vol. XXIX, no. 4
October/November/December 2008

The Iowa PERINATAL Letter

During the Iowa Statewide Perinatal Team hospital visits we often review records of patients who are diagnosed with preeclampsia. We have chosen to readdress the topic of preeclampsia; diagnosis and management in this issue of the Perinatal Letter. Unfortunately space limitations prevent a more thorough discussion but we hope the main points will be adequately addressed.

Preeclampsia/Eclampsia: An Immediate and Long Term Problem

Preeclampsia (PreE) refers to a syndrome characterized by the new onset of hypertension and proteinuria after 20 weeks of pregnancy in a previously normotensive woman. Preeclampsia affects 5-7% of all pregnancies, yet it represents 15% of all maternal-fetal morbidity and mortality. According to the Centers of Disease Control and Prevention, in 2005, 623 women in the United States died due to maternal causes. Fifty of these deaths were linked to preeclampsia and eclampsia [1]. Of the 14 maternal deaths reviewed in Iowa from 2004-2007, 3 were from complications of preeclampsia. In addition, there is an increasing amount of data suggesting that preeclampsia is an early marker for future cardiovascular disease in women [2-4].

continued on page 16

EDITOR: Stephen K. Hunter, M.D., Ph.D., Obstetrics and Gynecology. ASSOCIATE EDITOR: Michael J. Acarregui, M.D., Associate Professor, Pediatrics. EDITORIAL ASSISTANT: Kathy Brogden, Pediatrics. Call 319-356-2637 to be added to the mailing list.

The Iowa PERINATAL Letter
Statewide Perinatal Care Program
Department of Pediatrics
200 Hawkins Drive
Iowa City, IA 52242-1083

Preeclampsia/Eclampsia: An Immediate and Long Term Problem

continued from page 15

Recent data suggests that the sequelae of PreE such as fetal growth restriction may also predispose a fetus to long term consequences such as metabolic syndrome, hypertension, and infertility if the fetus survives into adulthood [5, 6]. Clearly, preeclampsia has immediate and potentially long term effects on both the fetus and mother. Yet to date, the pathogenesis and cure of preeclampsia, is largely unknown. Unfortunately it is currently not possible to predict who will develop PreE using laboratory, physiologic or ultrasound tests, therefore clinical risk factors remain the only predictive tool. Risk factors for PreE include past obstetrical history of PreE, first pregnancy, a family history, multiple gestation, obesity, preexisting hypertension, renal disease or collagen vascular disease, the antiphospholipid syndrome, advanced maternal age and a prolonged interval between pregnancies. Interestingly, tobacco smoking lowers the risk of preeclampsia by 30-50%. Although patients should obviously not be encouraged to smoke, there is ongoing research to help explain this phenomenon.

Diagnosis of Preeclampsia: Clinical and Laboratory Manifestations

The diagnosis of preeclampsia is made when a pregnant woman has a persistently elevated blood pressure of 140 mm Hg systolic or higher or 90 mm Hg diastolic or higher that occurs after 20 weeks of gestation on 2 occasions 6 hours apart (in a woman with previously normal blood pressures). Hypertension is generally the earliest clinical finding of preeclampsia and is the most common clinical clue to the presence of the disease. In addition to hypertension, proteinuria (defined as > 0.3 g protein in a 24 hour urine specimen) must be present in most cases to make the diagnosis of preeclampsia. In general, it is not necessary to repeat a 24 hour urine collection later in pregnancy once the criterion for proteinuria is met. In a patient who has a condition with baseline proteinuria, a repeat 24 urine collection for protein concentration may be necessary to determine the diagnosis of PreE. However, it must be remembered that 20 percent of women who develop eclampsia have no proteinuria and 10 percent of women who develop other clinical and/or histological findings of preeclampsia have no proteinuria. Therefore preeclampsia should be suspected in any pregnant woman with hypertension and characteristic signs/symptoms, even in the absence of proteinuria.

Preeclampsia can affect multiple organ systems and therefore can be associated with many other signs and symptoms. Findings indicative of renal involvement other than proteinuria include elevated serum creatinine, elevated serum uric acid levels and oliguria (< 500 mL in 24 hours). Renal failure is a rare complication that can occur in patients with severe disease. The clinical manifestations of liver involvement include right upper quadrant or epigastric pain, elevated transaminases and, in the most severe cases, subcapsular hemorrhage or hepatic rupture, which may represent HELLP (Hemolysis, Elevated Liver transaminases, and Low Platelets) syndrome. Central nervous system manifestations of preeclampsia include headache, blurred vision, scotomata, and rarely cortical blindness. Seizures in a woman with preeclampsia signify a change in diagnosis to eclampsia. Stroke leading to death or disability is the most serious central nervous system complication of severe preeclampsia/eclampsia. Hemolysis and thrombocytopenia are the most common hematologic findings in preeclampsia. The PT, PTT and fibrinogen concentration are typically not affected unless there are additional complications, such as placental abruption or severe liver involvement. Pulmonary edema can also be seen in preeclampsia. Given the potential of preeclampsia to affect these many organ systems laboratory evaluation should include a complete blood count, quantification of urinary protein excretion in a 24 hour sample, serum creatinine concentration, and serum alanine and aspartate aminotransferase concentrations (ALT and AST). Coagulation function tests are usually normal unless there is liver dysfunction or thrombocytopenia. The fetal consequences of preeclampsia include growth restriction and oligohydramnios and are usually the result of chronic placental hypoperfusion. Many of these examples of end organ damage help distinguish mild preeclampsia from severe preeclampsia.

As preeclampsia can affect so many different organ systems it is important to keep in mind the many mimickers of preeclampsia, such as different forms of thrombocytopenia, exacerbations of systemic lupus erythematosus, cerebral vascular accidents, migraine headaches, and liver disease such as hepatitis, cholestatsis and acute fatty liver of pregnancy. These mimickers of preeclampsia underscore the importance of obtaining baseline lab values in those patients with preexisting conditions such as chronic hypertension or diabetes where proteinuria may exist prior to pregnancy.

On the other hand, preeclampsia can mimic many other diseases such as flu, gallbladder disease, migraine headache etc. that may delay the diagnosis of preeclampsia. ***A delay in diagnosis of preeclampsia has had lethal consequences for both the fetus and mother.*** Therefore in the face of a pregnant patient with hyper-

Table 1. Criteria for Severe Preeclampsia

1. **Severe Blood Pressure Elevation** (SBP ≥ 160 mmHg of DBP ≥ 110 mmHg on two occasions at least six hours apart)
2. **Proteinuria** (5 or more grams in 24 hours)
3. **Oliguria** (< 500 ml in 24 hours)
4. **Symptoms of central nervous system dysfunction** (blurred vision, severe headache, altered mental status)
5. **Symptoms of liver capsule distention** (right upper quadrant or epigastric pain, nausea, vomiting)
6. **Hepatocellular injury** (elevated serum transaminases; ALT, AST)
7. **Severe fetal growth restriction**
8. **Pulmonary edema or cyanosis**
9. **Cerebral vascular accident**
10. **Thrombocytopenia** (Platelet count < 100,000 per cubic millimeter)

tension and proteinuria, the patient has preeclampsia until proven otherwise.

The diagnosis of preeclampsia is therefore largely based upon the characteristic clinical and laboratory features described above which develops after 20 weeks of gestation in a woman who was previously normotensive. Preeclampsia is classified as either mild or severe. Findings indicative of severe disease are listed in Table 1. The distinction between mild and severe preeclampsia is crucial as it has important ramifications on clinical management.

It is important to remember that preeclampsia is part of a spectrum of disease that encompasses all hypertension in pregnancy (see Table 2). Clinical and laboratory findings are used to differentiate gestational hypertension and chronic hypertension and preeclampsia, but signs and symptoms of these disorders often overlap.

Management and Treatment of Preeclampsia

The initial management goal is to support the diagnosis by excluding other disorders characterized by hypertension and proteinuria. The secondary goal is to assess the severity of disease, whether mild or severe. Laboratory evaluation helps to determine disease severity by characterizing the extent of end organ involvement. Fetal well-being is evaluated by nonstress test and/or biophysical profile, ultrasound to evaluate fetal growth, amniotic fluid and if possible umbilical artery Doppler velocimetry.

Table 2. The Spectrum of Hypertension in Pregnancy

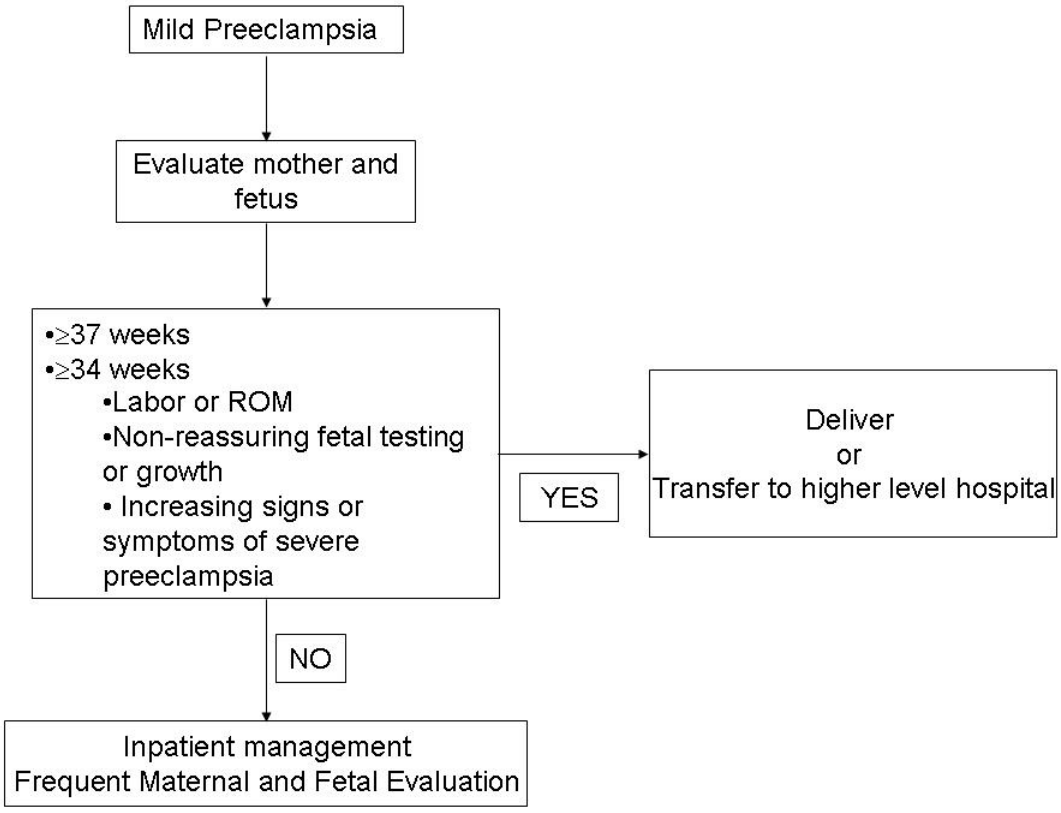
	Chronic Hypertension	Gestational Hypertension	Mild PreE	Severe PreE	CHTN with superimposed PreE	HELLP Syndrome
BP criteria	140/90	140/90	140/90	160/110	140/90	140/90, but HTN may be absent
GA at Dx	< 20 weeks	> 20 weeks	> 20 weeks	> 20 weeks	< 20 weeks	< 20 weeks
Proteinuria (300 mg / 24 hour)	May have >300mg	< 300 mg	> 300 mg	> 5 g	> 500 mg	> 500 mg
Other Labs	No criteria for HELLP	No criteria for HELLP	No criteria for HELLP	No criteria for HELLP	No criteria for HELLP	Bili > 1.2 mg/dl LDH > 600 IU/L SGOT > 72 IU/L Platelet < 100K/mm^3

Mild Preeclampsia

Delivery of the fetus and placenta is the only "cure" for preeclampsia. The timing of delivery is based predominantly on gestational age and severity of preeclampsia. The goal of antepartum, expectant management of preeclampsia is to maximize fetal benefits in the *in utero* environment while minimizing the related preeclamptic morbidities. The rationale for hospitalization of preeclamptics is to allow for rapid intervention in the face of sudden disease progression. Although there is some data arguing for outpatient management of preeclampsia, it is important to note that in these studies many of these women were diagnosed with gestational hypertension only [7]. At the University, we advocate the hospitalization of *all* preeclamptics until delivery given the risk of brisk disease progression. While in the hospital, activity is not restricted. Complete bedrest is not recommend as there are no published studies suggesting any improved outcome in preeclamptics in the face of increased risk for thromboembolism. Inpatient, expectant management of all types of preeclampsia should include frequent blood pressure measurements, at least every 4 to 8 hours, maternal symptoms and re-checking of laboratory values with any change in maternal signs or symptoms. The frequency and type of fetal surveillance depends on the type and severity of preeclampsia. Although there is no agreement on the appropriate surveillance schedule, most experts suggest NSTs 1-2 times per week from the time of diagnosis to time of delivery. Increasing frequency of surveillance may occur in the face of IUGR, non reassuring fetal status, abnormal Doppler studies, or worsening maternal status. Amniotic fluid index and umbilical artery doppler studies should be performed with growth ultrasounds as a minimum. Twice weekly AFI and umbilical artery doppler studies should be performed in the face of oligohydramnios or abnormal growth. These studies can help guide the timing of delivery.

Indications for delivery of a mild preeclamptic depends on gestational age. Any patient diagnosed with preeclampsia who is at 37 weeks or greater, should be delivered. Attempted vaginal delivery is desired and appropriate in most cases where contraindications for a vaginal delivery do not exist. A mild preeclamptic should be delivered at 34 weeks in the face of IUGR, abnormal fetal testing, PPROM or increasing signs and symptoms of severe preeclampsia. The management and delivery of a mild preeclamptic at 36 weeks or beyond can in most instances be performed in a level I hospital if there is no evidence of worsening disease or fetal abnormalities. Otherwise, consideration for transferring the patient to a level II or level III hospital may be most appropriate (see Figure 1).

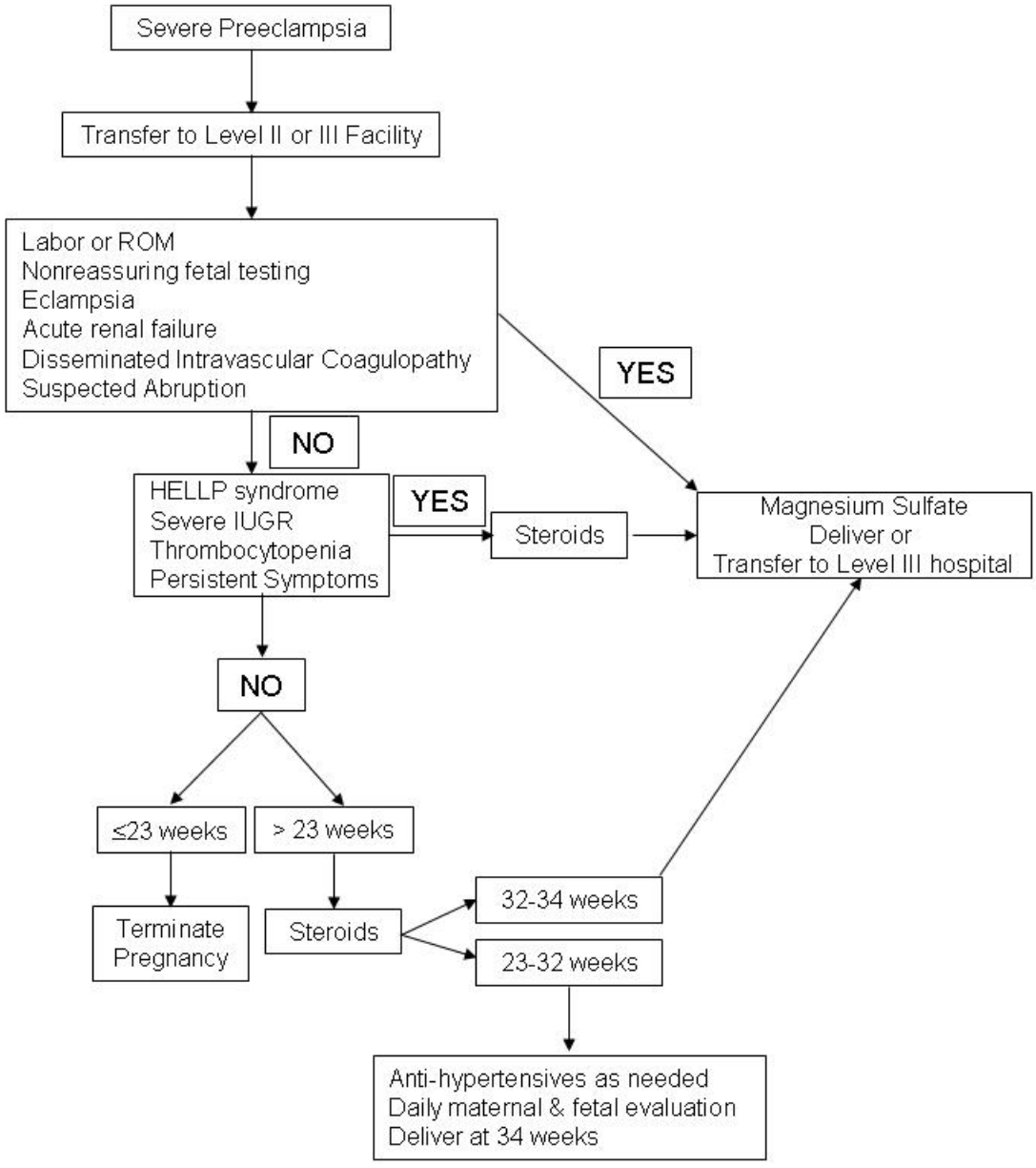
Figure 1. Management of Mild Preeclampsia



Severe Preeclampsia

The antepartum and intrapartum management of severe preeclampsia should be managed at a level II or level III facility whenever possible, especially when complex fetal abnormalities (i.e., severe IUGR, umbilical artery doppler abnormalities) are present and the diagnosis occurs remote from term (< 32 weeks). Expectant management of severe preeclampsia should only take place in a facility where there is immediate access to anesthesia given the elevated risk for eclampsia and severe placental abruption. The decision to deliver depends on the severity of concurrent conditions. Prompt delivery should be considered if the patient has conditions like eclampsia, abruption, HELLP syndrome or non-reassuring fetal status. It is important to note that a "prompt delivery" does not necessarily mean a cesarean delivery. To date, there are no data that support routine cesarean section for severe preeclampsia. The decision to perform a cesarean section should be based on gestational age, fetal well being, and bishop score. When the gestational age is significantly preterm, delivery may be delayed for 24 to 48 hours to allow for the administration of steroids in select cases. When the diagnosis of severe preeclampsia is made at less than 23 weeks, termination of pregnancy should be offered. If this diagnosis is made in the late first trimester, there is increasing concern for a molar pregnancy requiring dilation and curettage. The decision to deliver a patient at 23-32 weeks with severe preeclampsia should be based on worsening fetal or maternal status. By 34 weeks, all severe preeclamptics should be delivered (see Figure 2).

Figure 2. Management of Severe Preeclampsia



Medications

The following section briefly discusses medications commonly used in the management of preeclampsia.

i. Antihypertensives

As a group, antihypertensives decrease the rate of severe hypertension in mild to moderate hypertensive parturients, but do not decrease the progression to preeclampsia. In addition, there is no significant difference in those treated with antihypertensives versus controls in perinatal mortality, preterm birth, and incidence of small for gestational age babies [8]. In acute severe hypertension, the treatment of elevated blood pressures serves to prevent cardiovascular and cerebrovascular complications. Although a strict definition of sustained acute severe hypertension has not been delineated, experts argue that a systolic blood pressure in excess of 160-180 mmHg, diastolic blood pressure greater than 105-110 mmHg, or a mean arterial blood pressure of above 130 mmHg on multiple exams necessitates treatment.

Hydralazine is a common drug used for the treatment of severe hypertension in pregnancy. Intravenous bolus injections of 5 to 10 mg may be administered every 15 to 20 minutes for a maximum dose of 20 mg. IV labetalol is also commonly used. It may be administered 20 to 40 mg intravenously every 10 to 15 minutes for a maximum dose of 220 mg. Oral nifedipine is another alternative for the treatment of severe hypertension. It is dosed at 10-20 mg every 30 minutes for a maximum dose of 50 mg. Other antihypertensives such as nimodipine have also been evaluated for use in severe hypertension. To date, there has not been any reliable evidence to assert any conclusions about the comparative effects of any of these drugs [9]. At the University of Iowa, intravenous labetalol or hydralazine are the drugs of choice for the treatment of sustained acute severe hypertension.

ii. Magnesium Sulfate and Anti-eclampsia Medications

One success in the medical treatment of preeclampsia is magnesium sulfate. Magnesium sulfate decreases the risk of eclamptic seizures. This rate may be decreased by over 60 percent in the postpartum period [10]. Magnesium should be initiated at the onset of labor and maintained in the postpartum period. There is some controversy in the literature debating which preeclamptic patients should receive postpartum magnesium and for how long. Some studies would argue that mild preeclamptics do not require postpartum magnesium. Other studies have published diuresis criteria for the discontinuation of postpartum magnesium in mild and severe preeclamptics [11,12]. At the University of Iowa, patients with severe preeclampsia receive postpartum magnesium for at least 24 hours. In contrast, postpartum magnesium is discontinued in less than 24 hours in mild preeclamptics if the patient has a urine output of greater than or equal to 200 cc/hour for 4 *consecutive* hours.

In the setting of an acute ecclamptic event magnesium sulfate is still the drug of choice in the treatment of the seizure. Magnesium is administered 4-6 mg IV over 15-20 minutes. The dose may be repeated in the face of a repeat seizure. If a patient has recalcitrant seizure activity, diazepam 10mg IV may also be administered. Serum magnesium sultate levels may need to be monitored, especially in the setting of oliguria.

Remember, in the setting of preeclampsia magnesium sulfate is administered as a seizure prophylaxis. Any patient receiving magnesium sulfate for this purpose should be confined to bed (i.e., no ambulation orders, including bathroom), a foley catheter should be place so accurate hourly I/O's can be calculated, and the patient should be NPO, except for sips H_2O and ice chips, to minimize complications of aspiration if a seizure occurs.

iii. Steroids and Tocolytics

If the maternal and fetal clinical situation allows for expectant management, antenatal corticosteroids (betamethasone) should be administered to promote fetal lung maturity to women less than 34 weeks of gestation since preterm delivery is common.

Conclusions

Clearly, there is a need for more study to improve the prediction and prevention of preeclampsia. There are some successes in the management of preeclampsia. This management is dictated predominantly by the gestational age at diagnosis and the severity of disease. Yet, one of the most important considerations in treating preeclampsia is access to anesthesia and appropriate postpartum care for both the mother and the infant.

In summary I will address, by bullet points, the take-home points.

- Any pregnant woman with complaints that can be consistent with preeclampsia should be taken seriously and the diagnosis of preeclamopsia needs to be ruled out.
- The diagnosis of preeclampsia should be made in any pregnant woman who meets blood pressure and proteinuria criteria (140/90 on two separate occasions at least 6 hour apart and >300 mg/dl urinary protein on a 24 hour collection) after 20 weeks who was previously normotensive.
- There is usually no need to repeat 24 hour urines after the diagnosis of preeclampsia is made. A change in management plan is rarely affected by an increase in proteinuria without any other changes.

- We believe that all women who are given a diagnosis of preeclampsia should be hospitalized for the duration of their pregnancies.
- All mild preeclamptic patients should be delivered by 37 weeks. All women with severe preeclampsia should be delivered by 34 weeks, sooner if clinical condition warrants.
- We believe all women who are diagnosed with preeclampsia should receive intrapartum and postpartum magnesium sulfate. The duration of administration is discussed in the text.
- Any woman with preeclampsia who is on magnesium sulfate should be confined to bed with a foley catheter in place. (We have seen instances where patients are allowed to ambulate or have bathroom privileges. Remember they are receiving magnesium sulfate as a seizure prophylaxis, you would not want a patient to have a seizure in the bathroom.)
- Similarly, any woman with preeclampsia who is on magnesium sulfate should be NPO except for ice chips/sips of water. Aspiration is a significant risk with a seizure. We have seen several instances around the state where patients are allowed a general diet while receiving magnesium sulfate therapy.

—Mark Santillan, MD
Maternal-Fetal Medicine Fellow Associate
Obstetrics and Gynecology
University of Iowa Hospitals and Clinics

—Stephen K. Hunter, MD, PhD
Maternal-Fetal Medicine Specialist
Obstetrics and Gynecology
University of Iowa Hospitals and Clinics
Associate Director, Statewide Perinatal Care Program

References

1. Kung HC, H.D., Xu J, Murphy S (2008) *Deaths: Final Data for 2005*. National Vital Statistics Reports **Volume**, DOI
2. Kaaja, R.J. and I.A. Greer, *Manifestations of chronic disease during pregnancy.* JAMA, 2005. **294**(21): p. 2751-7.
3. Berends, A.L., et al., *Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease.* Hypertension, 2008. **51**(4): p. 1034-41.
4. Manten, G.T., et al., *Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction.* Hypertens Pregnancy, 2007. **26**(1): p. 39-50.
5 Godfrey, K.M., *The role of the placenta in fetal programming-a review.* Placenta, 2002. **23 Suppl A**: p. S20-7.
6. Swamy, G.K., T. Ostbye, and R. Skjaerven, *Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth.* JAMA, 2008. **299**(12): p. 1429-36.
7. Barton, J.R., G.J. Stanziano, and B.M. Sibai, *Monitored outpatient management of mild gestational hypertension remote from term.* Am J Obstet Gynecol, 1994. **170**(3): p. 765-9.
8. Abalos, E., et al., *Antihypertensive drug therapy for mild to moderate hypertension during pregnancy.* Cochrane Database Syst Rev, 2007(1): p. CD002252
9. Duley, L., D.J. Henderson-Smart, and S. Meher, *Drugs for treatment of very high blood pressure during pregnancy.* Cochrane Database Syst Rev, 2006. **3**: p. CD001449.
10. Altman, D., et al., *Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial.* Lancet, 2002. **359**(9321): p. 1877-90.
11. Fontenot, M.T., et al., *A prospective randomized trial of magnesium sulfate in severe preeclampsia: use of diuresis as a clinical parameter to determine the duration of postpartum therapy.* Am J Obstet Gynecol, 2005. **192**(6): p. 1788-93; discussion 1793-4.
12. Ehrenberg, H.M. and B.M. Mercer, *Abbreviated postpartum magnesium sulfate therapy for women with mild preeclampsia: a randomized controlled trial.* Obstet Gynecol, 2006. **108**(4): p. 833-8.

35th Annual Iowa Conference on Perinatal Medicine

When: April 8-9, 2009 (Wednesday & Thursday) Where: West Des Moines Marriott Hotel

The electronic version of the Perinatal Conference Brochure that includes the regristration form as well as information to register online can be found at:

http://www.medicine.uiowa.edu/cme/webTracker/webtracker.html

To register by phone, please call **319-335-8599.**

This letter is funded by a community award from the March of Dimes Iowa Chapter

73906/1-09 Printed by UI Printing Department