent of pregnant women used alcohol in 1999. Although this was down from 16 percent in 1995, it is unfortunate that rates of binge and frequent drinking during pregnancy have not declined.

Illicit Drug Use

It is estimated that 10 percent of fetuses are exposed to one or more illicit drugs **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).** Agents may include heroin and other opiates, cocaine, amphetamines, barbiturates, and marijuana. Chronic use of large quantities is harmful to the fetus.

Well-documented sequelae include fetal distress, low birth weight, and drug withdrawal soon after birth. Women who use such drugs frequently do not seek prenatal care or if they do, they may not admit to the use of such substances. **El-Mohandes et al. (2003)** reported that when women who use illicit drugs receive prenatal care, the risks for preterm birth and low birth weight are reduced.

The **American College of Obstetricians and Gynecologists, (1999)** has reviewed methods for screening women during pregnancy for use of illicit drugs and for alcohol abuse.

Domestic Violence Screening

The term domestic violence usually refers to violence against adolescent and adult females within the context of family or intimate relationships. Such violence has been increasingly recognized as a major public health problem. Unfortunately, most abused women continue to be victimized during pregnancy. With the possible exception of preeclampsia, domestic violence is more prevalent than any major medical condition detectable through routine prenatal screening **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists 2007).**

The prevalence during pregnancy is estimated to be between 4 and 8 percent. Physical Abuse—Intimate Partner Violence, intimate partner violence is associated with an increased risk of a number of adverse perinatal outcomes including preterm delivery, fetal-growth restriction, and perinatal death. The **American College of Obstetricians and Gynecologists (2006)** has provided methods for screening for domestic violence and recommends their use at the first prenatal visit, then again at least once per trimester, and again at the postpartum visit.

PHYSICAL EXAMINATION

A thorough, general physical examination should be completed at the initial prenatal encounter.

Pelvic Examination

The cervix is visualized employing a speculum lubricated with warm water or water-based lubricant gel. Bluish-red passive hyperemia of the cervix is characteristic, but not of itself diagnostic, of pregnancy. Dilated, occluded cervical glands bulging beneath the ectocervical mucosa—nabothian cysts—may be prominent. The cervix is not normally dilated except at the external os. To identify cytological abnormalities, a Pap smear is performed, and specimens for identification of Chlamydia trachomatis and Neisseria gonorrhea are obtained. Bimanual examination is completed by palpation, with special attention given to the consistency, length, and dilatation of the cervix; to uterine size and any adnexal masses; to the fetal presentation later in pregnancy; to the bony architecture of the pelvis; and to any anomalies of the vagina and perineum. All cervical, vaginal, and vulvar lesions are evaluated further by appropriate use of colposcopy, biopsy, culture, or dark-field examination. The perianal region should be visualized and digital rectal examination performed **(CDC, 2002b).**

LABORATORY TESTS

The Institute of Medicine recommends universal HIV testing, with patient notification and right of refusal, as a routine part of prenatal care. The **CDC (2006b)** as well as the **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007)** supports this recommendation. If a woman declines testing, this should be recorded in the prenatal record. Pregnant women should also be screened for hepatitis B virus.

Based on their prospective investigation of 1000 women, **Murray et al. (2002)** concluded that in the absence of hypertension, routine urinalysis beyond the initial prenatal visit was not necessary.

Chlamydial Infection

Chlamydia trachomatis is isolated from the cervix in 2 to 13 percent of pregnant women. The **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007)** recommend that all women be screened during the first prenatal visit, with additional third-trimester testing for those at increased risk. Risk factors include unmarried status, recent change in sexual partner or multiple concurrent partners; age less than 25 years, inner-city residence, history or presence of other sexually transmitted diseases, and little or no prenatal care. Following treatment, repeat testing is recommended in 3 weeks. A negative prenatal test for chlamydia or gonorrhea should not preclude postpartum screening **(Mahon et al., 2002).**

HIGH-RISK PREGNANCIES

There are many risk factors that can be identified and given appropriate consideration in pregnancy management. Examples of common risk factors proposed by the **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007)** are shown in **Table XXIII.**

TABLE XXIII. Recommended Consultation for Risk Factors Identified in Early Pregnancy [a] (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007):

Medical History and Conditions	
Asthma	
Symptomatic on medication	OBG
Severe (multiple hospitalizations)	MFM
Cardiac disease	
Cyanotic, prior myocardial infarction, aortic stenosis, pulmonary hypertension, Marfan syndrome, prosthetic valve, American Heart Association class II or greater	MFM
Other	OBG
Diabetes mellitus	
Class A–C	OBG

Class D or greater	MFM
Drug and alcohol use	OBG
Epilepsy (on medication)	OBG
Family history of genetic problems (Down syndrome, Tay-Sachs disease, phenylketonuria)	MFM
Hemoglobinopathy (SS, SC, S-thalassemia)	MFM
Hypertension	
Chronic, with renal or heart disease	MFM
Chronic, without renal or heart disease	OBG
Prior pulmonary embolus or deep vein thrombosis	OBG

Continue TABLE XXIII. Recommended Consultation for Risk Factors Identified in Early Pregnancy [a] (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007):

Obstetrical History and Conditions	
Psychiatric illness	OBG
Pulmonary disease	
Severe obstructive or restrictive	MFM
Moderate	OBG
Renal disease	
Chronic, creatinine ≥3 mg/dL, ± hypertension	MFM
Chronic, other	OBG
Requirement for prolonged anticoagulation	MFM
Severe systemic disease	MFM
Age ≥35 years at delivery	OBG
Cesarean delivery, prior classical or vertical incision	OBG
Incompetent cervix	OBG

Prior fetal structural or chromosomal abnormality	MFM
Prior neonatal death	OBG
Prior fetal death	OBG
Prior preterm delivery or preterm ruptured membranes	OBG
Prior low birthweight (<2500 g)	OBG
Second-trimester pregnancy loss	OBG
Uterine leiomyomas or malformation	OBG

Continue TABLE XXIII. Recommended Consultation for Risk Factors Identified in Early Pregnancy [a] (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007):

Initial Laboratory Tests

Human immunodeficiency virus (HIV)

Symptomatic or low CD4 count	MFM
Other	OBG
CDE (Rh) of other blood group isoimmunization (excluding ABO, Lewis)	MFM
Initial examination condylomata (extensive, covering vulva or vaginal opening)	OBG

- [a] At the time of consultation, continued patient care should be determined by collaboration with the referring care provider or by transfer of care.
- OBG = obstetrician-gynecologist; MFM = Maternal-fetal medicine specialist.

In addition, **Table XXIV** lists ongoing risk factors for which consultation may be indicated. Some conditions may require the involvement of a maternal-fetal medicine sub-specialist, geneticist, pediatrician, anesthesiologist, or other medical specialist in the evaluation, counseling, and care of the woman and her fetus.

SUBSEQUENT PRENATAL VISITS

Subsequent prenatal visits have been traditionally scheduled at intervals of 4 weeks until 28 weeks, and then every 2 weeks until 36 weeks and weekly thereafter. Women with complicated pregnancies often require return visits at 1- to 2-week intervals. For example, **Luke et al. (2003)** found that a specialized prenatal care program that emphasized nutrition and education and that required return visits every 2 weeks resulted in improved outcomes in twin pregnancies.

TABLE XXIV. Recommended Consultation for Ongoing Risk Factors Identified during Pregnancy [a] (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007):

Medical History and Conditions	
Drugs/alcohol use	OBG
Proteinuria (≥2+ on catheterized sample, unexplained by urinary infection)	OBG
Pyelonephritis	OBG
Severe systemic disease that adversely affects pregnancy	OBG
Obstetrical History and Conditions	
Blood pressure elevation (diastolic BP ≥90 mm Hg), no proteinuria	OBG
Fetal-growth restriction suspected	OBG
Fetal abnormality suspected by sonography	
Anencephaly	OBG
Other	MFM
Fetal demise	OBG
Gestational age 41 weeks	OBG
Herpes, active lesion at 36 weeks	OBG
Hydramnios or oligohydramnios by sonography	OBG
Hyperemesis, persistent, beyond first trimester	OBG
Multifetal gestation	OBG
Preterm labor, threatened	OBG
Premature rupture of membranes	OBG
Vaginal bleeding ≥14 weeks	OBG

Continue TABLE XXIV. Recommended Consultation for Ongoing Risk Factors Identified during Pregnancy [a] (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007):

Examination and Laboratory Findings	
Abnormal MSAFP (high or low)	OBG
Abnormal Pap smear result	OBG
Anemia (hematocrit <28 percent, unresponsive to iron therapy)	OBG
Condylomata (extensive, covering labia and vaginal opening)	OBG
HIV	
Symptomatic or low CD4 count	MFM
Other	OBG
CDE (Rh) or other blood group isoimmunization (excluding ABO, Lewis)	MFM

- [a] At the time of consultation, continued patient care should be determined by collaboration with the referring care provider or by transfer of care.
- OBG = obstetrician-gynecologist; MFM = Maternal-fetal medicine specialist.

WHO conducted a multicenter randomized trial with almost 25,000 women comparing routine prenatal care with an experimental model designed to minimize visits. In the new model, women were seen once in the first trimester and screened for certain risk factors. Those without any anticipated complications—80 percent of the women screened—were seen again at 26, 32, and 38 weeks. Compared with routine prenatal care, which required a median of eight visits, the new model required a median of only five visits **(Villar et al., 2001).** No disadvantages were found in women with fewer visits, and these findings were consistent with other randomized trials **(McDuffie et al., 1996; Clement et al., 1999).**

Prenatal Surveillance

At each return visit, steps are taken to determine the well-being of mother and fetus **(Table XXV).** Certain information is considered especially important-an example is assessment of gestational age and accurate measurement of blood pressure **(Jones et al., 2003).**

TABLE XXV. Evaluation of maternal and fetal well-being typically includes:

Fetal

- Heart rate(s)
- Size—current and rate of change
- Amount of amnionic fluid
- Presenting part and station (late in pregnancy)
- Activity

Maternal

- Blood pressure—current and extent of change
- Weight—current and amount of change
- Symptoms—including headache, altered vision, abdominal pain, nausea and vomiting, bleeding, vaginal fluid leakage, and dysuria
- Height in centimeters of uterine fundus from symphysis
- Vaginal examination late in pregnancy often provides valuable information to include:
    1. Confirmation of the presenting part and its station.
    2. Clinical estimation of pelvic capacity and its general configuration.
    3. Consistency, effacement, and dilatation of the cervix.

ASSESSMENT OF GESTATIONAL AGE

This is one of the most important determinations at prenatal examinations. Precise knowledge of gestational age is important because a number of pregnancy complications may develop for which optimal treatment will depend on fetal age. Fortunately, it is possible to identify gestational age with considerable precision through an appropriately timed, carefully performed clinical examination, coupled with knowledge of the time of onset of the last menstrual period **(Worthen and Bustillo, 1980).**

Fundal Height

Between 20 and 34 weeks, the height of the uterine fundus measured in centimeters correlates closely with gestational age in weeks**.** The fundal height should be measured as the distance over the abdominal wall from the top of the symphysis pubis to the top of the fundus. The bladder must be emptied before making the measurement **(Jimenez al., 1983; Quaranta al., 1981).**

For example, **Worthen and Bustillo (1980)** demonstrated that at 17 to 20 weeks, fundal height was 3 cm higher with a full bladder. Obesity may also distort this relationship. Unfortunately, using fundal height alone, fetal-growth restriction may be undiagnosed in up to a third of cases **(American College of Obstetricians and Gynecologists, 2000).**

Fetal Heart Sounds

The fetal heart can first be heard in most women between 16 and 19 weeks when carefully auscultated with a standard non-amplified stethoscope. The ability to hear unamplified fetal heart sounds will depend on factors such as patient size and hearing acuity of the examiner **(American College of Obstetricians and Gynecologists, 2004c).**

Herbert et al. (1987) reported that the fetal heart was audible by 20 weeks in 80 percent of women. By 21 weeks, audible fetal heart sounds were present in 95 percent,

and by 22 weeks they were heard in all. The fetal heart rate now ranges from 110 to 160 bpm and is heard as a double sound resembling the tick of a watch under a pillow. Because the fetus moves freely in amnionic fluid, the site on the maternal abdomen where fetal heart sounds can be heard best will vary.

Instruments incorporating Doppler ultrasound instruments are often used to easily detect fetal heart action, almost always by 10 weeks. Using real-time sonography with a vaginal transducer, fetal cardiac activity can be seen as early as 5 menstrual weeks **(American College of Obstetricians and Gynecologists, 2004c).**

Sonography

In the United States, about two thirds of women have at least one prenatal sonographic examination **(Martin et al., 2005).** And within the past decade, many women have an initial sonographic evaluation as part of first-trimester aneuploidy screening, followed by a standard examination in the second trimester to evaluate fetal anatomy **(American College of Obstetricians and Gynecologists, 2009).**

The **American College of Obstetricians and Gynecologists, (2009)** has concluded that a physician is not obligated to perform sonography without a specific indication in a low-risk patient, but that if she requests sonography, it is reasonable to honor her request.

SUBSEQUENT LABORATORY TESTS

If initial results in **(Table XXV)** were normal, most tests need not be repeated. Fetal aneuploidy screening may be performed at 11 to 14 weeks and/or at 15 to 20 weeks, depending on the protocol selected. Serum screening for neural-tube defects is offered at 15 to 20 weeks **(Hollier et al., 2003).**

Hematocrit or hemoglobin determination, along with syphilis serology if it is prevalent in the population, should be repeated at 28 to 32 weeks. Women who are D (Rh) negative and are unsensitized should have an antibody screening test repeated at 28

to 29 weeks, with administration of anti-D immune globulin if they remain unsensitized **(Hollier et al., 2003).**

Cystic fibrosis carrier screening should be offered to couples with a family history of cystic fibrosis and to Caucasian couples of European or Ashkenazi Jewish descent planning a pregnancy or seeking prenatal care. Ideally, screening is performed before conception or during the first or early second trimester. Information about cystic fibrosis screening also should be provided to patients in other racial and ethnic groups who are at lower risk (**Kiss et al., 2004).**

Group B Streptococcal (GBS) Infection

The **American College of Obstetricians and Gynecologists (2002c)** and the **CDC (2002b)** recommend that vaginal and rectal GBS cultures be obtained in all women between 35 and 37 weeks. Intrapartum antimicrobial prophylaxis is given for those whose cultures are positive. Women with GBS bacteriuria or a previous infant with invasive disease are given empirical intrapartum prophylaxis.

Gestational Diabetes

All pregnant women should be screened for gestational diabetes mellitus, whether by history, clinical factors, or routine laboratory testing. Although laboratory testing between 24 and 28 weeks is the most sensitive approach, there may be pregnant women at low risk who are less likely to benefit from testing **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).**

Gonococcal Infection

Risk factors for gonorrhea are similar for those for Chlamydia **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).** The **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007)** recommend that pregnant women with risk factors or

symptoms be tested for gonorrhea at an early prenatal visit and again in the third trimester. Treatment is given for gonorrhea as well as possible coexisting chlamydial infection.

Special Screening for Genetic Diseases

Selected screening should be offered to couples at increased risk based on family history or the ethnic or racial background **(American College of Obstetricians and Gynecologists, 2004c; 2005c).** Some examples include testing for Tay-Sachs disease for people of Eastern European Jewish or French Canadian ancestry; β-thalassemia for those of Mediterranean, Southeast Asian, Indian, Pakistani, or African ancestry; α-thalassemia for people of Southeast Asian or African ancestry; and sickle-cell anemia for people of African, Mediterranean, Middle Eastern, Caribbean, Latin American, or Indian descent.

NUTRITION

Recommendations for Weight Gain

For the first half of the 20th century, it was recommended that weight gain during pregnancy be limited to less than 20 lb or 9.1 kg. It was believed that such restriction would prevent gestational hypertension and fetal macrosomia. By the 1970s, however, women were encouraged to gain at least 25 lb or 11.4 kg to prevent preterm birth and fetal-growth restriction, a recommendation supported by subsequent research **(Ehrenberg et al., 2003).**

In 1990, the Institute of Medicine recommended a weight gain of 25 to 35 lb—11.5 to 16 kg—for women with a normal prepregnancy body mass index (BMI). Weight gains recommended by the **Institute of Medicine (1990)** according to pre-pregnant BMI categories are shown in **Table 7**and these guidelines have been endorsed by **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007).** It is problematic, however, that in 2003, 46 percent of women had weight gains above these guidelines **(Catalano, 2007).**

TABLE XXVI. Recommended Ranges of Weight Gain during Singleton Gestations Stratified by Pre-pregnancy Body Mass Index [a] (Institute of Medicine, 1990):

Weight-for-Height Category		Recommended Total Weight Gain	
Category	**BMI**	**kg**	**lb**
Low	< 19.8	12.5–18	28–40
Normal	19.8–26	11.5–16	25–35
High	26–29	7–11.5	15–25
Obese	> 29	≥7	≥15

[a] The range for twin pregnancy is 35 to 45 lb (16 to 20 kg). Young adolescents (< 2 years after menarche) and African-American women should strive for gains at the upper end of the range. Shorter women (<62 in. or <157 cm) should strive for gains at the lower end of the range. BMI = body mass index.

It has been emphasized by **Catalano (2007)** that when the Institute of Medicine guidelines were written, concern was focused on the low-birth weight infant, whereas currently the focus is on the obesity epidemic. This likely explains renewed interest in lower weight gains during pregnancy. Obesity is associated with significantly increased risks for gestational hypertension, preeclampsia, gestational diabetes, macrosomia, and cesarean delivery.

The risk appears "dose related" to prenatal weight gain. In a population-based cohort of more than 120,000 obese pregnant women, **Kiel et al. (2007)** found that those who gained less than 15 pounds had the lowest rates of preeclampsia, large-for-gestational age infants, and cesarean delivery.

Among 100,000 women with normal pre-pregnancy body mass index, **DeVader et al. (2007)** found that those who gained less than 25 pounds during pregnancy had a lower risk for preeclampsia, failed induction, cephalopelvic disproportion, cesarean delivery, and large-for-gestational age infants. This cohort, however, had an increased risk for small-for-gestational age infants.

Over-nutrition

There is irrefutable evidence that maternal weight gain during pregnancy influences birth weight. **Martin et al. (2009)** studied this using birth certificate data for 2006.

As shown in **Figure (26),** 60 percent of pregnant women gained 26 lb or more. Maternal weight gain had a positive correlation with birth weight and women with the greatest risk—14 percent—for delivering an infant weighing less than 2500 g were those with weight gains less than 16 lb. Nearly nineteen percent of births to women with such low weight gains were preterm **(Martin et al., 2009).**

Cohen et al. (2001) studied more than 4000 pregnant women and concluded that ethnic differences in pregnancy outcomes were not explained by nutritional variations.

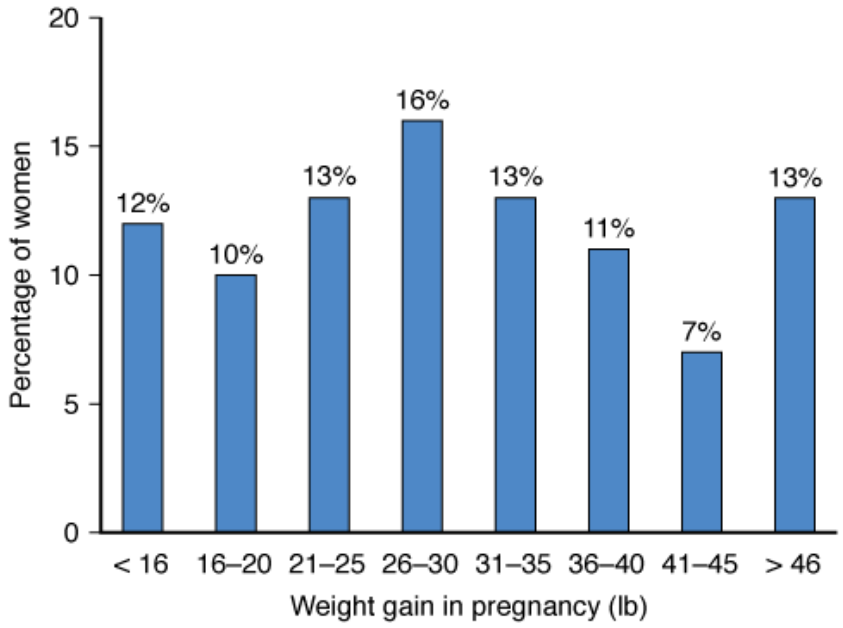

FIGURE 26. Maternal weight gains in the United States reported on the birth certificate in 2006 (From Martin et al., 2009).

Severe Under-nutrition

Meaningful studies of nutrition in human pregnancy are exceedingly difficult to design because experimental dietary deficiency is not ethical. In those instances in which severe nutritional deficiencies have been induced as a consequence of social, economic, or political disaster, coincidental events often have created many variables, the effects of which are not amenable to quantification. Some past experiences suggest, however, that in otherwise healthy women, a state of near starvation is required to establish clear differences in pregnancy outcome. During the severe European winter of 1944–1945, nutritional deprivation of known intensity prevailed in a well-circumscribed area of The Netherlands occupied by the German military **(Kyle and Pichard, 2006).**

At the lowest point during this Dutch Hunger Winter, rations reached 450 kcal/day, with generalized rather than selective malnutrition. **Smith (1947)** analyzed the outcomes of pregnancies that were in progress during this 6-month famine. Median infant birth weights decreased approximately 250 g and rose again after food became available. This indicated that birth weight can be influenced significantly by starvation during later pregnancy. The perinatal mortality rate, however, was not altered, nor was the incidence of malformations significantly increased. Interestingly, the frequency of pregnancy "toxemia" was found to decline.

Evidence of impaired brain development has been obtained in some animal fetuses whose mothers had been subjected to intense dietary deprivation. Subsequent intellectual development was studied by **Stein et al. (1972)** in young male adults whose mothers had been starved during pregnancy. The comprehensive study was made possible because all males at age 19 underwent compulsory examination for military service. It was concluded that severe dietary deprivation during pregnancy caused no detectable effects on subsequent mental performance.

A number of studies of the long-term consequences to this cohort of children born to nutritionally deprived women have been performed and were reviewed by **Kyle and Pichard (2006).** Progeny exposed in mid to late pregnancy were lighter, shorter, and

thinner at birth, and they had a higher incidence of subsequent diminished glucose tolerance, hypertension, reactive airway disease, dyslipidemia, and coronary artery disease.

Weight Retention after Pregnancy

Not all the weight gained during pregnancy is lost during and immediately after delivery **(Hytten, 1991). Schauberger et al. (1992)** studied prenatal and postpartum weights in 795 Wisconsin women. Their average weight gain was 28.6 lb or 12.8 kg.

Most maternal weight loss was at delivery—approximately 12 lb or 5.5 kg—and in the ensuing 2 weeks thereafter—approximately 9 lb or 4 kg. An additional 5.5 lb or 2.5 kg was lost between 2 weeks and 6 months postpartum. Thus, average total weight loss resulted in an average retained pregnancy weight of 3 lb or 1.4 kg. Overall, the more weight gained during pregnancy, the more that was lost postpartum. Interestingly, there is no relationship between pre-pregnancy BMI or prenatal weight gain and weight retention **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).**

Recommended Dietary Allowances:

Periodically, the **Food and Nutrition Board of the Institute of Medicine (2008)** publishes recommended dietary allowances, including those for pregnant or lactating women. The latest recommendations are summarized in **table XXVII.** Certain prenatal vitamin–mineral supplements may lead to intakes well in excess of the recommended allowances. Moreover, the use of excessive supplements, which often are self-prescribed, has led to concern about nutrient toxicities during pregnancy.

Those with potentially toxic effects include iron, zinc, selenium, and vitamins A, B6, C, and D. In particular, excessive vitamin A—more than 10,000 IU per day—may be teratogenic. Vitamin and mineral intake more than twice the recommended daily dietary allowance shown in **table XXVII** should be avoided **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).**

TABLE XXVII. Recommended Daily Dietary Allowances for Adolescent and Adult Pregnant and Lactating Women (From the Food and Nutrition Board of the Institute of Medicine, 2008):

	Pregnant		Lactating	
Age (years)	14–18	19–50	14–18	19–50
Fat-soluble vitamins				
Vitamin A	750 µg	770 µg	1200 µg	1300 µg
Vitamin D[a]	5 µg	5 µg	5 µg	5 µg
Vitamin E	15 mg	15mg	19 mg	19 mg
Vitamin K[a]	75 µg	90 µg	75 µg	90 µg
Water-soluble vitamins				
Vitamin C	80 mg	85 mg	115 mg	120 mg
Thiamin	1.4 mg	1.4 mg	1.4 mg	1.4 mg
Riboflavin	1.4 mg	1.4 mg	1.6 mg	1.6 mg
Niacin	18 mg	18 mg	17 mg	17 mg
Vitamin B6	1.9 mg	1.9 mg	2 mg	2 mg
Folate	600 µg	600 µg	500 µg	500 µg
Vitamin B12	2.6 µg	2.6 µg	2.8 µg	2.8 µg
Minerals				
Calcium[a]	1300 mg	1000 mg	1300 mg	1000 mg
Sodium[a]	1.5 g	1.5 g	1.5 g	1.5 g
Potassium[a]	4.7 g	4.7 g	5.1 g	5.1 g
Iron	27 mg	27 mg	10 mg	9 mg
Zinc	12 mg	11 mg	13 mg	12 mg
Iodine	220 µg	220 µg	290 µg	290 µg

Selenium	60 µg	60 µg	70 µg	70 µg

Continue TABLE XXVII. Recommended Daily Dietary Allowances for Adolescent and Adult Pregnant and Lactating Women (From the Food and Nutrition Board of the Institute of Medicine, 2008):

Other				
Protein	71 g	71 g	71 g	71 g
Carbohydrate	175 g	175 g	210 g	210 g
Fiber[a]	28 g	28 g	29 g	29 g

a Recommendations measured as Adequate Intake (AI).

Calories

As shown in **Figure 27,** pregnancy requires an additional 80,000 kcal—most are accumulated in the last 20 weeks. To meet this demand, a caloric increase of 100 to 300 kcal per day is recommended during pregnancy **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).**

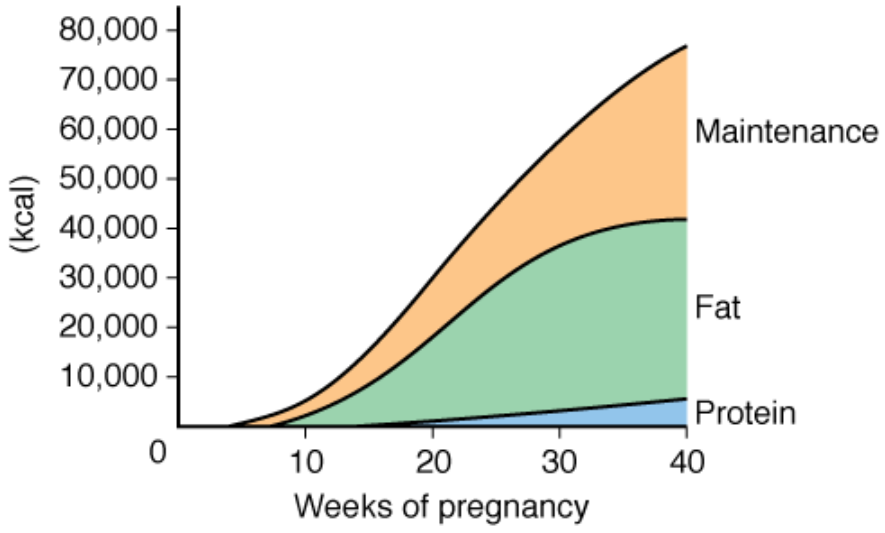

FIGURE 27. Cumulative kilocalories required for pregnancy (From Chamberlain and Broughton-Pipkin, 1998).

Calories are necessary for energy, and whenever caloric intake is inadequate, protein is metabolized rather than being spared for its vital role in fetal growth and development. Total physiological requirements during pregnancy are not necessarily the sum of ordinary non-pregnant requirements plus those specific to pregnancy. For example, the additional energy required during pregnancy may be compensated in whole or in part by reduced physical activity **(Hytten, 1991).**

Protein

To the basic protein needs of the non-pregnant woman are added the demands for growth and remodeling of the fetus, placenta, uterus, and breasts, as well as increased maternal blood volume. During the second half of pregnancy, approximately 1000 g of protein are deposited, amounting to 5 to 6 g/day **(Hytten and Leitch, 1971).**

Minerals

The intakes recommended by the **Institute of Medicine (2008)** for a variety of minerals are presented in Table 8. With the exception of iron, practically all diets that supply sufficient calories for appropriate weight gain will contain enough minerals to prevent deficiency if iodized foods are ingested.

Iron

Of the approximately 300 mg of iron transferred to the fetus and placenta and the 500 mg incorporated into the expanding maternal hemoglobin mass, nearly all is used after mid-pregnancy. During that time, iron requirements imposed by pregnancy and maternal excretion total approximately 7 mg per day **(Pritchard and Scott, 1970).**

Scott et al. (1970) established that as little as 30 mg of elemental iron, supplied as ferrous gluconate, sulfate, or fumarate and taken daily throughout the latter half of pregnancy, provides sufficient iron to meet the requirements of pregnancy and to protect preexisting iron stores. This amount will also provide for iron requirements for lactation. The pregnant woman may benefit from 60 to 100 mg of iron per day if she is large, has twin fetuses, begins supplementation late in pregnancy, takes iron irregularly, or has a somewhat depressed hemoglobin level. The woman who is overtly anemic from iron deficiency responds well to oral supplementation with iron salts.

Because iron requirements are slight during the first 4 months of pregnancy, it is not necessary to provide supplemental iron during this time. Withholding iron supplementation during the first trimester of pregnancy avoids the risk of aggravating nausea and vomiting.Ingestion of iron at bedtime or on an empty stomach aids absorption and appears to minimize the possibility of an adverse gastrointestinal reaction **(Gill et al., 2009).**

Calcium

The pregnant woman retains approximately 30 g of calcium, most of which is deposited in the fetus late in pregnancy **(Pitkin, 1985).** This amount of calcium represents only approximately 2.5 percent of total maternal calcium, most of which is in bone, and which can readily be mobilized for fetal growth. Moreover, **Heaney and Skillman (1971)** demonstrated increased calcium absorption by the intestine and progressive retention throughout pregnancy. Efforts to prevent preeclampsia using calcium supplementation have not proven efficacious, and it is not recommended for routine use during pregnancy.

Zinc

Severe zinc deficiency may lead to poor appetite, suboptimal growth, and impaired wound healing. Profound zinc deficiency may cause dwarfism and hypogonadism. Although the level of zinc supplementation that is safe for pregnant women has not been clearly established, recommended daily intake during pregnancy is approximately 12 mg **(Osendrap et al., 2001).**

Goldenberg et al. (1995) randomly assigned 580 indigent women to daily 25-mg zinc supplementation or placebo beginning at mid-pregnancy. Plasma zinc levels were significantly higher in women who received supplements. Infants born to zinc-supplemented women were slightly larger-mean increase 125 g-and had a slightly larger head circumference-mean 4 mm.

Later, **Osendarp et al. (2001)** randomly assigned 420 women in Bangladesh to receive either daily 30-mg zinc supplementation or placebo from 12 to 16 weeks until delivery. Although supplementation did not improve birth weight, low-birth weight infants of mothers who received zinc had reduced risks of acute diarrhea, dysentery, and impetigo. In a follow-up study of these infants at 13 months, zinc supplementation was not found to confer any benefits on developmental outcome **(Hamadani et al., 2002).**

Iodine

The use of iodized salt and bread products is recommended during pregnancy to offset the increased fetal requirements and maternal renal losses of iodine. Despite this, iodine intake has declined substantially in the past 15 years, and in some areas, it is probably inadequate. Interest in increasing dietary iodine was heightened by reports linking subclinical maternal hypothyroidism to adverse pregnancy outcomes and possible neuro developmental defects in children studied at age 7 years **(Casey et al., 2005; Haddow et al., 1999).**

Severe maternal iodine deficiency predisposes offspring to endemic cretinism, characterized by multiple severe neurological defects. In parts of China and Africa where this condition is endemic, iodide supplementation very early in pregnancy prevents some cases of cretinism **(Cao et al., 1994).**

Magnesium

Deficiency of magnesium as the consequence of pregnancy has not been recognized. Undoubtedly, during prolonged illness with no magnesium intake, the plasma level might become critically low, as it would in the absence of pregnancy. It has been observed that magnesium deficiency during pregnancy complicated by the consequences of previous intestinal bypass surgery. **Sibai et al. (1989)** randomly assigned 400 normotensive primigravid women to 365 mg elemental magnesium supplementation or placebo tablets from 13 to 24 weeks. Supplementation did not improve any measures of pregnancy outcome.

Trace Metals

Copper, selenium, chromium, and manganese all have important roles in certain enzyme functions. In general, most are provided by an average diet. A severe geochemical selenium deficiency has been identified in a large area of China. Deficiency is manifested by a frequently fatal cardiomyopathy in young children and women of childbearing age. Conversely, selenium toxicity resulting from over-supplementation also has been observed **(Food and Nutrition Board of the Institute of Medicine, 2008).**

Potassium

The concentration of potassium in maternal plasma decreases by approximately 0.5 mEq/L by mid-pregnancy. Potassium deficiency develops in the same circumstances as when a woman is not pregnant **(Brown et al., 1986).**

Fluoride

There is no evidence that supplemental fluoride during pregnancy is beneficial **(Institute of Medicine, 1990)**.

Horowitz and Heifetz (1967) concluded that there were no additional benefits from maternal ingestion of fluoridated water if the offspring ingested such water from birth.

Sa RorizFonteles et al. (2005) studied microdrill biopsies of deciduous teeth and concluded that prenatal fluoride provided no additional fluoride uptake compared with postnatal fluoride alone. Supplemental fluoride ingested by lactating women does not increase the fluoride concentration in breast milk **(Ekstrand et al., 1981).**

Folic Acid

The **CDC (2004)** estimated that the number of pregnancies affected by neural-tube defects has decreased from 4000 pregnancies per year to approximately 3000 per year since mandatory fortification of cereal products with folic acid in 1998. Perhaps more than half of all neural-tube defects can be prevented with daily intake of 400 ug of folic acid throughout the peri-conceptional period **(CDC, 1999).**

ACOG, 2003b stated that Putting 140 μg of folic acid into each 100 μg of grain products may increase the folic acid intake of the average American woman of childbearing age by 100 μg per day. Because nutritional sources alone are insufficient, however, folic acid supplementation is still recommended

ins. Unfortunately, surveys continue to suggest that many women, especially among minorities, remain unaware of the recommendations regarding folic acid supplementation **(Perlow, 2001; Rinsky-Eng and Miller, 2002).**

Vitamin A

Dietary intake of vitamin A in the United States appears to be adequate, and routine supplementation during pregnancy is not recommended by the **ACOG (1998b).** Conversely, there is an association of birth defects with very high doses during pregnancy—10,000 to 50,000 IU daily. These malformations are similar to those produced by the vitamin A derivative isotretinoin—Accutane—which is a potent teratogen. Beta-carotene, the precursor of vitamin A found in fruits and vegetables, has not been shown to produce vitamin A toxicity.

Vitamin A deficiency is an endemic nutrition problem in the developing world. **West (2003)** estimates that worldwide, 6 million pregnant women suffer from night blindness secondary to vitamin A deficiency.

Vitamin B12

Maternal plasma vitamin B12 levels decrease in normal pregnancy and result mostly from reduced plasma levels of carrier proteins—transcobalamins. Vitamin B12 occurs naturally only in foods of animal origin, and strict vegetarians may give birth to infants whose B12 stores are low. Likewise, because breast milk of a vegetarian mother contains little vitamin B12, the deficiency may become profound in the breast-fed infant **(Higginbottom et al., 1978).** Excessive ingestion of vitamin C also can lead to a functional deficiency of vitamin B12. Although its role is still controversial, low levels of vitamin B12 preconceptionally, similar to folate, may increase the risk of neural-tube defects **(Molloy et al., 2009; Thompson et al., 2009).**

Vitamin B6—Pyridoxine

Limited clinical trials in pregnant women have failed to demonstrate any benefits of vitamin B6 supplements **(Thaver et al., 2006).**

For women at high risk for inadequate nutrition—for example, substance abusers, adolescents, and those with multifetal gestations—a daily 2-mg supplement is recommended **(Staroselsky et al., 2007).**

Vitamin B6, when combined with the antihistamine doxylamine, has been found helpful in many cases of nausea and vomiting of pregnancy **(Boskovic et al., 2003; Staroselsky et al., 2007).**

Vitamin C

The recommended dietary allowance for vitamin C during pregnancy is 80 to 85 mg/day—about 20 percent more than when non-pregnant (Table 8). A reasonable diet should readily provide this amount. The maternal plasma level declines during pregnancy,

whereas the cord level is higher, a phenomenon observed with most water-soluble vitamins **(Gregory et al., 2006).**

Pragmatic Nutritional Surveillance

Institute of Medicine,(2008) stated that although the science of nutrition continues in its perpetual struggle to identify the ideal amounts of protein, calories, vitamins, and minerals for the pregnant woman and her fetus, those directly responsible for their care may best discharge their duties as follows:

1. In general, advise the pregnant woman to eat what she wants in amounts she desires and salted to taste.
2. Ensure that there is ample food available in the case of socioeconomically deprived women.
3. Monitor weight gain, with a goal of approximately 25 to 35 lb in women with a normal BMI.
4. Periodically explore food intake by dietary recall to discover the occasional nutritionally absurd diet.
5. Give tablets of simple iron salts that provide at least 27 mg of iron daily. Give folate supplementation before and in the early weeks of pregnancy.
6. Recheck the hematocrit or hemoglobin concentration at 28 to 32 weeks to detect any significant decrease.

COMMON CONCERNS

Employment

In the absence of complications, most women can continue to work until the onset of labor **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).** More than half of the children in the United States are born to working mothers. Federal law prohibits employers from excluding women from job categories on the basis that they are or might become pregnant **(Annas, 1991).** The Family Medical Leave Act requires that covered employers must grant up to 12

workweeks of unpaid leave to an employee for the birth and care of a newborn child **(United States Department of Labor, 2008).**

Some types of work, however, may increase pregnancy complication risks. **Mozurkewich et al. (2000)** reviewed 29 studies that involved more than 160,000 pregnancies. With physically demanding work, women had a 20- to 60-percent increase in rates of preterm birth, fetal-growth restriction, or gestational hypertension. In a prospective study of more than 900 healthy nulliparas, **Higgins et al. (2002)** found that women who worked had a fivefold risk of preeclampsia.

Newman et al. (2001) reported outcomes in 2929 women with singleton pregnancies studied by the Maternal-Fetal Medicine Units Network. Occupational fatigue-estimated by the number of hours standing, intensity of physical and mental demands, and environmental stressors—was associated with an increased risk of preterm membrane rupture. For women reporting the highest degrees of fatigue, the risk was 7.4 percent.

Thus, any occupation that subjects the pregnant woman to severe physical strain should be avoided. Ideally, no work or play should be continued to the extent that undue fatigue develops. Adequate periods of rest should be provided. It seems prudent to advise women with previous pregnancy complications that are at risk to recur-for example, preterm birth-to minimize physical work.

Exercise

In general, pregnant women do not need to limit exercise, provided they do not become excessively fatigued or risk injury **(Clapp et al., 2000).**

Clapp et al. (2000) randomly assigned 46 pregnant women who did not exercise regularly to either no exercise or to weight-bearing exercise beginning at 8 weeks. Exercise consisted of treadmill running, step aerobics, or stair stepper use for 20 minutes three to five times each week. They did this throughout pregnancy at intensity between 55

and 60 percent of the pre-conceptional maximum aerobic capacity. Both placental size and birth weight were significantly greater in the exercise group.

The **American College of Obstetricians and Gynecologists (2002b)** advises a thorough clinical evaluation be conducted before recommending an exercise program. In the absence of contraindications listed in **Table XXVIII,** pregnant women should be encouraged to engage in regular, moderate-intensity physical activity 30 minutes or more a day. Each activity should be reviewed individually for its potential risk. Activities with a high risk of falling or abdominal trauma should be avoided. Similarly, scuba diving should be avoided because the fetus is at an increased risk for decompression sickness.

TABLE XXVIII. Absolute and Relative Contraindications to Aerobic Exercise during Pregnancy (American College of Obstetricians and Gynecologists, 2002b):

Absolute Contraindications

- Hemodynamically significant heart disease
- Restrictive lung disease
- Incompetent cervix/cerclage
- Multifetal gestation at risk for preterm labor
- Persistent second- or third-trimester bleeding
- Placenta previa after 26 weeks
- Preterm labor during the current pregnancy
- Ruptured membranes
- Preeclampsia/pregnancy-induced hypertension

Relative Contraindications

- Severe anemia
- Unevaluated maternal cardiac arrhythmia

- Chronic bronchitis
- Poorly controlled type 1 diabetes
- Extreme morbid obesity
- Extreme underweight (BMI <12)
- History of extremely sedentary lifestyle
- Fetal-growth restriction in current pregnancy
- Poorly controlled hypertension
- Orthopedic limitations
- Poorly controlled seizure disorder
- Poorly controlled hyperthyroidism
- Heavy smoker

In the setting of certain pregnancy complications, it is wise to abstain from exercise and even limit physical activity. For example, some women with hypertensive disorders caused by pregnancy may benefit from being sedentary, as many women with preterm labor, placenta previa, or multifetal gestation; those suspected of having a growth-restricted fetus; or those with severe cardiac or pulmonary disease **(American College of Obstetricians and Gynecologists, 2002b).**

Fish Consumption

Fish are an excellent source of protein, are low in saturated fats, and contain omega-3 fatty acids. Because nearly all fish and shellfish contain trace amounts of mercury, pregnant and lactating women are advised to avoid specific types of fish with potentially high methylmercury levels **(Hibbeln et al., 2007).**

These include shark, swordfish, king mackerel, and tile fish. It is further recommended that pregnant women ingest no more than 12 ounces or two servings of canned tuna per week and no more than 6 ounces of albacore or "white" tuna **(United States Environmental Protection Agency, 2008).** If the mercury content of locally caught fish is unknown, then overall fish consumption should be limited to 6 ounces per

week. The recent Avon Longitudinal Study of Parents and Children (ALSPAC) study, however, reported beneficial effects on pregnancy outcomes in women who consumed 340 g or more of seafood weekly **(Hibbeln et al., 2007).**

Travel

Automobile Travel

The **American College of Obstetricians and Gynecologists (1998a)** has formulated guidelines for use of automobile passenger restraints during pregnancy. Women should be encouraged to wear properly positioned three-point restraints throughout pregnancy while riding in automobiles.

The lap belt portion of the restraining belt should be placed under the abdomen and across her upper thighs. The belt should be comfortably snug. The shoulder belt also should be snugly positioned between the breasts. Available information suggests that airbags should not be disabled for the pregnant woman **(American College of Obstetricians and Gynecologists, 1998a).**

Air Travel

In general, air travel by the healthy woman has no harmful effect on pregnancy **(Aerospace Medical Association, 2003).** Travel in properly pressurized aircraft offers no unusual risk. Thus, in the absence of obstetrical or medical complications, the **American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2007)** have concluded that pregnant women can safely fly up to 36 weeks. It is recommended that pregnant women observe the same precautions for air travel as the general population, including periodic movement of the lower extremities, ambulation at least hourly, and use of seatbelts while seated. A significant risk with travel, especially international travel, is acquisition of infectious diseases or developing a complication remote from adequate facilities **(Ryan et al., 2002).**

Coitus

It is generally accepted that in healthy pregnant women, sexual intercourse usually is not harmful. Whenever abortion or preterm labor threatens, however, coitus should be avoided. Nearly 10,000 women enrolled in a prospective investigation by the Vaginal Infection and Prematurity Study Group was interviewed regarding sexual activity **(Read and Klebanoff, 1993).** They reported a decreased frequency of sexual intercourse with advancing gestation. By 36 weeks, 72 percent had intercourse less than once weekly. According to **Bartellas et al. (2000),** the decrease is attributed to decreased desire in 58 percent and fear of harm to the pregnancy in 48 percent.

Intercourse late in pregnancy specifically has not been found to be harmful. **Grudzinskas et al. (1979)** found no association between gestational age at delivery and the frequency of coitus during the last 4 weeks of pregnancy.

Sayle et al. (2001) found no increased and actually a decreased risk of delivery within 2 weeks of intercourse. **Tan et al. (2007)** studied women scheduled for nonurgent labor induction and found that spontaneous labor ensued in half of each group who had and did not have intercourse.

Dental Care

Examination of the teeth should be included in the prenatal examination, and good dental hygiene is encouraged. Periodontal disease has been linked to preterm labor. Unfortunately, its treatment improves dental health but does not prevent preterm birth **(Michalowicz et al., 2006).** Dental caries are not aggravated by pregnancy. Importantly, pregnancy is not a contraindication to dental treatment including dental radiographs **(Giglio et al., 2009).**

Immunization

Current recommendations for immunizations during pregnancy are summarized in Table 10. Over the past decade, well-publicized concerns regarding childhood exposure to the thimerosal preservative in some vaccines led to parental prohibition. These results

have proven groundless, but controversy continues **(Sugarman, 2007; Thompson et al., 2007; Tozzi et al., 2009).**

Thus, they are recommended for use in pregnancy. The **American College of Obstetricians and Gynecologists (2003a)** stresses that current information on the safety of vaccines given during pregnancy is subject to change **(Table XXIX).**

TABLE XXIX. Recommendations for Immunization during Pregnancy (Adapted from the CDC, Recommendations of the Advisory Committee on Immunization Practices, 2003; 2005; 2006a):

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Live Attenuated Virus Vaccines			
Measles	Contraindicated	Single dose SC, preferably as MMR (Two doses necessary for students entering institutions of higher education, newly hired medical personnel, and travel abroad)	Vaccinate susceptible women postpartum. Breast feeding is not a contraindication
Mumps	Contraindicated	Single dose SC, preferably as MMR	Vaccinate susceptible women postpartum
Rubella	Contraindicated, but congenital rubella syndrome has never been described after vaccine	Single dose SC, preferably as MMR	Teratogenicity of vaccine is theoretical and not confirmed to date; vaccinate susceptible women postpartum
Poliomyelitis Oral = live attenuated; injection =	Not routinely recommended for women in the	Primary: Two doses of enhanced-potency inactivated virus SC at 4–8 week intervals and a 3rd dose	Vaccine indicated for susceptible women traveling in endemic

enhanced-potency inactivated virus	United States, except women at increased risk of exposure	6–12 months after 2nd dose Immediate protection: One dose oral polio vaccine (in outbreak)	areas or in other high-risk situations

Continue TABLE XXIX. Recommendations for Immunization during Pregnancy (Adapted from the CDC, Recommendations of the Advisory Committee on Immunization Practices, 2003; 2005; 2006a):

Immunobiological Agent	**Indications for Immunization During Pregnancy**	**Dose Schedule**	**Comments**
Yellow fever	Travel to high-risk areas	Single dose SC	Limited theoretical risk outweighed by risk of yellow fever
Varicella	Contraindicated, but no adverse outcomes reported in pregnancy	Two doses needed: 2nd dose given 4–8 weeks after 1st dose	Teratogenicity of vaccine is theoretical. Vaccination of susceptible women should be considered postpartum
Smallpox (vaccinia)	Contraindicated in pregnant women and in their household contacts	One dose SC, multiple pricks with lancet	Only vaccine known to cause fetal harm
Other			
Influenza	All pregnant women, regardless of trimester during flu season (Nov.-Mar.)	One dose IM every year	Inactivated virus vaccine
Rabies	Indications for prophylaxis not altered by pregnancy; each case considered	Public health authorities to be consulted for	Killed-virus vaccine

individually	indications, dosage, and route of administration	

Continue TABLE XXIX. Recommendations for Immunization during Pregnancy (Adapted from the CDC, Recommendations of the Advisory Committee on Immunization Practices, 2003; 2005; 2006a):

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Hepatitis B	Pre-exposure and postexposure for women at risk of infection	Three-dose series IM at 0, 1, and 6 months	Used with hepatitis B immune globulin for some exposures. Exposed newborn needs birth-dose vaccination and immune globulin as soon as possible. All infants should receive birth dose of vaccine
Hepatitis A	Pre-exposure and postexposure if at risk (international travel)	Two-dose schedule IM, 6 months apart	Inactivated virus
Inactivated Bacterial Vaccines			
Pneumococcus	Indications not altered by pregnancy. Recommended for women with asplenia; metabolic, renal, cardiac, or pulmonary diseases; immunosuppression; or smokers	In adults, one dose only; consider repeat dose in 6 years for high-risk women	Polyvalent polysaccharide vaccine
Meningococcus	Indications not altered by	One dose; tetravalent	Antimicrobial prophylaxis if

	pregnancy; vaccination vaccine recommended in outbreaks		significant exposure

Continue TABLE XXIX. Recommendations for Immunization during Pregnancy (Adapted from the CDC, Recommendations of the Advisory Committee on Immunization Practices, 2003; 2005; 2006a):

Immunobiological Agent	**Indications for Immunization During Pregnancy**	**Dose Schedule**	**Comments**
Typhoid	Not recommended routinely except for close, continued exposure or travel to endemic areas	Killed Primary: 2 injections IM 4 weeks apart Booster: One dose; schedule not yet determined	Killed, injectable vaccine or live attenuated oral vaccine. Oral vaccine preferred
Anthrax		Six-dose primary vaccination, then annual booster vaccination	Preparation from cell-free filtrate of *B. anthracis*. No dead or live bacteria. Teratogenicity of vaccine theoretical
Toxoids			
Tetanus-diphtheria	Lack of primary series, or no booster within past 10 years	Primary: Two doses IM at 1–2 month interval with 3rd dose 6–12 months after the 2nd Booster: Single dose IM every 10 years after completion of primary series	Combined tetanus-diphtheria toxoids preferred: adult tetanus-diphtheria formulation. Updating immune status should be part of antepartum care

Continue TABLE XXIX. Recommendations for Immunization during Pregnancy (Adapted from the CDC, Recommendations of the Advisory Committee on Immunization Practices, 2003; 2005; 2006a):

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Specific Immune Globulins			
Hepatitis B	Postexposure prophylaxis	Depends on exposure	given with hepatitis B virus vaccine; exposed newborn needs immediate prophylaxis
Rabies	Postexposure prophylaxis	1/2 dose at injury site, half dose in deltoid	Used in conjunction with rabies killed-virus vaccine
Tetanus	Postexposure prophylaxis	One dose IM	Used in conjunction with tetanus toxoid
Varicella	Considered for exposed pregnant women to protect against maternal, not congenital, infection	One dose IM within 96 hours of exposure	Indicated also for newborns or women who developed varicella within 4 days before delivery or 2 days following delivery
Standard Immune Globulins			
Hepatitis A virus vaccine should be used with hepatitis A immune globulin	Postexposure prophylaxis and high risk	0.02 mL/kg IM in one dose	Immune globulin should be given as soon as possible & within 2 weeks of exposure; infants born to women who incubating the virus or are acutely ill at delivery should receive one dose of 0.5 mL as soon as possible after birth

ID = intradermally; IM = intramuscularly; MMR = measles, mumps, rubella; PO = orally: and SC = subcutaneously.

All women who will be pregnant during the influenza season should be offered vaccination, regardless of their stage of pregnancy. Those with underlying medical

conditions that increase the risk for complications should be offered the vaccine before flu season starts **(American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2007).**

Zaman et al. (2008) showed that prenatal maternal vaccination reduced influenza incidence in the first 6 months by 63 percent in infants born to these women. Moreover, it reduced all febrile respiratory illnesses in these children by a third.

Women who are susceptible to rubella during pregnancy should receive MMR—measles-mumps-rubella—vaccination postpartum. Although this vaccine is not recommended during pregnancy, congenital rubella syndrome has never resulted from its inadvertent use. There is no contraindication to MMR vaccination while breast feeding **(ACOG, 2002d).**

Biological Warfare and Vaccines

The tragic events of September 11, 2001, and the ongoing threat of bioterrorism require familiarity with smallpox and anthrax vaccines during pregnancy. The smallpox vaccine is made with live attenuated vaccinia virus related to smallpox and to cowpox viruses. Fetal vaccinia infection is rare, but it may result in abortion, stillbirth, or neonatal death **(CDC, 2006a).**

Thus, in non-emergency circumstances, vaccination is contraindicated during pregnancy and in women who might become pregnant within 28 days of vaccination **(CDC, 2006a).** If, however, vaccination is inadvertently performed in early pregnancy, this is not grounds for termination **(Suarez and Hankins, 2002).**

If the pregnant woman is at risk because of exposure to smallpox—either as a direct victim of a bioterrorist attack or as a close contact of an individual case—the risks from clinical smallpox substantially outweigh any potential risk from vaccination **(Suarez and Hankins, 2002).**

Anthrax vaccination has been limited principally to individuals who are occupationally exposed, such as special veterinarians, laboratory workers, and members of the armed forces. The vaccine contains no live virus and thus would not be expected to pose significant risk to the fetus. **Wiesen and Littell (2002)** studied the reproductive outcomes of 385 women in the United States Army who became pregnant after vaccination and reported no adverse effects on fertility or pregnancy outcome.

Caffeine

In 1980, the FDA advised pregnant women to limit caffeine intake. The Fourth International Caffeine Workshop concluded shortly thereafter that there was no evidence that caffeine had increased teratogenic or reproductive risks **(Dews et al., 1984).** Caffeine is not a teratogen for small laboratory animals, but if given in massive doses it potentiates mutagenic effects of radiation and some chemicals. When infused intravenously into sheep, caffeine decreases uterine blood flow by 5 to 10 percent **(Conover et al., 1983). American Dietetic Association (2002)** recommends that caffeine intake during pregnancy be limited to less than 300 mg daily, or approximately three, 5-oz cups of percolated coffee.

Nausea and Vomiting

These are common complaints during the first half of pregnancy. Nausea and vomiting of varying severity usually commence between the first and second missed menstrual period and continue until 14 to 16 weeks. Although nausea and vomiting tend to be worse in the morning—thus erroneously termed morning sickness, they frequently continue throughout the day.

Seldom is the treatment of nausea and vomiting of pregnancy so successful that the affected expectant mother is afforded complete relief. Fortunately, the unpleasantness and discomfort usually can be minimized. Eating small meals at more frequent intervals but stopping short of satiation is valuable. **Borrelli et al. (2005)** did a systematic literature search and reported that the herbal remedy, ginger, was likely effective. Mild symptoms usually respond to vitamin B6 given along with doxylamine, but some women

require phenothiazine or H1-receptor blocker anti-emetics. In some women, vomiting may be so severe that dehydration, electrolyte and acid–base disturbances, and starvation ketosis become serious problems. This is termed hyperemesis gravidarum **(American College of Obstetricians and Gynecologists, 2004b).**

Backache

Low back pain to some extent is reported in nearly 70 percent of pregnant women **(Wang et al., 2004).** Minor degrees follow excessive strain or fatigue and excessive bending, lifting, or walking. **Orvieto et al. (1994)** studied 449 women and reported that back pain increased with duration of gestation. Prior low back pain and obesity were risk factors. Back pain can be reduced by having women squat rather than bend over when reaching down, providing back support with a pillow when sitting down, and avoiding high-heeled shoes. Severe back pain should not be attributed simply to pregnancy until a thorough orthopedic examination has been conducted. Muscular spasm and tenderness, which often are classified clinically as acute strain or fibrositis, respond well to analgesics, heat, and rest. Some women with severe back and hip pain may have pregnancy-associated osteoporosis **(Dunne et al., 1993).**

Norén et al. (2002) studied the long-term outcomes of 231 women who had some type of back pain during pregnancy. Residual pain 3 years after delivery was reported by approximately 20 percent. Women with lumbar back and posterior pelvic pain were at greatest risk for disability, which was attributed to impaired back extensor and hip abductor muscle functions.

Varicosities

These enlarged veins generally result from congenital predisposition and are exaggerated by prolonged standing, pregnancy, and advancing age. Usually varicosities become more prominent as pregnancy advances, as weight increases, and as the length of time spent upright is prolonged. Femoral venous pressure increases appreciably as pregnancy advances. The symptoms produced by varicosities vary from cosmetic blemishes and mild discomfort at the end of the day to severe discomfort that requires

prolonged rest with elevated feet. Treatment is generally limited to periodic rest with leg elevation, elastic stocking use, or both. Surgical correction during pregnancy generally is not advised, although occasionally the symptoms may be so severe that injection, ligation, or even stripping of the veins is necessary. Vulvar varicosities may be aided by application of a foam rubber pad suspended across the vulva by a belt. Rarely, large varicosities may rupture, resulting in profuse hemorrhage **(Higgins et al., 2002).**

Hemorrhoids

Varicosities of the rectal veins may first appear during pregnancy because of increased venous pressure. More often, pregnancy causes an exacerbation or a recurrence of previous hemorrhoids. Pain and swelling usually are relieved by topically applied anesthetics, warm soaks, and stool-softening agents. Thrombosis of an external hemorrhoid can cause considerable pain, but the clot usually can be evacuated by incising the vein wall under topical anesthesia **(Higgins et al., 2002).**

Heartburn

This symptom is one of the most common complaints of pregnant women and is caused by reflux of gastric contents into the lower esophagus. The increased frequency of regurgitation during pregnancy most likely results from the upward displacement and compression of the stomach by the uterus, combined with relaxation of the lower esophageal sphincter **(Chamberlain and Broughton-Pipkin, 1998).**

In most pregnant women, symptoms are mild and are relieved by a regimen of more frequent but smaller meals and avoidance of bending over or lying flat. Antacids may provide considerable relief. Aluminum hydroxide, magnesium trisilicate, or magnesium hydroxides alone or in combination are given **(Chamberlain and Broughton-Pipkin, 1998).**

Pica

The cravings of pregnant women for strange foods are termed pica. At times, nonfoods such as ice-pagophagia, starch-amylophagia, or clay—geophagia may predominate. This desire has been considered by some to be triggered by severe iron deficiency. Although some women crave these items, and although the craving usually is ameliorated after correction of iron deficiency, not all pregnant women with pica are necessarily iron deficient. Indeed, if strange "foods" dominate the diet, iron deficiency will be aggravated or will develop eventually **(Dutta, 1992).**

Patel et al. (2004) from the University of Alabama at Birmingham prospectively completed a dietary inventory on more than 3000 women during the second trimester. The prevalence of pica was 4 percent. The most common nonfood items ingested were starch in 64 percent, dirt in 14 percent, sourdough in 9 percent, and ice in 5 percent. The prevalence of anemia was 15 percent in women with pica compared with 6 percent in those without it. The rate of spontaneous preterm birth at less than 35 weeks was twice as high in women with pica.

Ptyalism

Women during pregnancy are occasionally distressed by profuse salivation. Although usually unexplained, the cause of such ptyalism sometimes appears to be stimulation of the salivary glands by the ingestion of starch **(CDC, 2008a).**

Sleeping and Fatigue

Beginning early in pregnancy, many women experience fatigue and need increased amounts of sleep. This likely is due to the soporific effect of progesterone(s). Moreover, sleep efficiency is diminished because rapid eye movement sleep is decreased and non-REM sleep prolonged **(Pien and Schwab, 2004).**

Fatigue and non-restful sleep may be exacerbated by morning sickness. By the late second trimester, total nocturnal sleep duration is decreased, and women usually begin to complain of sleep disturbances. Approximately half of women begin snoring **(Izci et al., 2005).**

By the third trimester, nearly all women have altered sleep. Although total nocturnal sleep time is similar to non-pregnancy, sleep efficiency is perturbed because REM sleep is decreased. Daytime naps and mild sedatives at bedtime such as diphenhydramine (Benadryl) are usually helpful (**Pien and Schwab, 2004).**

Leukorrhea

Pregnant women commonly develop increased vaginal discharge, which in many instances is not pathological. Increased mucus secretion by cervical glands in response to hyperestrogenemia is undoubtedly a contributing factor. Occasionally, troublesome leukorrhea is the result of vulvovaginal infection. The majority of these in adult women are caused by bacterial vaginosis, candidiasis, or trichomoniasis **(Eckert, 2006).**

Cord Blood Banking

In the past 20 years, umbilical cord blood transplantation has been successfully performed more than 7000 times to treat hematopoietic cancers and a variety of genetic conditions in children and adults **(Moise, 2005).**

There are two types of cord blood banks. Public banks promote allogenic donation, for use by a related or unrelated recipient, similar to blood product donation. Whereas private banks were initially developed to store stem cells for future autologous use, these banks charge fees for initial processing and annual storage. The **American College of Obstetricians and Gynecologists (2008)** has concluded that if woman requests information on umbilical cord banking, information regarding advantages and disadvantages of public versus private banking should be disclosed. Some states have passed legislation that requires physicians to inform patients about cord blood banking

options. Importantly, few transplants have been performed by using cord blood stored in the absence of a known indication in the recipient **(Thornley et al., 2009).**

The likelihood that cord blood would be used for the donor couple's child or family member is considered remote—at most, approximately 1 in 2700 individuals. It is recommended that directed donation be considered when an immediate family member carries the diagnosis of a specific condition known to be treatable by hematopoietic transplantation **(American College of Obstetricians and Gynecologists, 2008).**

Antenatal Care in Egypt

One of the priorities of the Egyptian government's maternal and child health program is to provide medical care during pregnancy to ensure the survival of both mother and child **(Roudi-Fahimi, 2003).**

Maternal mortality is a major global concern that affects families and thus society. Surveys to determine the causes of maternal deaths (MD) are the primary tools on which interventions have been based. Two National Maternal Mortality Surveys (NMMSs) were performed in 1992–93 and 2000 in Egypt. The results from these surveys indicated that the maternal mortality ratio (MMR) in Egypt had decreased by 52% from 174/100 000 live births in 1992–93 to 84/100 000 live births in 2000 **(Campbell and Gipson, 1993; 2001).**

The 1992 maternal health survey identified both unavoidable and avoidable factors contributing to maternal deaths in Egypt. Substandard care was a major avoidable factor that caused maternal mortality in 1992–93 and it remained the second key factor in 2000. Access to ANC, recognizing danger signs and seeking professional care can be effective only if quality professional services are available **(Attaweel and Gipson, 1996).**

In response, the Ministry of Health and Population (MOHP), in collaboration with international partners such as the USAID-funded Healthy Mother/Healthy Child program, implemented by John Snow Inc., designed and implemented a series of activities to improve quality of care. For example, the ministry upgraded maternal and neonatal health

facilities and improved the logistics system throughout the country, but with a special focus on Upper Egypt and rural hospitals. The interventions paid special attention to essential obstetric care and the management of obstetric and neonatal emergencies. They included extensive training needs assessments, detailed situational analyses and community diagnoses, and studies that show maternal mortality can be reduced in all socioeconomic settings through investment in the appropriate interventions to ensure essential obstetric care and appropriate management of obstetric emergencies. Efforts are being made to strengthen those aspects of antenatal care most likely to have an effect on the outcome of pregnancy **(Gipson, 1998).**

It is important for the pregnant woman to be cared for by a physician who can correctly take a full history and conduct a complete physical examination, then diagnose any problems and manage the pregnancy. Women, families, and traditional birth attendants (days) need to have enough information to recognize the danger signs of pregnancy and the *puerperium* so they can seek care promptly in an appropriate facility **(WHO, 2005).**

The Egypt National Maternal Mortality Study 2001 reported that poor quality antenatal care was found to contribute to 15% of maternal deaths and to 13 maternal deaths per 100,000 live births. It played a more important role in death associated with hypertensive diseases (34%). In cardiac disease lack of antenatal care and poor quality antenatal dare were considered to be avoidable factors in19% and 28% of cases, respectively. To obtain information on the utilization of antenatal care services, the **Egypt Demographic and Health Survey (EDHS)** included several questions relating to the source of antenatal care, number and timing of visits, and tetanus toxoid vaccinations. This section discusses these antenatal care issues **(Copeland and Gipson, 2002).**

Source of Antenatal Care

According to EDHS, the survey results indicate that many mothers do not seek antenatal care. Among births in the five years before the EDHS, only53 percent received antenatal care from a trained medical provider **(EDHS, 1993).**

In virtually all cases, the mother received antenatal care from a doctor. Antenatal care was more likely to be sought from a private sector provider than at a government health facility; mothers reported that they went to a private provider in the case of 77 percent of the births in which antenatal care was received. Antenatal care from a trained provider is much more common for urban births (69 percent) than rural births (43 percent).The proportion of births whose mothers received antenatal care from a trained provider is highest in the Urban Governorates (74 percent), followed by urban areas in Lower Egypt (68 percent) and Upper Egypt (62 percent). The mothers of more than half the live births in rural areas in both Lower Egypt and Upper Egypt did not receive any antenatal care during pregnancy **(EDHS, 1993).**

Number and Timing of Antenatal Care Visits

Both the number and timing of antenatal care visits are considered to be of great importance with respect to pregnancy outcome. Antenatal care can be more effective when it is sought early in the pregnancy and is received regularly throughout the pregnancy. If an Egyptian mother seeks antenatal care, she is likely to make more than one visit. However, even among mothers who seek care, the median number of visits is only 3.5. Among mothers who obtained antenatal care, the majority report the first pregnancy check occurred at or before the fifth month of pregnancy. The median time at which mothers started antenatal visits is 3.2monthesthe number of antenatal care visits is related to the likelihood that a birth occurred at a health facility. The percentage delivered at a health facility was 13 percent among births in which no antenatal care was received compared to 25 percent among births in which the mother reported 1-3 antenatal care

visits and 58 percent among births in which there were 4 or more antenatal visits **(EDHS, 1993).**

Tetanus Toxoid Vaccinations

Neonatal tetanus is one of the major causes of death in young infants. To fully protect against neonatal tetanus, it is recommended that mothers receive two tetanus toxoid injections during pregnancy. However, if a woman has been vaccinated during a previous pregnancy, she may only require a booster dose for a current pregnancy, and five doses of tetanus toxoid are considered to provide lifetime protection. In order to estimate the extent of tetanus toxoid coverage during pregnancy, the EDHS collected data on whether the women received tetanus toxoid vaccinations for each pregnancy in the five years preceding the survey and if so, the number of injections. For more than two-fifths of the births (43 percent), mothers did not receive a tetanus toxoid vaccination; for 17 percent, the mothers received one dose, and, for 41 percent, the mothers received two or more doses **(Graham et al., 2001).**

The current level of tetanus toxoid coverage is five times higher than the level reported in the 1988 EDHS when mothers reported receiving tetanus toxoid vaccinations for only 11 percent of births **(Sayed et al., 1989).** The marked increase is most likely a response to a public campaign to improve tetanus toxoid coverage that was conducted during the period between the two EDHS surveys. A documented, reduction in MMR over a relatively short time demonstrates the collective effect of an integrated national Safe Motherhood programme aimed at making improvements at the community, health-care delivery site and health-care professional levels. The intensive training received by the medical personnel apparently had a positive effect on reducing the MMR in the 1990s in Egypt. It is more difficult to quantify what direct impact infrastructural improvements, increased utilization of ANC and the presence of skilled attendants at birth have had **(Graham et al., 2001).**

PATIENT AND METHODS

TYPE AND SITE OF THE STUDY:

This prospective study was conducted to evaluate the importance of antenatal care booking of pre-eclampsia risk factors and its effect on maternal and fetal outcomes. It was carried on 150 pregnant women who attending the Department of Obstetrics and Gynecology.

INCLUSION CRITERIA OF THE STUDIED WOMEN

On admission to the hospital, eligible women were approached by the physician and informed of the study. A written consent was obtained. The included pregnant women had diagnosed with preeclampsia according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification **(National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000).**

Preeclampsia is defined as hypertension of at least 140/90 mmHg measured on 2 separate occasions at least 4 hours apart and arising de novo in previously normotensive women after the 20^{th} week of gestation, accompanied by significant proteinuria with or without suggestive clinical symptoms, all of which are resolved by 6 weeks post-partum.

Definition of Pre-eclampsia in pregnancy:

- Systolic blood pressure of ≥140 mmHg in on 2 or more separate occasions at least 4 hours apart or,

- Diastolic blood pressure of ≥90 mmHg in on 2 or more separate occasions at least 4 hours apart.

Definition of severe Pre-eclampsia in pregnancy:

- Systolic blood pressure of ≥170 mmHg in any one occasion or,
- Diastolic blood pressure of ≥110 mmHg in any one occasion.

Definition of proteinuria in pregnancy:

- Significant proteinuria in one 24 hours collection with total protein excretion of ≥300mg/l of per 24 hours or,
- Two clean-catch mid-stream or catheter specimens of urine collected ≥4 hours apart with ≥2+ on reagent strip.

Suggestive clinical symptoms:

- Symptoms including headache, photophobia, visual disturbance, epigastric pain and alteration in the conscious state.

The women with or without regular antenatal care follow-up of pregnancy were recruited from outpatient clinic of Gynecology and Obstetrics Department.

METHODS

All the patients were subjected to:

FULL MEDICAL HISTORY:

- Demographic data.
- Complaint and history of present illness.
- Obstetric history.
- Socioeconomic status.
- Drug history.

- Co-morbid conditions.
- Review of other systems.
- Past history.
- Family history.

RECORDING BLOOD PRESSURE IN PREGNANCY:

- Blood pressure was determined using an average of two consecutive sitting blood pressure readings using mercury sphygmomanometer, five minutes apart then the mean value was calculated.
- The woman should be seated comfortably with her legs resting on a flat surface.
- The supine posture was avoided because of the supine hypotension syndrome.
- Measurement of blood pressure was undertaken in both arms at the initial visit to exclude rare vascular abnormalities such as aortic coarctation, subclavian stenosis and aortic dissection.
- The systolic blood pressure wass accepted as the first sound heard (Korotkoff 1) and the diastolic blood pressure was accepted as the disappearance of sounds completely (Korotkoff 5).
- When Korotkoff 5 is absent, Korotkoff 4 (muffling) was accepted.
- Appropriate cuff size was used for accurate blood pressure recording. A large cuff with an inflatable bladder covering 80% of the arm circumference was used if the upper arm circumference is greater than 33 cm. This helps to minimise over-diagnosis of hypertension during pregnancy.
- In labour, the blood pressure was measured in the left arm in lateral recumbent position.

LABORATORY INVESTIGATIONS:

- Complete blood picture (CBC): for RBCs count, hemoglobin level, white blood cells (WBCs), differential of WBCs, platelet count (using Sysmex K-800 cell counter).
- Fasting blood sugar (using Dimension ES chemical auto-analyzer).

- Liver function tests (using Dimension ES chemical auto-analyzer):
  - Serum aspartate transaminase (AST).
  - Serum alanine transaminase (ALT).
  - Albumin.
- Kidney function tests included; blood urea and serum creatinine (using Dimension ES chemical auto-analyzer).
- Complete urine analysis for the presence of protein, casts, red blood cells (RBCs) and pus.
- Protein in 24 hours urine collection.

ULTRASOUND SETTINGS:

A 3.5 MHz real-time linear array ultrasound scanner was used to follow-up the fetal growth during antenatal care settings.

CARDIOTOCOGRAM (CTG):

CTG was used to monitor several different measures: uterine contractions and four fetal heart rate features - baseline heart rate, variability, accelerations, and decelerations.

APGAR SCORE:

It was performed for all newborns at both 1 and 5 min, for the assessment of the neonatal outcome. It depends upon observing certain signs concerning the vital functions as pulse, respiratory rate, color and cerebral oxygenation as tone and reflex irritability.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

A sample size of 150 women was required to obtain a power of 90% with an assumption of α as 0.05. Data collected throughout history, basic clinical examination, laboratory investigations and ultrasound results were coded, entered and analyzed using

Microsoft Excel software. Gathered data were then imported and processed using Statistical Package of Social Sciences version 20 (IBM SPSS version 20 Inc., Chicago, IL, USA). Quantitative data were expressed as means ± standard deviation (SD) and qualitative data were expressed as frequency (numbers) and percentages. The results for all categorical variables were given in the form of rates (%).

The independent data of the study was conducted and analyzed. Definitive statistics were used for the analysis of the socio-demographic and other variables. Firstly, the relation between the dependent and independent variables was studied using the t-test. T-test was used to test significance of differences for the studied variables that follow normal distribution. Second, the significant variables were subjected to multivariate logistic regression analysis. Logistic regression analysis was performed to identify predictors that associated with maternal and fetal outcomes. P value was set at <0.05 for significant results.

ETHICAL CONSIDERATIONS

- An informed consent was taken from all the participants before taking any data or doing any investigations.

The consent contained:

  - Explanation of the study aim in a simple manner to be understood by the common people.
  - No harmful maneuvers was performed or used.
  - All data were considered confidential and were not used outside this study without patient's approval.
  - All samples were used in the research only.
  - Researcher phone number and all possible communicating methods were identified to the participants to return at any time for any explanation.
  - All participants were announced by the result of the study.

- Participants have the right to withdraw from the study at any time without giving any reason.
- Signature or fingerprints of the participants.

- Patients were received proper health education and suitable medical treatment.

TIME TABLE

	1st-3rd months	**4th-6th months**	**7th-9th months**	**10th-12th months**
Preparatory period				
Data collection & field work				
Data management				
Finishing & printing				

RESULTS

This prospective study was conducted to evaluate the importance of antenatal care booking of pre-eclampsia risk factors and its effect on maternal and fetal outcomes. It was carried on 150 pregnant women with pre-eclampsia aged between 19-35 years, who attending the Department of Obstetrics and Gynecology, Suez Canal University Hospital.

Table (1) shows the socio-demographic characteristics of the studied patients. The most common age of the patients was between 20-30 years (40%) (Chart 1). The majority of the patients were from rural regions (80%) (Chart 2). About 57% of the studied women were primipara, while about 43% of them were multipara (Chart 3). Almost all patients were not working (92.7%). Only 5.3% of the patients had smoking history. The majority of the patients were of middle social class (80%) and also of middle education (76%). About 83% of them were complaining of lower abdominal pain, 9.3% complaining of decreased fetal movements and 6% complaining of headache.

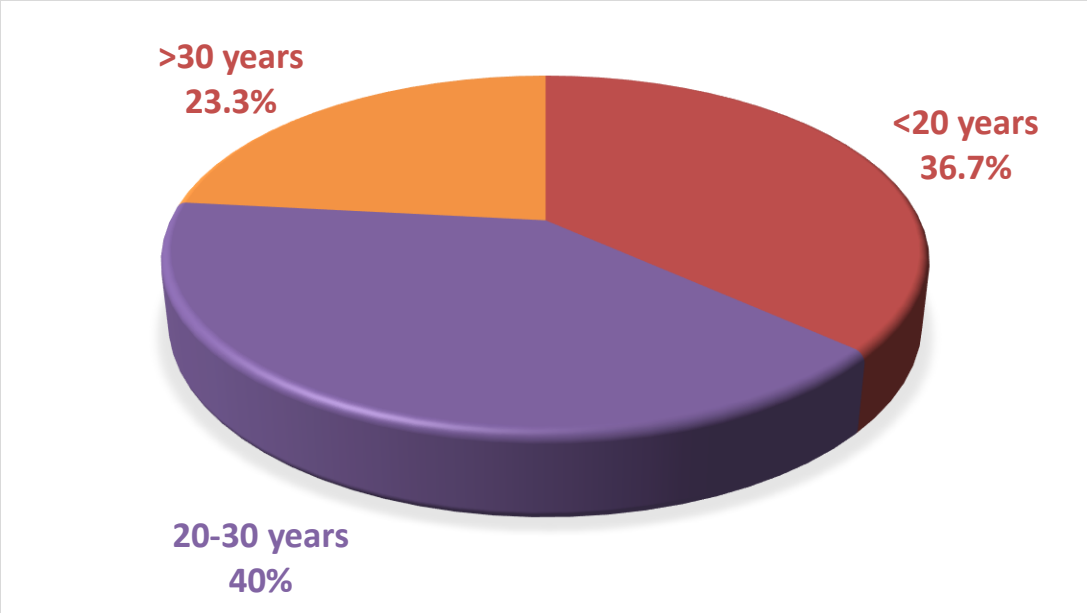

Chart 1. The age distribution among the studied patients.

Table (1) Socio-demographic characteristics of the studied patients (n=150):

		Total (n=150)	
		No.	**%**
Age	<20 years	55	36.7
	20-30 years	60	40.0
	>30 years	35	23.3
Residence	Urban	30	20.0
	Rural	120	80.0
Parity	Primiparous	86	57.3
	Multiparous	64	42.7
Occupation	Employed	11	7.3
	Unemployed	139	92.7
Smoking	Smoker	8	5.3
	Non-smoker	142	94.7

Social class	Low	29	19.3
	Middle	120	80.0
	High	1	0.7
Education	Low	30	20.0
	Middle	114	76.0
	High	6	4.0
Complaint	Lower abdominal pain	125	83.4
	Decrease fetal movements	14	9.3
	Headache	9	6.0

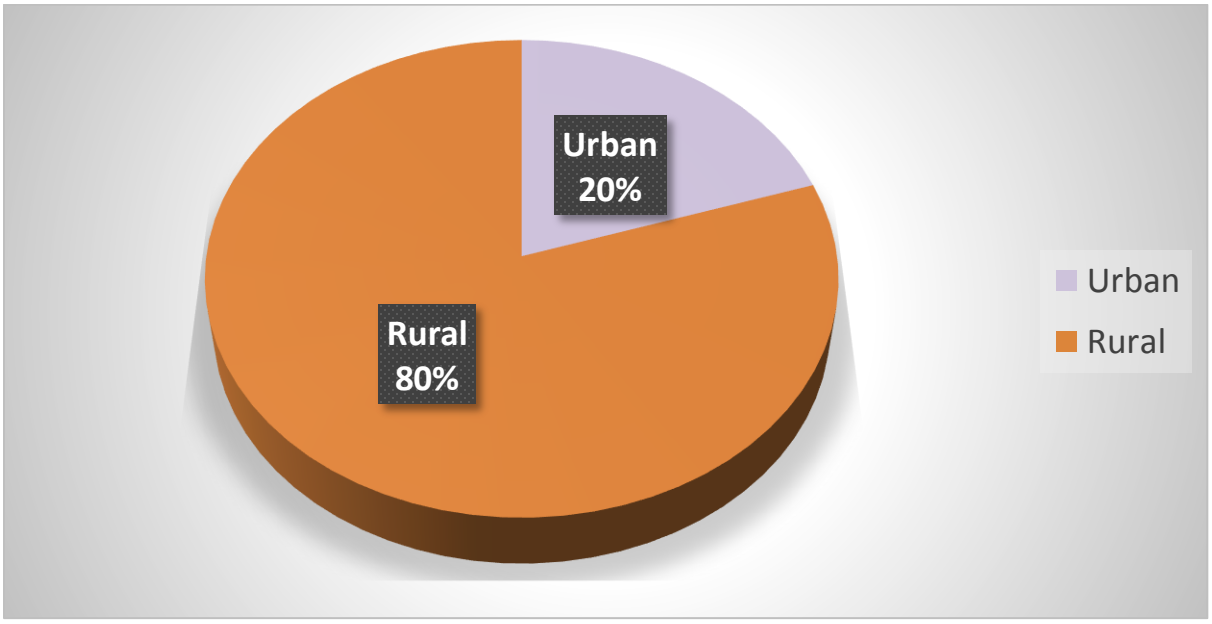

Chart 2. The distribution of the studied patients according to residence.

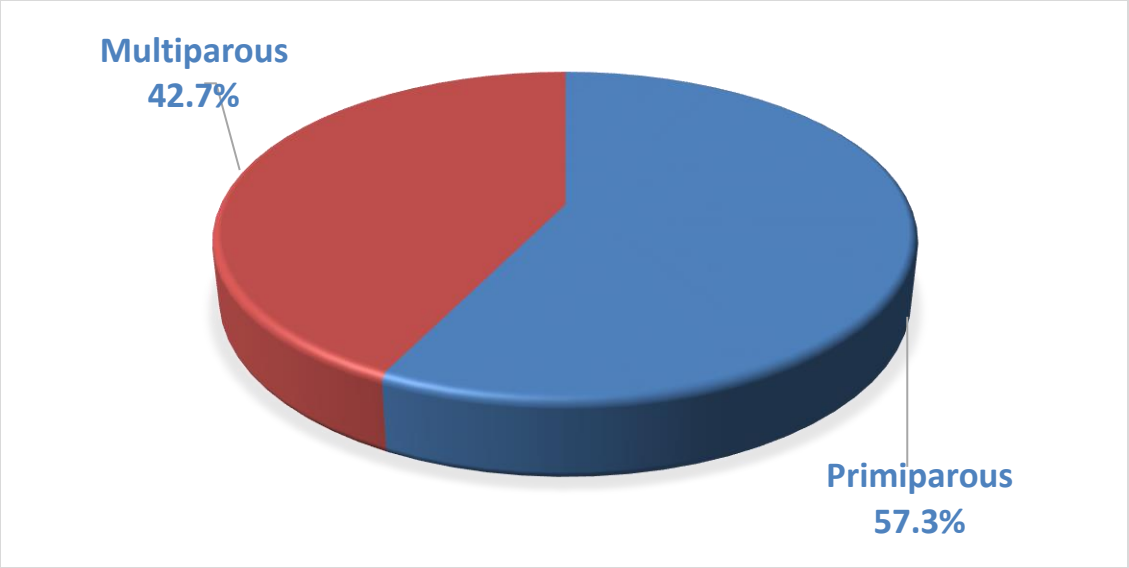

Chart 3. The distribution of the studied patients according to parity.

Table (2) shows the complications occurred to the studied patients during the current pregnancy. In the first trimester, 2.7% of the patients suffered from hyperemesis gravidarum, 12.7% suffered from urinary tract infections, and 4.7% suffered from threatened abortion. Gestational diabetes affect 9.3% of the patients in the second trimester and 16% of the patients in the third trimester, while gestational hypertension affect 37.3% of the patients in the second trimester and 86.6% of the patients in the third trimester. During third trimester, 10.7% of the patients gave a history of vaginal bleeding, 34.7% gave a history of premature rupture of membranes and 57.3% gave a history of abdominal pain.

Table (2) Complications occurred to the studied patients during the current pregnancy (n=150):

		Total (n=150)	
		No.	**%**
1st trimester			
Hyperemesis gravidarum	No	146	97.3
	Yes	4	2.7
Urinary tract infections	No	131	87.3
	Yes	19	12.7
Threatened abortion	No	143	95.3
	Yes	7	4.7
Vaginal discharge	No	102	68.0
	Yes	48	32.0
2nd trimester			
Gestational diabetes	No	136	90.7
	Yes	14	9.3

Gestational hypertension	No	94	62.7
	Yes	56	37.3
Alarming signs	No	141	94.0
	Yes	9	6.0
3rd trimester			
Gestational diabetes	No	126	84.0
	Yes	24	16.0
Gestational hypertension	No	20	13.3
	Yes	130	86.7
Vaginal bleeding	No	134	89.3
	Yes	16	10.7
Premature rupture of membranes	No	98	65.3
	Yes	52	34.7
Abdominal pain	No	64	42.7
	Yes	86	57.3

Table (3) shows the history of complications occurred to the studied patients during previous pregnancies. About 13% of the patients had previous history of postpartum hemorrhage, 12.7% had previous history of preterm labor, 10.7% had previous history of gestational hypertension, and 10.7% had previous history of pre-eclampsia.

Table (3) History of complications occurred to the studied patients during previous pregnancies (n=150):

	Total (n=150)	
	No.	**%**

Gestational Diabetes	1	0.7
Gestational hypertension	16	10.7
Preterm labor	19	12.7
Oligo-hydramnios	2	1.3
Postpartum hemorrhage	20	13.3
Previous history of pre-eclampsia	16	10.7

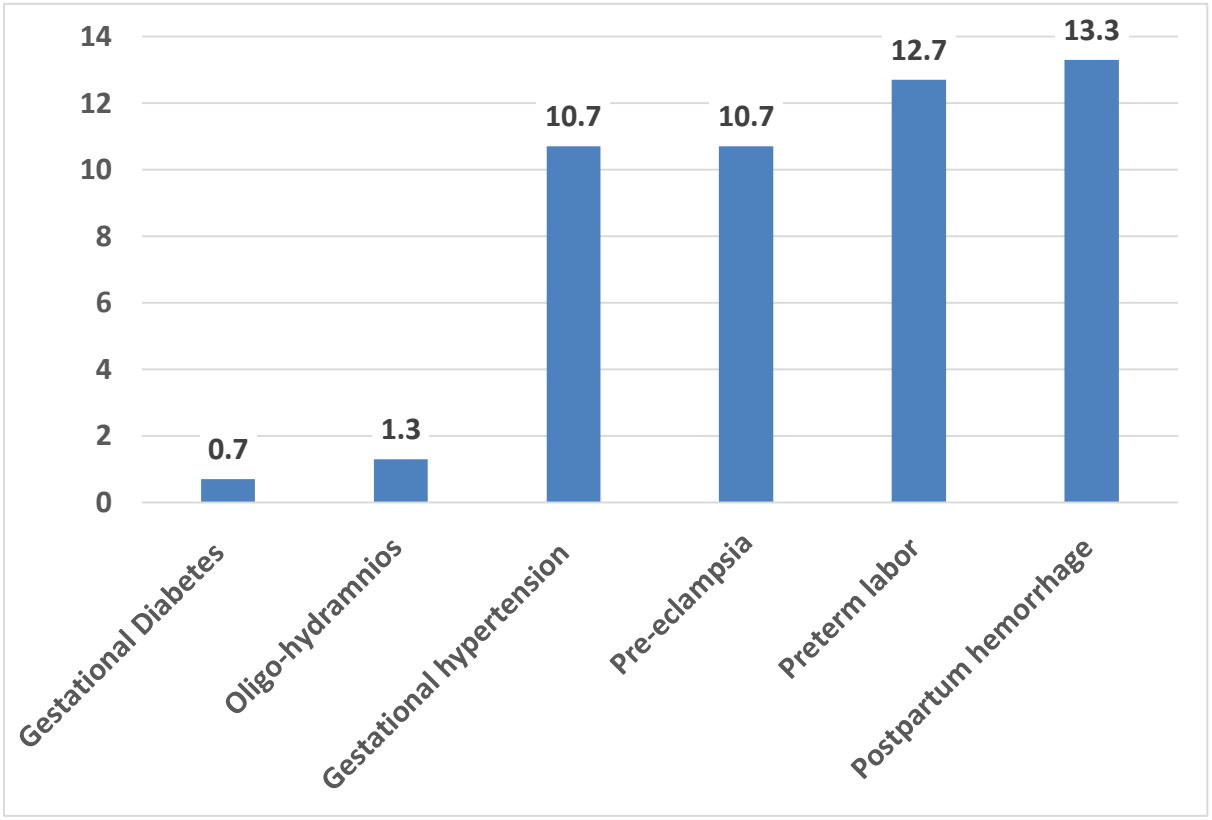

Chart 4. History of complications occurred to the studied patients during previous pregnancies.

Table (4) shows the antenatal control during 1st trimester of the studied patients. About 63% of the patients came for antenatal care from 3 to ≥4 times, while approximately 37% of them came for antenatal care from 0 to 2 times. Sixty eight percent of the studied patients came for blood pressure control and 67.3% of them came for ultrasonographic evaluations. Only 4.7% of the studied women administrated of methyldopa during this period.

Table (4) Antenatal control during 1st trimester of the studied patients (n=150):

		Total (n=150)	
		No.	**%**
1st trimester			
No. of antenatal visits	0-2	56	37.3
	3-≥4	94	62.7
Blood pressure control	No	48	32.0
	Yes	102	68.0
Ultrasonographic evaluation	No	49	32.7
	Yes	101	67.3
Administration of methyldopa	No	143	95.3
	Yes	7	4.7

Table (5) shows the antenatal control during 2nd trimester of the studied patients. About 71% of the patients came for antenatal care from 3 to ≥4 times, while approximately 29% of them came for antenatal care from 0 to 2 times. About 75% of the patients came for blood pressure control and 74% of them came for ultrasonographic evaluations. CTG was performed for 8.7% of the studied women and Doppler examination was performed for 36% of them. Only 8% of the studied women administrated of methyldopa during this period.

Table (5) Antenatal control during 2nd trimester of the studied patients (n=150):

		Total (n=150)	
		No.	**%**
2nd trimester			
No. of antenatal visits	0-2	44	29.4
	3-≥4	106	70.6
Blood pressure control	No	38	25.3
	Yes	112	74.7
Ultrasonographic evaluation	No	39	26.0
	Yes	111	74.0
Cardiotocography (CTG)	No	137	91.3
	Yes	13	8.7
Doppler examination	No	96	64.0
	Yes	54	36.0
Administration of methyldopa	No	138	92.0

	Yes	12	8.0

Table (6) shows the antenatal control during 3rd trimester of the studied patients. About 82% of the patients came for antenatal care from 3 to ≥4 times, while approximately 18% of them came for antenatal care from 0 to 2 times. About 91% of the patients came for blood pressure control and 92% of them came for ultrasonographic evaluations. CTG was performed for 38.7% of the studied women and Doppler examination was performed for 54.7% of them. The majority of the studied women (82%) administrated of methyldopa during this period.

Table (6) Antenatal control during 3rd trimester of the studied patients (n=150):

		Total (n=150)	
		No.	**%**
3rd trimester			
No. of antenatal visits	0-2	27	18.0
	3-≥4	123	82.0
Blood pressure control	No	13	8.7
	Yes	137	91.3
Ultrasonographic evaluation	No	12	8.0
	Yes	138	92.0
Cardiotocography (CTG)	No	92	61.3
	Yes	58	38.7
Doppler examination	No	68	45.3
	Yes	82	54.7
Administration of methyldopa	No	27	18.0
	Yes	123	82.0

Table (7) shows the vital signs and laboratory investigations of the studied patients. The mean systolic blood pressure and diastolic blood pressure were elevated (140.4±14.4 mmHg and 92.9±7.3 mmHg, respectively). The mean body mass index was 29.3±3.2 kg/m^2, which is overweight range.

Table (7) Vital signs and laboratory investigations of the studied patients (n=150):

	Total (n=150)	
	Mean	**SD**
Systolic blood pressure	140.40	14.384
Diastolic blood pressure	92.85	7.338
Heart rate	92.56	8.448
Temperature	36.28	3.148
Respiratory rate	16.14	1.722
Body mass index	29.27	3.151
Hemoglobin	11.26	7.153
Hematocrit	32.86	6.988
Red blood corpuscles	4.42	3.394
White blood count	11.57	12.413
Prothrombin time	16.85	14.804
Partial thromboplastin time	33.91	24.588
International normalized ratio	2.22	11.460
Random blood sugar	112.69	85.688
Platelets	225.86	103.304
Alanine transaminase	34.71	45.975
Aspartate transaminase	44.44	105.477
Serum creatinine	1.17	1.867

Table (8) shows maternal outcome measures of the studied patients. The incidence of postpartum hemorrhage, eclampsia, intensive care unit (ICU) admission, blood transfusion, infection, maternal mortality, and overall bad maternal outcome among the studied patients were 4%, 4%, 8.7%, 13.3%, 9.3%, 1.3%, and 22.7%, respectively.

Table (8) Maternal outcome measures of the studied patients (n=150):

		No.	%
Maternal outcome			
Postpartum hemorrhage	No	144	96.0
	Yes	6	4.0
Eclampsia	No	144	96.0
	Yes	6	4.0
Intensive care unit admission	No	137	91.3
	Yes	13	8.7
Blood transfusion	No	130	86.7
	Yes	20	13.3
Infection	No	136	90.7
	Yes	14	9.3
Maternal mortality	No	148	98.7
	Yes	2	1.3
Overall maternal outcome	Good outcome	116	77.3
	Bad outcome	34	22.7

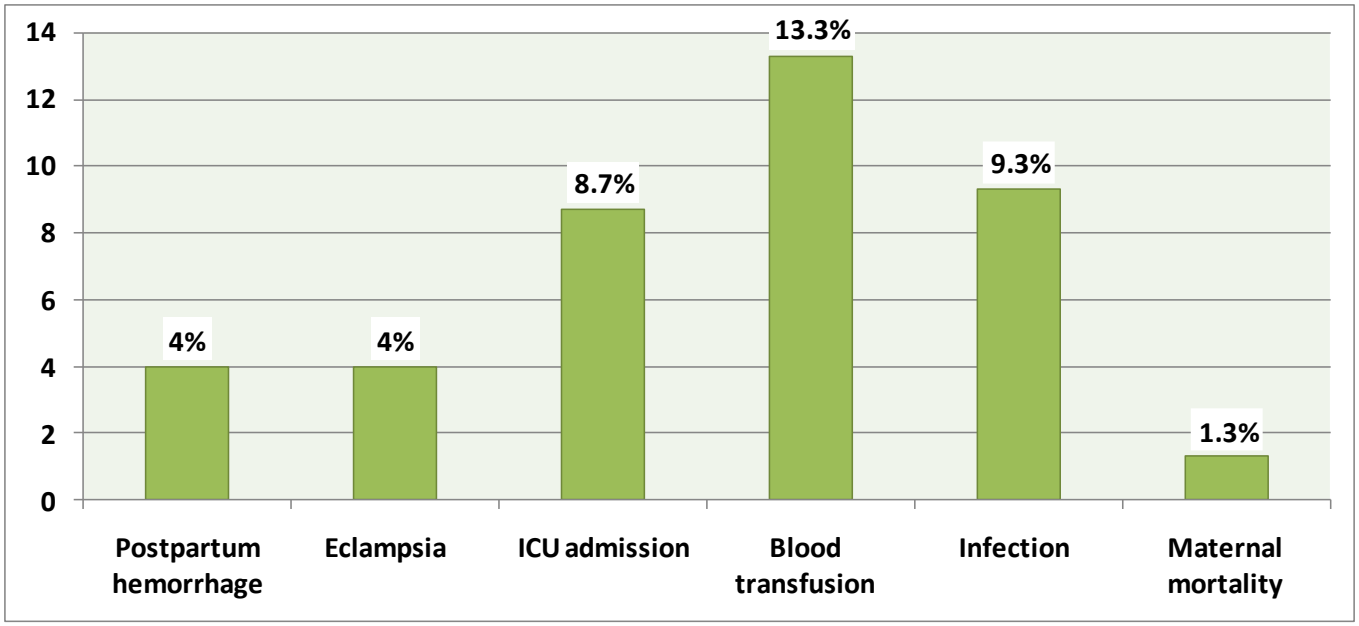

Chart 5. Maternal outcome measures of the studied patients.

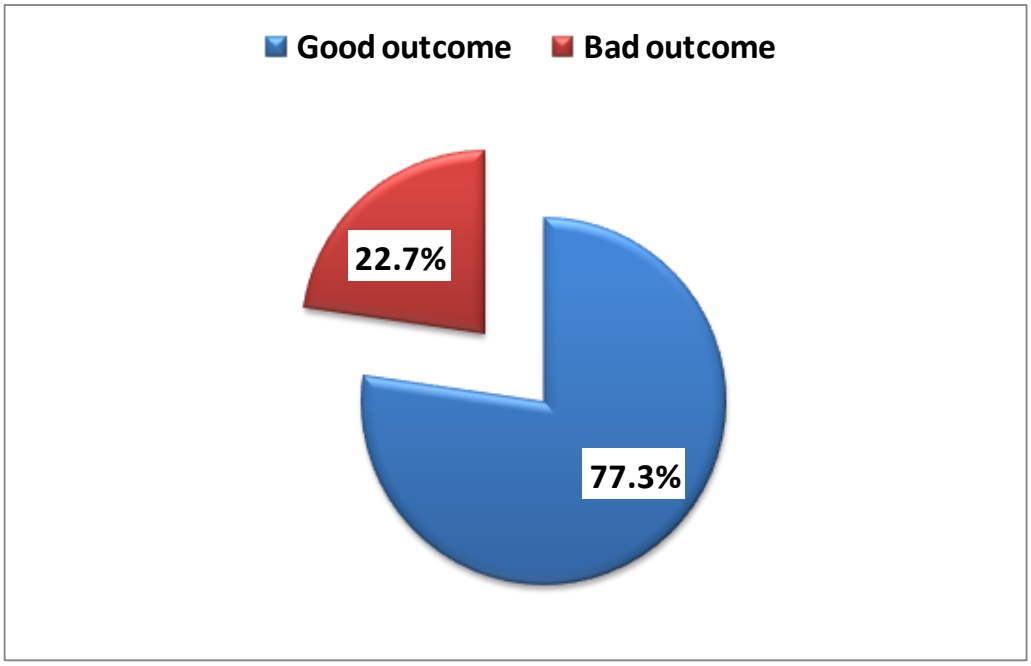

Chart 6. Overall maternal outcome of the studied patients.

Table (9) shows fetal outcome measures of the studied patients. The incidence rate of low birth-weight, intra-uterine growth retardation (IUGR), low Apgar score, no spontaneous cry, cyanosis, no spontaneous breathing, negative neonatal reflexes,

congenital anomalies, abnormal cardiac examination, neonatal intensive care unit (NICU) admission, infection, neonatal mortality, and overall bad fetal outcome among the studied patients were 11.3%, 3.3%, 13.3%, 33.3%, 30%, 29.3%, 26%, 13.3%, 19.3%, 13.3%, 6.7%, 38.7%, 5.3%, and 40.7%, respectively.

Chart 7. Fetal outcome measures of the studied patients.

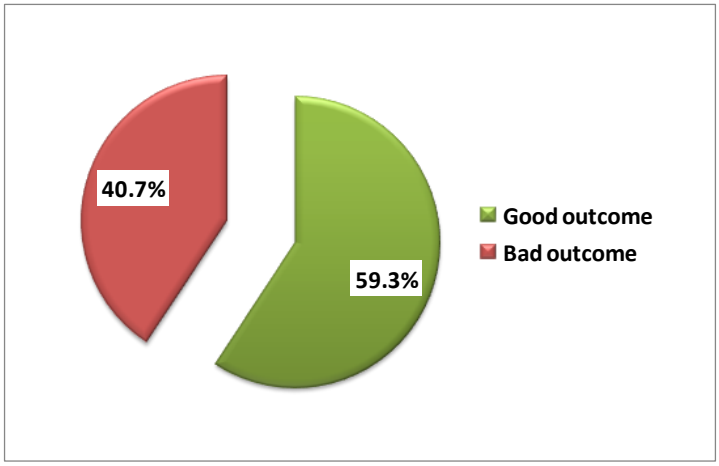

Chart 8. Overall fetal outcome of the studied patients.

Table (9) Fetal outcome measures of the studied patients (n=150):

	No.	%
Fetal outcome		

Gender	Male	80	53.3
	Female	70	46.7
Weight	≤2.5 kg	17	11.3
	>2.5 kg	133	88.7
Intra-uterine growth retardation (IUGR)	No	145	96.7
	Yes	5	3.3
Apgar score at 5 minutes	<7	20	13.3
	≥7	130	86.7
Spontaneous cry	No	50	33.3
	Yes	100	66.7
Cyanosis	No	105	70.0
	Yes	45	30.0
Spontaneous breathing	No	44	29.3
	Yes	106	70.7
Neonatal reflexes	Positive	111	74.0
	Negative	39	26.0
Congenital anomalies	No	130	86.7
	Yes	20	13.3
Cardiac examination	Normal	121	80.7
	Abnormal	29	19.3
Neonatal intensive care unit admission	No	130	86.7
	Yes	20	13.3
Infection	No	140	93.3
	Yes	10	6.7
Preterm (<37 weeks)	No	92	61.3
	Yes	58	38.7

Neonatal mortality	No	142	94.7
	Yes	8	5.3
Overall fetal outcome	Good outcome	89	59.3
	Bad outcome	61	40.7

Table (10) shows the socio-demographic predictors of maternal outcome in the studied patients. Women with higher age (>30 years) had about 3-folds (OR=3.2) higher risk of developing bad outcome. Smoker patients had about 2-folds (OR=2.2) higher risk of developing bad outcome. Low social class women had about 4-folds (OR=3.6) higher risk of developing bad outcome. Women complaining of decreased fetal movements had about 3-folds (OR=3.1) higher risk of developing bad outcome.

Table (10) Regression analysis model of socio-demographic predictors of maternal outcome in the studied patients (n=150):

	Coefficients		**Odds ratio (OR)**	**p-value**
	B	**Beta**		
(Constant)	9.422		4.679	0.002**
Age (>30 years)	0.479	0.851	3.214	0.015*
Residence	0.227	0.282	1.971	0.089
Parity (primiparous)	-0.293	-0.281	1.73	0.127
Unemployed	.119	.082	0.999	0.320
Smokers	.197	.180	2.202	0.029*
Low social class	-0.429	-0.533	3.568	0.009**
Low educational level	-0.063	-0.122	0.841	0.428
Low fetal movement	-0.52	-0.557	3.078	0.018*

**Significant p<0.05, **highly significant p<0.01.*

Table (11) shows the current pregnancy predictors of maternal outcome in the studied patients. Women with hyperemesis gravidarum had about 3-folds (OR=2.9) higher risk of developing bad outcome. Women with gestational diabetes had about 4-folds (OR=3.9) higher risk of developing bad outcome. Women with gestational hypertension had about 3-folds (OR=3.4) higher risk of developing bad outcome. Women with vaginal bleeding had about 3-folds (OR=2.6) higher risk of developing bad outcome. Women with premature rupture of membranes (PROM) had about 3-folds (OR=2.7) higher risk of developing bad outcome.

Table (11) Regression analysis model of current pregnancy predictors of maternal outcome in the studied patients (n=150):

	Coefficients		Odds ratio (OR)	p-value
	B	Beta		
(Constant)	.524		3.667	0.0001**
Hyperemesis	.621	.239	2.913	0.004**
Urinary tract infection	.111	.088	0.987	0.325
Threatened abortion	-.186	-.094	1.141	0.256
Vaginal discharge	-.153	-.171	1.897	0.060
Alarming signs	.294	.167	1.844	0.067
Gestational diabetes	-.683	-.731	3.927	0.006**
Gestational hypertension	-.655	-.780	3.402	0.01**
Vaginal bleeding	.292	.216	2.603	0.01**
PROM	-.492	-.763	2.739	0.029*
Abdominal pain	.011	.013	0.137	0.892

**Significant p<0.05, **highly significant p<0.01, premature rupture of membranes (PROM).*

Table (12) shows the previous pregnancies predictors of maternal outcome in the studied patients. Women with previous history of gestational diabetes had about 3-folds (OR=2.6) higher risk of developing bad outcome. Women with previous history of gestational hypertension had about 2-folds (OR=1.9) higher risk of developing bad outcome. Women with previous history of oligo-hydramnios had about 3-folds (OR=2.9) higher risk of developing bad outcome. Women with previous history of postpartum hemorrhage had about 4-folds (OR=3.8) higher risk of developing bad outcome.

Table (12) Regression analysis model of previous pregnancies predictors of maternal outcome in the studied patients (n=150):

	Coefficients		Odds ratio (OR)	p-value
	B	Beta		
(Constant)	.077		1.603	0.114
Previous history of gestational Diabetes	-1.16	-.462	2.631	0.01**
Previous history of gestational hypertension	-.283	-.378	1.904	0.05*
Previous history of preterm labor	-.027	-.040	0.292	0.772
Previous history of oligo-hydramnios	.988	.550	2.867	0.006**
Previous history of postpartum hemorrhage	.439	.671	3.783	0.007**
Previous history of pre-eclampsia	-.164	-.229	1.149	0.255

**Significant p<0.05, **highly significant p<0.01.*

Table (13) shows the antenatal control predictors of maternal outcome in the studied patients. Women with uncontrolled blood pressure during first trimester had about 2-folds (OR=1.9) higher risk of developing bad outcome. Women who didn't perform ultrasonographic evaluation during second and third trimesters had about 2-folds and 3-folds (OR=1.8 and 2.8, respectively) higher risk of developing bad outcome. Women who didn't administrate methyldopa during third trimester had about 3-folds (OR=2.8) higher risk of developing bad outcome.

Table (13) Regression analysis model of antenatal control predictors of maternal outcome in the studied patients (n=150):

	Coefficients		Odds ratio (OR)	p-value
	B	Beta		
1st number visits	.051	.161	0.807	0.421
1st blood pressure control	-.409	-.455	1.948	0.05*
1st ultrasonography	.114	.127	0.599	0.550
1stmedication	-.002	-.001	0.012	0.991
2nd number visits	.049	.146	0.590	0.556
2nd blood pressure control	.089	.093	0.518	0.605
2nd ultrasonography	-.366	-.384	1.761	0.05*
2nd CTG	-.065	-.044	0.557	0.578
2nd Doppler	.033	.038	0.369	0.713
2nd medication	.023	.015	0.188	0.851
3rd number visits	-.056	-.123	0.865	0.389
3rd blood pressure control	.050	.034	0.278	0.782
3rd ultrasonography	-.521	-.338	2.780	0.006**
3rdCTG	-.063	-.074	0.632	0.529
3rdDoppler	.061	.073	0.678	0.499
3rd administration of methyldopa	.391	.501	2.769	0.028*

**Significant p<0.05, **highly significant p<0.01.*

Table (14) shows the vital signs and laboratory predictors of maternal outcome in the studied patients. The significant predictors of bad maternal outcome were higher systolic blood pressure, higher diastolic blood pressure, lower hart rate, lower hemoglobin, higher hematocrit, higher partial thromboplastin time, and higher international normalized ratio.

Table (14) Regression analysis model of vital signs and laboratory predictors of maternal outcome in the studied patients (n=150):

	Coefficients		Odds ratio (OR)	p-value
	B	Beta		
(Constant)	-2.636		-2.86	0.005**
Systolic blood pressure	-0.019	-0.588	-3.747	0.007**
Diastolic blood pressure	-0.016	-0.399	-3.814	0.007**
Heart rate	.016	.321	2.926	0.004**
Temperature	.001	.011	.131	0.896
Respiratory rate	.009	.038	.440	0.660
Body mass index	.012	.097	1.147	0.254
Hemoglobin	0.125	0.666	2.673	0.032*
Hematocrit	-0.065	-1.02	-3.578	0.009**
Red blood corpuscles	-.005	-.047	-.576	0.566
White blood count	.000	.013	.148	0.883
Prothrombin time	.025	.971	1.990	0.049*
Partial thromboplastin time	-.010	-.628	-2.05	0.043*
International normalized ratio	-.027	-.825	-2.11	0.037*
Random blood sugar	.000	.103	1.020	0.310
Platelets	.000	-.089	-1.01	0.315
Alanine transaminase	-.001	-.058	-.374	0.709
Aspartate transaminase	.001	.107	.720	0.473
Serum creatinine	.028	.140	1.128	0.262

**Significant p<0.05, **highly significant p<0.01.*

Table (15) shows the fetal outcome predictors of overall maternal outcome in the studied patients. Women with low birth-weight neonates had about 2-folds (OR=1.8) higher risk of developing bad outcome. Women who had neonates without spontaneous crying, with cyanosis and/or admitted to NICU had about 2-folds (OR=2.3, 2.3 and 2.1, respectively) higher risk of developing bad outcome.

Table (15) Regression analysis model of fetal outcome predictors of overall maternal outcome in the studied patients (n=150):

	Coefficients		Odds ratio (OR)	p-value
	B	Beta		
(Constant)	.469		2.727	0.007**
Gender	.001	.001	0.031	0.976
Weight (≤2.5 kg)	.004	.159	1.828	0.05*
Spontaneous cry	.159	.192	2.325	0.022*
Cyanosis	.149	.168	2.270	0.025*
Spontaneous breathing	.053	.062	0.742	0.459
Neonatal reflexes	.075	.084	1.294	0.198
Congenital anomalies	.099	.088	1.087	0.279
Cardiac examination	-.001	-.001	0.007	0.994
NICU admission	.235	.208	2.118	0.036*
Infection	.043	.028	0.545	0.587
Neonatal mortality	-.155	-.033	0.739	0.461

**Significant p<0.05, **highly significant p<0.01, beat per minute (bpm), neonatal intensive care unit (NICU).*

Table (16) shows the number and percentage of adequate and inadequate antenatal care booking visits among the studied patients. Approximately 84% of the studied patients attended adequate antenatal care visits (>4 visits), while 16% of them attended inadequate antenatal care visits (0-3 visits).

Table (16) Number and percentages of adequate and inadequate antenatal care booking visits among the studied patients (n=150):

Booking visits	Total (n=150)	
	No.	%
Adequate (>4)	126	84.0
Inadequate (0-3)	24	16.0

Table (17) shows the maternal outcome according to number of antenatal care booking visits of the studied patients. There were significantly higher incidence rate and higher risk of postpartum hemorrhage, eclampsia and ICU admission among women with inadequate booking visits than among women with adequate booking visits (16.7% versus 1.6%, OR=12.4; 20.8% versus 0.8%, OR=32.9; and 37.5% versus 3.2%, OR=18.3; respectively).

Women with no or inadequate booking visits also had significantly higher frequencies of blood transfusion and infection in comparison to women with adequate booking visits (45.8% and 25% versus 7.1% and 6.3%, respectively).

Overall, there was 12-folds higher risk of bad maternal outcome among women with inadequate booking visits than among women with adequate booking visits (66.7% versus 14.3%, respectively; OR=12, CI=4.5-32.1 & $p<0.0001$).

Table (17) Incidence rate of maternal outcome, odds ratio (OR) and 95% confident interval (CI) among women with adequate and inadequate antenatal care booking visits (n=150):

		Adequate booking visits (>4) (n=126)		Inadequate booking visits (0-3) (n=24)		OR	95% CI	p-value
		No.	%	No.	%			
Postpartum hemorrhage	No	124	98.4	20	83.3	12.4	2.1-72.2	0.006**
	Yes	2	1.6	4	16.7			
Eclampsia	No	125	99.2	19	79.2	32.9	3.6-297	0.0004**
	Yes	1	0.8	5	20.8			
ICU	No	122	96.8	15	62.5	18.3	5.02-66.8	<0.0001**
	Yes	4	3.2	9	37.5			
Blood transfusion	No	117	92.9	13	54.2	11.0	3.8-31.5	<0.0001**
	Yes	9	7.1	11	45.8			
Infection	No	118	93.7	18	75.0	4.9	1.5-15.8	0.011*
	Yes	8	6.3	6	25.0			
Maternal mortality	No	125	99.2	23	95.8	5.4	0.3-90	0.30
	Yes	1	0.8	1	4.2			
Preterm labor	No	88	69.8	4	16.7	11.6	3.7-36.2	<0.0001**
	Yes	38	30.2	20	83.3			
Overall maternal outcome	Good outcome	108	85.7	8	33.3	12	4.5-32.1	<0.0001**
	Bad outcome	18	14.3	16	66.7			

ICU (intensive care unit), Odds ratio (OR), confident interval (CI).

Table (18) shows the fetal outcome according to number of antenatal care booking visits of the studied patients. There were significantly higher incidence rate and higher

risk of low neonatal birth-weight, no spontaneous cry and cyanotic babies, NICU admission, preterm neonates and neonatal mortality among women with inadequate booking visits than among women with adequate booking visits (33.3% versus 7.1%, OR=6.5; 58.3% versus 28.6%, OR=3.5; 50% versus 26.2%, OR=2.8; 37.5% versus 8.7%, OR=6.3; 83.3% versus 30.2%, OR=11.6; and 29.2% versus 0.8%, OR=51.5; respectively).

Overall, there was 53-folds higher risk of bad fetal outcome among women with inadequate booking visits than among women with adequate booking visits (95.8% versus 30.2%, respectively; OR=53.3, CI=7-408.8 & $p<0.0001$).

Table (18) Incidence rate of fetal outcome, odds ratio (OR) and 95% confident interval (CI) among women with adequate and inadequate antenatal care booking visits (n=150):

		Adequate booking visits (>4) (n=126)		Inadequate booking visits (0-3) (n=24)		OR	95% CI	p-value
		No.	%	No.	%			
Weight	≤2.5 kg	9	7.1	8	33.3	6.5	2.2-19.2	0.001**
	>2.5 kg	117	92.9	16	66.7			
IUGR	No	122	96.8	23	95.8	1.3	0.14-12.4	0.59
	Yes	4	3.2	1	4.2			
Apgar score at 5 minutes	<7	14	11.1	6	25.0	2.7	0.91-7.8	0.072
	≥7	112	88.9	18	75.0			
Spontaneous cry	No	36	28.6	14	58.3	3.5	1.4-8.6	0.009**
	Yes	90	71.4	10	41.7			
Cyanosis	No	93	73.8	12	50.0	2.8	1.2-6.9	0.037*
	Yes	33	26.2	12	50.0			
Spontaneous breathing	No	33	26.2	11	45.8	2.4	0.97-5.8	0.052
	Yes	93	73.8	13	54.2			
Neonatal reflexes	Positive	95	75.4	16	66.7	1.5	0.6-3.9	0.52
	Negative	31	24.6	8	33.3			
Congenital anomalies	No	109	86.5	21	87.5	0.92	0.25-3.4	0.60
	Yes	17	13.5	3	12.5			
Cardiac examination	Normal	101	80.2	20	83.3	0.81	0.25-2.5	0.79
	Abnormal	25	19.8	4	16.7			

NICU admission	No	115	91.3	15	62.5	6.3	2.2-17.6	<0.0001**
	Yes	11	8.7	9	37.5			
Infection	No	118	93.7	22	91.7	1.3	0.27-6.7	0.50
	Yes	8	6.3	2	8.3			
Preterm (<37 weeks)	No	88	69.8	4	16.7	11.6	3.7-36.1	<0.0001**
	Yes	38	30.2	20	83.3			
Neonatal mortality	No	125	99.2	17	70.8	51.5	6-444.4	<0.0001**
	Yes	1	0.8	7	29.2			
Overall fetal outcome	Good outcome	88	69.8	1	4.2	53.3	7-408.8	<0.0001**
	Bad outcome	38	30.2	23	95.8			

NICU (neonatal intensive care unit), Odds ratio (OR), confident interval (CI).

DISCUSSION

Pre-eclampsia occurs in about 3-5% of pregnancies and is an important cause of fetal and maternal morbidity and mortality worldwide. Studies have shown that women with a history of pre-eclampsia are at increased risk of cardiovascular diseases, suggesting that pre-eclampsia and cardiovascular diseases may share common causes or mechanisms **(Irgens et al., 2001; Smith et al., 2001; Rodie et al., 2004; Ray et al., 2005).**

In healthy pregnancies adaptive changes take place in women's physiology to meet demands of the rapidly developing fetus. Gestational hyperlipidemia, a degree of insulin resistance, and up-regulation of inflammatory markers are among changes that occur. In pregnancies complicated by pre-eclampsia these normally adaptive metabolic responses are further exaggerated **(Rodie et al., 2004).**

Several studies have shown that women with preeclampsia have unfavorable risk profiles in pregnancy, associated with levels of serum lipids, body mass, and blood pressure **(Rodie et al., 2004; Ray et al., 2005).**

It remains uncertain if these characteristics reflect primary causes of pre-eclampsia or if they are secondary markers of the disease process. It is also uncertain whether the increased risk of cardiovascular disease subsequent to pre-eclampsia is due to exposures during that pregnancy or due to underlying biological traits of the mother **(Magnussen et al., 2007).**

In the developed world, antenatal care serves an integral role in facilitating improved pregnancy outcome, leading to a reduction in perinatal death **(Failing et al., 2004).**

The concept of the unbooked mother has traditionally been associated with women in developing countries who are unable or unwilling to access healthcare facilities **(Mutihir and Nyiputen, 2007).**

In studies of unbooked deliveries in African countries, older women of lower socioeconomic status **(Fawcus et al., 1992)** and high parity **(Mutihir and Nyiputen, 2007)** have been identified as the groups most likely not to book for antenatal care and therefore more likely to have preterm babies and incur maternal mortality **(Mutihir and Nyiputen, 2007; Owolabi et al., 2008).**

Treacy et al. (2002), reporting on the perinatal outcome of unbooked women in Ireland, had a disproportionately high rate of preterm delivery, low birth-weight babies and NICU admissions.

The concept of being unbooked may be changing in that instead of the typical picture of the unbooked woman being older, of low socioeconomic status **(Fawcus et al., 1992)** and high parity **(Mutihir and Nyiputen, 2007),** unbooked women may now be young healthy women with poor knowledge on how to access health care in the country.

Kotelchuck (1994) developed the adequacy of prenatal care utilization (APCU) index. It categorized ANC utilization by two independent and distinctive dimensions: adequacy of initiation of antenatal care and adequacy of received services. The adequacy of the timing of initiation of antenatal care indicated by early initiation, WHO recommended that registration before or at 16 weeks of gestation, is considered as "early initiation" (**Alexnder et al., 1996).**

By studying risk factors, these issues could be tackled. Few studies have investigated potentially risk factors in relation to risk of pre-eclampsia. We carried out this prospective study to reach an overall estimate for the importance of antenatal care booking of the risk of pre-eclampsia. This provides an evidence-based from which healthcare professionals can assess each pregnant woman's risk of pre-eclampsia at her booking visit and tailor her antenatal care according to need.

This study included 150 women. The most common age of the patients was between 20-30 years (40%). About 57% of the studied women were primipara, while

about 43% of them were multipara. Women with pre-eclampsia had lower prevalence of smoking history (5.3%). Women with higher educational level had lower risk of pre-eclampsia (4%).

A similar study was performed by **Magnussen et al. (2007).** They included 133 women. The mean age at baseline was 25.4 years for women. The proportion of nulliparous women was higher than multiparous women (64% versus 36.1%, respectively). Smoker women had a lower risk of pre-eclampsia compared with women who did not smoke (18.7% versus 81.3%, respectively). Higher educational level was associated with reduced risk of pre-eclampsia (6%).

Women aged ≥ 40 had approaching twice the risk of developing pre-eclampsia, whether they were primiparous or multiparous (relative risk 1.68, 95% confidence interval 1.23 to 2.29, and 1.96, 1.34 to 2.87, respectively) **(Bianco et al., 1996).** National-wide data suggest that the risk of pre-eclampsia increases by 30% for every additional year of age past 34 years **(Saftlas et al., 1990).**

As mentioned, our study observed that about 57% of the studied women were primipara, while about 43% of them were multipara with a higher risk ratio of preeclampsia (1.3) in primiparous women. Parity was not a significant predictor of poor maternal outcomes (t=-1.7, p=0.13).

In three cohort studies, nulliparity almost triples the risk for pre-eclampsia (2.91, 1.28 to 6.61) **(Coonrod et al., 1995; Lawoyin and Ani, 1996; Lee et al., 2000);** this is supported by adjusted odds ratios for nulliparity from two other cohort studies **(Khan et al., 1996; Hartikainen et al., 1998).** In several studies, women with pre-eclampsia are twice as likely to be nulliparous as women without pre-eclampsia (2.35, 1.80 to 3.06) **(Eskenazi et al., 1991; Stone et al., 1994; Chen et al., 2000; Odegard et al., 2000; Stamilio et al., 2000; Duckitt and Harrington, 2005).**

In our study, despite only 5.3% of the patients had smoking history, the presence of smoking history was a significant predictor of bad maternal outcome (t=2.2, p=0.029).

The results of studies that examine the effects of smoking on pre-eclampsia had controversial findings. On one side, **Salafia and Shiverick (1999)** found similar results as ours that women who smoke and develop pre-eclampsia seem to have a poorer outcome than women with preeclampsia who do not smoke.

On the other side, several studies have indicated that the risk of preeclampsia is lower in women who smoke than in women who do not smoke, but it is not fully understood how smoking may reduce the risk **(Conde-Agudelo et al., 1999; Bainbridge et al., 2005; Magnussen et al., 2007).**

Exposure to nicotine, carbon monoxide, stimulation of nitric oxide production, lowering of anti-angiogenic factors, or a decreased immune response have been advanced as possible explanations for this observation **(Conde-Agudelo et al., 1999; Bainbridge et al., 2005; Beste et al., 2005).** This may indicate a synergy between smoking and pre-eclampsia or, alternatively, that smoking may mask the symptoms of pre-eclampsia.

In our study, about 13% had previous history of preterm labor, about 11% had previous history of pre-eclampsia, about 11% had previous history of hypertension, and about 1% had history of diabetes. History of diabetes and hypertension, but not previous pre-eclampsia, was significant predictors of bad maternal outcomes. The prevalence of postpartum hemorrhage, eclampsia, ICU admission, blood transfusion, infection, maternal mortality, and overall bad maternal outcome among the studied pre-eclamptic patients were 4%, 4%, 8.7%, 13.3%, 9.3%, 1.3%, and 22.7%, respectively. The prevalence of NICU admission, infection, neonatal mortality, and overall bad fetal outcome among the studied pre-eclamptic patients were 13.3%, 6.7%, 5.3%, and 40.7%, respectively.

In the same way, **Magnussen and his colleagues (2007)** found that about 27% of the studied women had preterm labor, 11.3% had previous pre-eclampsia, 5% had hypertension, and 1.5% had previous history of diabetes.

Attia et al. (2012) data revealed that pregnancy outcomes in the unbooked mothers were poorer than in the booked mothers due higher incidence of preeclampsia and PROM, where its percentage was as follow; 8% in unbooked mothers versus 2% booked mothers and 17% in unbooked mothers versus 11% booked mothers, respectively. Results of this study showed high prevalence of NICU admission and perinatal morbidity (15% and 20%).

The higher incidence of antenatal complications such as pregnancy induced hypertension is a factor that leads to poor outcomes in the infant and the mother **(Owolabi et al., 2008).**

Other studies have assessed cardiovascular risk factors measured in ongoing pregnancies **(Wolf et al., 2002; Duckitt and Harrington, 2005; Ray et al., 2006),** and some have reported associations between pre-eclampsia and pre-pregnancy obesity, chronic hypertension, and hypercholesterolaemia **(Thadhani et al., 1999; O'Brien et al., 2003).**

Women who have pre-eclampsia in a first pregnancy have seven times the risk of pre-eclampsia in a second pregnancy (7.19, 5.85 to 8.83) **(Lee et al., 2000; Makkonen et al., 2000; Dukler et al., 2001).** Women with pre-eclampsia in their second pregnancy are also more than seven times more likely to have a history of pre-eclampsia in their first pregnancy than women in their second pregnancy who do not develop pre-eclampsia (7.61, 4.3 to 13.47) **(Chen et al., 2000; Odegard et al., 2000; Makkonen et al., 2000; Stamilio et al., 2000; Dukler et al., 2001; Duckitt and Harrington, 2005).**

The likelihood of pre-eclampsia nearly quadruples if diabetes is present before pregnancy (3.56, 2.54 to 4.99) **(Lee et al., 2000; Maxwell et al., 2001).** Pre-existing hypertension, in a population based nested case-control study, **Davies et al. (1970)** found that the prevalence of chronic hypertension was higher in women who developed pre-

eclampsia than women who did not (12.1% v 0.3%). **McCowan et al. (1996)** compared outcomes in 129 women with chronic hypertension who did not develop superimposed pre-eclampsia with 26 women with chronic hypertension who did.

Women with superimposed pre-eclampsia had significantly higher rates of perinatal morbidity (odds ratio 8.8, 2.6 to 39.0), small for gestational age infants (5.6, 1.8 to 16.0), and delivery before 32 weeks (15.0, 5.7 to 38.0). A diastolic blood pressure before 20 weeks of either ≥ 110 mm Hg (5.2, 1.5 to 17.2) or ≥ 100 mm Hg (3.2, 1.0 to 7.8) is most predictive of the development of superimposed pre-eclampsia **(Duckitt and Harrington, 2005).**

Healthy pregnancies are typically characterized by insulin resistance compared with the non-pregnant state, including up-regulation of maternal carbohydrate and lipid metabolism **(Rodie et al., 2004; Sibai et al., 2005).**

These adaptive responses to pregnancy meet demands of the rapidly developing fetus, and in pre-eclamptic pregnancies these metabolic up-regulations seem to be exaggerated compared with uncomplicated pregnancies **(Rodie et al., 2004; Sibai et al., 2005).**

Therefore the excessive metabolic changes of pre-eclamptic pregnancies may be regarded as a stress test for maternal cardiovascular function **(Sattar and Greer, 2002).**

Several studies have linked pre-eclampsia with higher risk of future cardiovascular disease of the mother **(Irgens et al., 2001; Smith et al., 2001; Ray et al., 2005),** suggesting that pre-eclampsia and cardiovascular diseases may share common patho-physiological mechanisms **(Rodie et al., 2004).**

The pathogenesis of pre-eclampsia is uncertain, but predisposition to endothelial dysfunction is thought to play a crucial part **(Rodie et al., 2004; Sibai et al., 2005; Ness and Sibai, 2006).**

Risk factors for pre-eclampsia such as chronic hypertension, renal disease, and diabetes are all conditions where endothelial dysfunction is a common feature **(Rodie et al., 2004; Sibai et al., 2005).**

Furthermore, unfavorable lipid levels are associated with endothelial dysfunction and may precede the development of atheromatous disease **(Goode et al., 1995).** Studies have also shown acute atherosis in vessels of the placenta bed in pre-eclamptic women. Finally, it would be possible to test the causal effect of some of these risk factors—such as increased low density lipoprotein cholesterol or triglyceride levels—on risk of pre-eclampsia by relating genotypes associated with different average levels of these factors to risk of pre-eclampsia and utilizing the principle of mendelian randomization **(Smith and Ebrahim, 2004).**

Regarding the antenatal control of our studied patients, about 63% of the patients came for antenatal care from 3 to 4 times during the first trimester of pregnancy. About 71% of the patients came for antenatal care from 3 to 4 times during the second trimester. About 82% of the patients came for antenatal care from 3 to 4 times during the third trimester.

Attia et al. (2012) study found that 46% of booked mothers attended first ANC visit during first 16 weeks of pregnancy, 38% of booked mothers attended first ANC visit in the period between 16th and 28th weeks of pregnancy and 16% of booked mothers attended first ANC visit after 28 weeks of pregnancy.

Early initiation of prenatal care is important to prevent and treat obstetric and medical complications (as preeclampsia). It reduces the risk of occurrence of the congenital anomalies which may arise from exposure of the fetus to irradiation, drugs or intrauterine infections in the early pregnancy **(WHO, 1997).**

In our study, the mean systolic blood pressure and diastolic blood pressure were elevated (140.4±14.4 mmHg and 92.9±7.3 mmHg, respectively). The mean body mass index was 29.3±3.2 kg/m^2, which is overweight range. Higher systolic and diastolic blood pressures, but not high body mass index, significantly predict bad maternal outcome.

Also, one of the significant predictors of bad maternal outcome was uncontrolled blood pressure during first trimester.

Similarly, **Magnussen and his colleagues (2007)** found that about 41% of the studied women had systolic blood pressure ≥130 mmHg and 38% of them had diastolic blood pressure ≥78 mmHg. About 52% of those women had body mass index ≥25 kg/m^2 (overweight).

Regarding blood pressure at booking, **Reiss et al. (1987)** matched 30 women with pre-eclampsia for age, race, and parity with normotensive control women. Both systolic and diastolic blood pressures were significantly higher in the first trimester for women who later developed pre-eclampsia. **Sibai et al. (1995)** found that higher systolic and diastolic blood pressures at the first visit were associated with an increased incidence of pre-eclampsia (3.8% in women with diastolic blood pressure of < 55 mm Hg, 7.4% in those with diastolic blood pressure 70-84 mm Hg). However, their recruitment was limited to women with a first blood pressure reading of ≤ 135/85 mm Hg.

In a population based nested case-control study **Odegard et al. (2000)** found that a systolic blood pressure ≥ 130 mm Hg compared with < 110 mm Hg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (adjusted odds ratio 3.6, 2.0 to 6.6). The association with a diastolic pressure ≥ 80 mm Hg compared with < 60 mm Hg was similar but not significant (1.8, 0.7 to 4.6).

In a case-control study **Stamilio et al. (2000)** found that a mean arterial pressure > 90 mm Hg at the first prenatal visit was significantly associated with the development of severe pre-eclamptic toxaemia (relative risk 3.7, 2.1 to 6.6).

In our study, the mean body mass index was 29.3±3.2 kg/m^2, which is overweight range. Body mass index was not a significant predictor of poor maternal outcomes (t=1.1, p=0.25). Confounding factors can affect the relation between body mass index and maternal outcomes as women with raised body mass index may be older and more at risk of chronic hypertension.

Although the studies that looked at body mass index before pregnancy all used different ranges, they all showed effects in the same direction, suggesting an overall doubling of risk of pre-eclampsia with a raised body mass index (2.47, 1.66 to 3.67) **(Lee et al., 2000; Stone et al., 1994; Fields et al., 1996; Bianco et al., 1998; Thadhani et al., 1999).**

One cohort study showed that women with a body mass index > 35 before pregnancy had over four times the risk of pre-eclampsia compared with women with a pre-pregnancy body mass index of 19-27 (4.39, 3.52, 5.49) **(Bianco et al., 1998).**

All studies that looked at raised compared with normal body mass index at booking found that the risk of pre-eclampsia is increased by 50% **(Sibai et al., 1997; Bowers et al., 1999; Van Hoorn et al., 2002; Duckitt and Harrington, 2005).**

Notably, a body mass index > 35 at booking doubles the pre-eclampsia risk (one cohort study, 2.12, 1.56 to 2.88) **(Sibai et al., 1997).** A study comparing low and normal body mass index at booking found that the risk of pre-eclampsia was significantly reduced with a body mass index < 20 (odds ratio 0.76, 0.62 to 0.92) **(Sebire et al., 2001).**

Several advantages and potentially success factors of this study must be considered.

Firstly, socio-demographic factors are potential risk factors and significant predicators of adverse maternal outcomes. In the present study, we accounted for five of these factors (maternal age, residence, occupation, social class and maternal education), and we were able to evaluate the relation between these socioeconomic factors and maternal outcomes because these data were sufficient for statistical calculation. Two of these socio-demographic factors were significant predictors of bad maternal outcome (higher age, and lower social class).

Secondly, our study was population-based. So, the effect of different racial origin on adverse maternal outcomes was neglected and the results had not been confounded by

this matter as the results were similar among the homogenous population characteristics considered in our study.

Thirdly, the accuracy of specific diagnoses on this study has been extensively investigated and the main researcher had applied the defined criteria appropriately.

Fourthly, adjustments for several variables were performed and this decreases the potential hazards for the confounding factors.

Fifthly, accuracy of gestational age estimated from the date of last menstrual period and confirmed by ultrasonographic evaluation is a well recognized accurate method in epidemiological research. When we replicated the entire analyses using gestational age estimated from physical and neurological assessments of the new-born in comparison to that based on last menstrual period and ultrasonographic evaluation, the results were essentially unchanged.

Finally, it should be emphasized that our study was carried out in developing countries and its findings may therefore be applicable to other similar developing populations.

In conclusion, antenatal care booking with addressing of pre-eclampsia risk factors provided an effective method to identify the significant predictors of poor maternal and fetal outcomes.

SUMMARY

Pre-eclampsia occurs in about 3-5% of pregnancies and is an important cause of fetal and maternal morbidity and mortality worldwide. Studies have shown that women with a history of pre-eclampsia are at increased risk of cardiovascular diseases, suggesting that pre-eclampsia and cardiovascular diseases may share common causes or mechanisms.

In the developed world, antenatal care serves an integral role in facilitating improved pregnancy outcome, leading to a reduction in perinatal death. The concept of the unbooked mother has traditionally been associated with women in developing countries who are unable or unwilling to access healthcare facilities.

By studying risk factors, these issues could be tackled. Few studies have investigated potentially risk factors in relation to risk of pre-eclampsia. We carried out this prospective study to reach an overall estimate for the importance of antenatal care booking of the risk of pre-eclampsia. This provides an evidence-based from which healthcare professionals can assess each pregnant woman's risk of pre-eclampsia at her booking visit and tailor her antenatal care according to need.

This study included 150 women. The most common age of the patients was between 20-30 years (40%). About 57% of the studied women were primipara, while about 43% of them were multipara. Parity was not a significant predictor of poor maternal outcomes (t=-1.7, p=0.13).

Women with pre-eclampsia had lower prevalence of smoking history (5.3%). Women with higher educational level had lower risk of pre-eclampsia (4%).

In our study, despite only 5.3% of the patients had smoking history, the presence of smoking history was a significant predictor of bad maternal outcome (t=2.2, p=0.029).

In our study, about 13% had previous history of preterm labor, about 11% had previous history of pre-eclampsia, about 11% had previous history of hypertension, and

about 1% had history of diabetes. History of diabetes and hypertension, but not previous pre-eclampsia, was significant predictors of bad maternal outcomes. The prevalence of postpartum hemorrhage, eclampsia, ICU admission, blood transfusion, infection, maternal mortality, and overall bad maternal outcome among the studied pre-eclamptic patients were 4%, 4%, 8.7%, 13.3%, 9.3%, 1.3%, and 22.7%, respectively. The prevalence of NICU admission, infection, neonatal mortality, and overall bad fetal outcome among the studied pre-eclamptic patients were 13.3%, 6.7%, 5.3%, and 40.7%, respectively.

Regarding the antenatal control of our studied patients, about 63% of the patients came for antenatal care from 3 to 4 times during the first trimester of pregnancy. About 71% of the patients came for antenatal care from 3 to 4 times during the second trimester. About 82% of the patients came for antenatal care from 3 to 4 times during the third trimester.

In our study, the mean systolic blood pressure and diastolic blood pressure were elevated (140.4±14.4 mmHg and 92.9±7.3 mmHg, respectively). The mean body mass index was 29.3±3.2 kg/m^2, which is overweight range. Higher systolic and diastolic blood pressures, but not high body mass index, significantly predict bad maternal outcome. Also, one of the significant predictors of bad maternal outcome was uncontrolled blood pressure during first trimester.

In our study, the mean body mass index was 29.3±3.2 kg/m^2, which is overweight range. Body mass index was not a significant predictor of poor maternal outcomes ($t=1.1$, $p=0.25$). Confounding factors can affect the relation between body mass index and maternal outcomes as women with raised body mass index may be older and more at risk of chronic hypertension.

In conclusion, antenatal care booking with addressing of pre-eclampsia risk factors provided an effective method to identify the significant predictors of poor maternal and fetal outcomes.

CONCLUSIONS

Regarding the collected results of the present work the following conclusions can be suggested:

- **Predictors of maternal outcome includes:**
  - Higher age (triple risk).
  - Smoking (double risk).
  - Low social class (quadruple risk).
  - Decreased fetal movements (triple risk).
  - Hyper-emesis gravidarum (triple risk).
  - Gestational diabetes (quadruple risk).
  - Gestational hypertension (triple risk).
  - Vaginal bleeding (triple risk).
  - PROM (triple risk).
  - Previous history of gestational diabetes (triple risk).
  - Previous history of gestational hypertension (double risk).
  - Previous history of oligo-hydramnios (triple risk).
  - Previous history of postpartum hemorrhage (quadruple risk).
  - Uncontrolled blood pressure during 1^{st} trimester (double risk).
  - Not performing ultrasonography evaluation during 2^{nd} & 3^{rd} trimesters (double and triple risk, respectively).
  - Not administrating methyldopa during 3^{rd} trimester (triple risk).
  - Higher systolic and diastolic blood pressure (quadruple risk).
  - Lower heart rate (triple risk).
  - Lower hemoglobin (triple risk).
  - Higher PT, PTT and INR (double risk).
  - Low neonatal birth-weight (double risk).
  - Neonates without spontaneous crying, with cyanosis and/or admitted to NICU (double risk).
- Approximately 16% of the studied patients attended inadequate antenatal care visits (0-3 visits).
- There were significantly higher incidence rate and higher risk of postpartum hemorrhage, eclampsia, ICU admission, blood transfusion, infection and overall bad maternal outcome

among women with inadequate booking visits than among women with adequate booking visits.

- There were significantly higher incidence rate and higher risk of low neonatal birth-weight, no spontaneous cry and cyanotic babies, NICU admission, preterm neonates, neonatal mortality and overall bad fetal outcome among women with inadequate booking visits than among women with adequate booking visits.
- Overall conclusion, the antenatal care booking visits during pregnancy of the studied patients are inadequate and it had significant effects of on maternal and fetal outcomes.

RECOMMENDATIONS

Regarding the collected results of the present work the following recommendation can be suggested:

- There is an urgent need to promote antenatal care utilization, ensure supervised delivery by trained attendants and eliminate deliveries under substandard conditions.
- Improvement in the socioeconomic conditions of the population and the removal of fee for service in maternal care services will go a long way to improve the availability and accessibility of good quality antenatal care and delivery services that are urgently needed.
- The need to clear information on general aspects of ANC to the expectant mother should be established.
- Training on simple and effective way of providing ANC should be given to health care providers.
- Further studies including larger sample size and other factors affecting the maternal and fetal outcomes are recommended.

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