# Hypertensive Disease in Twin Pregnancies: A Review

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Reports over the past seventy years show that twin gestations lead to an increased risk of hypertensive disorders. Numerous studies discuss the incidence of hypertensive disease in twin versus singleton gestations, as well as effects of parity, race, age, income level, smoking, zygosity and heritability on this condition. The range of relative risk of gestational hypertension, preeclampsia and eclampsia for twin compared to singleton gestations is 1.2 to 2.7, 2.8 to 4.4 and 3.4 to 5.1 respectively. Parity, African-American ethnicity, and young maternal age are all factors that increase the relative risk of acquiring hypertensive disease to 4.0, 1.8 and 1.5 in mothers of twin gestations. Factors such as maternal smoking, income level and zygosity have a negligible effect on the relative risk of acquiring hypertensive disease in twin gestations. In addition to twin mothers exhibiting a higher incidence of hypertensive disease compared to their singleton counterparts, they also exhibit an earlier onset of hypertensive disease at both 35 and 37 weeks of gestation comparatively. Uric acid levels measured at 30–31 weeks of gestation in twin mothers predicted the onset of preeclampsia with a sensitivity of 73% and a specificity of 74%. The range of risks presented in the literature is wide and the therapies avocated are diverse. We therefore decided to summarize the risks in a comparative fashion and to review current therapeutic strategies for the convenience of clinicians who confront increasing numbers of multiple pregnancies. The tables bring all recent published risks together in the first comparative analysis in which the data has been converted to relative risks and confidence intervals. Because the literature is relatively silent on specific management of hypertensive disease in twin pregnancies, general management recommendations for singleton gestations should be used by practitioners caring over twin gestations.

Eclampsia, the end stage of a series of conditions comprising the hypertensive disease of pregnancy, was described in ancient Egypt, China, and India. Until de Sauvages coined the modern term "eclampsia" in 1739 (Chelsey, 1984), the medical community previously considered convulsions associated with pregnancy as a form of epilepsy. According to Chelsey, the preeminent American authority on this topic during the late 20th century, specific references from the ancient world remain unconvincing. In terms of the authority of their descriptions, in Chelsey's opinion, the Greeks were first to specifically recognize preeclampsia, and the occurrence of seizures related to pregnancy. The next significant mention of preeclampsia and eclampsia appeared in a standard textbook of midwifery in Europe entitled *Der Swangern Frawen und Hebammen Rosengarten* published in 1513 (Chelsey, 1984). Over the next two hundred years, the obstetric literature increasingly began to address eclampsia as French physicians became more involved in the practice of midwifery. Mauriceau, a leading French authority, published several books in the late 1600s, all mentioning eclampsia, as well as making important observations such as "primigravidas are at far greater risk of convulsions than are multiparas." By 1775, Hamilton after examining data collected by Hinselmann (Chelsey, 1984) noted that twin gestation predisposed mothers to hypertensive disorders of pregnancy. Of 7748 cases of eclampsia recorded by Hinselmann, 6.4% were in mothers of multiples, a rate 5.8 times higher in than that of single gestations.

American contributions to the study of hypertensive disorders in twin pregnancy began in 1939, and the ensuing decade represents the period from which the classic studies now cited in the modern literature were published. These investigations, conducted at well-known U.S. hospitals, studied mothers of twins and focused on gestational hypertension, preeclampsia, and eclampsia as well as maternal and perinatal mortality. Following this brief period of interest, relatively few additional studies were published until the mid-1970s, when a resurgence of interest in hypertensive disorders in pregnancy took place. These later investigations contrasted the percentages of hypertensive disorders occurring in twin versus singleton pregnancies, the latter serving as controls. As the twentieth century closed, investigative methodologies for comparisons between study groups began to favor the use of relative risk in place of percentages for easier clinical and statistical applicability.

We conducted a Medline search using keywords: "preeclampsia, twin pregnancy and hypertension"; a total of 220 articles were written after 1966. This number was reduced to 23 cohort studies; the bibliographies of these primary references provided secondary references before 1966. Specific data were extracted from the original papers, and relative risks with confidence intervals were calculated for the construction of the tables presented below.In 1937 McClure, followed by his American counterparts, began recording the incidence of hypertensive disorders in twin

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pregnancies. Throughout the next twelve years, the recorded incidence of hypertensive disorders in twin pregnancies was 2 to 4 times that of general hospital statistics (Bender, 1952)[1]. Later studies, beginning with McFarlane and Scott in 1976, provide useful information by comparing the rates of gestational hypertension, preeclampsia and eclampsia in twin versus singleton pregnancies. Gestational hypertension in twin pregnancies occurs 1.2 to 2.7 times as frequently, compared to singleton pregnancies (see Table 1) (Bender, 1952; Campbell & MacGillivray, 1999; McFarlane & Scott, 1976; Ros et al., 1998; Sibai et al., 2000; Spellacy et al., 1990). The relative risk of preeclampsia is 2.8 to 4.4 times in twin compared to singleton pregnancies (see Table 2) (Campbell & MacGillivray, 1999; Coonrod et al., 1995; Long & Oats, 1987; McFarlane & Scott, 1976; Rose et al., 1998; Sibai et al., 2000). The relative risk of eclampsia in twin pregnancies is even higher than that of gestational hypertension and preeclampsia, ranging from 3.4 to 5.1, and rising to 12.3 when nulliparous and multiparous data are combined (see Table 3) (Campbell & MacGillivray, 1999).

Several causes of the increased incidence of hypertensive disease in twins have been suggested in the literature to date, but none represents an acceptable hypothesis for all circumstances. Generally, twin pregnancies are at greater risk for more severe hypertensive disease and, if factors such

**Table 1**

Relative Risk of Gestational Hypertension in Twin vs. Singleton Gestations

| Authors | Study Type | Duration of Study | Patient Source | No. affected over total in twin vs. singleton pregnancies | Controlled for parity/ race | Relative Risk | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Bender et al., 1952 [3] | Retrospective cohort | 1946–1950 | Liverpool (GB) Maternity Hospital & Mill Road Maternity Hospital | 113/472 vs. 6.4% of population | No/No | 3.75 | |
| McFarlane et al., 1976 [4] | Retrospective cohort | 1953–1973 | Leeds Maternity Hospital | 140/603 vs. 103/603 | Yes/No | 1.35 | 1.23–1.47 |
| Spellacy et al., 1990, [5] | Retrospective cohort | 1982–1987 | University of Illinois Perinatal Network | 162/1253 vs. 287/5119 | No/Yes (adjusted for) | 2.3 | 2.26–2.34 |
| Ros et al., 1998 [6] | Retrospective | 1987–1993 | Swedish Medical Birth Registrar | 5/78 vs. 461/10,503 | Yes/Yes | 1.45 (all nullip) | 1.01–1.89 |
| Campbell et al., 1999 [7] | Retrospective cohort | 1950–1995 | Aberdeen Maternity Hospitalv& Neonatal Databank | 363/1576 vs. 23,701/136,259 | Yes/N/A | 1.32 | 1.27–1.37 |
| Sibai et al., 2000 [8] | Retrospective cohort | Not stated | Network of MFM Units for the NICH and Human Development | 45/266 vs. 186/2946 | Yes/Yes (adjusted for) | 2.68 (all nullip) | 1.98–3.62 |

**Table 2**

Relative Risk of Preeclampsia in Twin vs. Singleton Gestations

| Authors | Study Type | Duration of Study | Patient Source | No. affected over total in twin vs. singleton pregnancies | Controlled for parity/ race | Relative Risk | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|
| McFarlane et al., 1976 [4] | Retrospective cohort | 1953–1973 | Leeds Maternity Hospital | 114/603 vs. 35/603 | Yes/No | 3.26 | 3.08–3.44 |
| Long et al., 1987 [9] | Retrospective cohort | 1971–1982 | Mercy Maternity Hospital, Melbourne | 166/642 vs. 2434/26,172 | Yes/No | 2.78 | 2.71–2.85 |
| Coonrod et al., 1995 [10] | Retrospective cohort | 1984–1988 | Washington State Birth Records | 298/3221 vs. 257/8066 | No/No | 2.9 | 2.82–2.98 |
| Ros et al., 1998 [6] | Retrospective cohort | 1987–1993 | Swedish Medical Birth Registrar | 14/78 vs. 543/10,503 | Yes/Yes | 3.53 (all nullip) | 3.28–3.78 |
| Campbell et al., 1999 [7] | Retrospective cohort | 1950–1995 | Aberdeen Maternity Hospitalv& Neonatal Databank | 207/1576 vs. 4145/136,259 | Yes/N/A | 4.37 | 4.30–4.44 |
| Sibai et al., 2000 [8] | Retrospective cohort | Not stated | Network of MFM Units for NICH & Human Development | 52/266 vs. 143/2946 | Yes/Yes (adjusted for) | 4.03 (all nullip) | 3.01–5.39 |



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**Table 3**

Relative Risk of Eclampsia in Twin vs. Singleton Gestations

| Authors | Study Type | Duration of Study | Patient Source | No. affected over total in twin vs. singleton pregnancies | Controlled for parity/ race | Relative Risk | 95% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Long et al., 1987 [9] | Retrospective cohort | 1971–1982 | Mercy Maternity Hospital, Melbourne | 6/166 vs. 320/45,722 | Yes/No | 5.14 | 4.74–5.54 |
| Coonrod et al., 1995 [10] | Retrospective cohort | 1984–1988 | Washington State Birth Records | 5/3221 vs. 3/8066 | No/No | 4 | 3.27–4.73 |
| Campbell et al., 1999 [7] | Retrospective cohort | 1950–1995 | Aberdeen Maternity Hospitalv& Neonatal Databank | 17/1576 vs. 120/136,259 | Yes/N/A | 12.3 | 12.0–12.6 |
| Sibai et al., 2000 [8] | Retrospective cohort | Not stated | Network of MFM Units for NICH & Human Development | 4/266 vs. 13/2946 | Yes/Yes (adjusted for) | 3.41 (all nullip) | 1.12–10.38 |

as parity and race are examined individually when relative risk is determined, the differences between twin and singleton pregnancies are even greater.

## Risk Factors

Just as multiple pregnancy is an important risk factor for gestational hypertensive disorders, factors such as parity, race, and age increase the incidence and severity of hypertensive disorders; in contrast, factors such as income level, smoking, zygosity and heritability tend to have a negligible effect. Parity substantially influences the development of preeclampsia in twin gestations. Nulliparity increases the relative risk of preeclampsia four times in twin gestation (Coonrod et al., 1995). The combination of twin pregnancy and nulliparity increases the overall risk of preeclampsia 14 times, compared to that in a multiparous singleton mother. Race plays an important role, with American black mothers of twins being at a 1.8 relative risk compared to their white counterparts (Coonrod et al., 1995). Young mothers (< 17 years of age) with twin pregnancies are at a relative risk 1.5 times higher for developing preeclampsia compared to those aged 17 to 25, and at an even higher risk compared to those older than 25 years (Coonrod et al., 1995).

Factors such as maternal smoking, income level and zygosity have no significant effect on the development of preeclampsia; maternal smoking increases the risk of preeclampsia in singleton pregnancies (Coonrod et al., 1995) but not in twin pregnancies. Preeclampsia was inappropriately considered to be a disease of the wealthy well into the twentieth century (Chelsey, 1984), because upper-class women were attended by physicians who published their observations, whereas the less affluent were attended by midwives who did not. In the 1930s, Nelson substantiated that poor women were as susceptible to preeclampsia as affluent women (Chelsey, 1984). Later, data from Coonrod et al. (1995) showed no significant difference in the incidence of preeclampsia based on family income. Twin zygosity does not influence the development of preeclampsia (Campbell & MacGillivray, 1999; MacFarlane & Scott, 1976) and studies (Stevenson et al., 1976; Thornton & Macdonald, 1999; Treloar et al., 2000) show that genetic influence varies from low to nil, based on comparison of consanguineous marriages and the development of preeclampsia in mothers who are twins. Conflicting data exist on the influence of twin gender on the development of preeclampsia (MacFarlane & Scott, 1976; Stevenson et al., 1971).

## Clinical Manifestations

Hypertensive disease in twin pregnancies is often more severe and exhibits an earlier disease onset than is the case in singletons. Early onset gestational hypertension, defined as the onset of hypertension before 37 weeks of gestation in twins and 35 weeks of gestation in singletons, occurs 7.9 and 12.4 times as often respectively (Sibai et al., 2000). Likewise, preeclampsia beginning before 37 weeks and 35 weeks of gestation, occurs at a rate of 2.8 to 3.7 times and 6.7 times, respectively, compared to singleton pregnancies (Long & Oates, 1987; Sibai et al., 2000). Severe hypertension, defined as a diastolic pressure greater than 110 mm/Hg, occurs 2.2 times and proteinuria 1.25 times more often in twin pregnancies compared to singleton pregnancies (Long & Oates, 1987). Preeclamptic twin pregnancies are 8.2 times as likely to develop abruptio placentae compared to singleton counterparts and 5.4 times as likely compared to normotensive twin pregnancies (Long & Oates, 1987). It is not clear whether perinatal mortality is higher in hypertensive mothers with twin pregnancies compared to singleton pregnancies, but gestational hypertension and preeclampsia in twin pregnancies tend to significantly lower the risk of perinatal death compared to the risk observed in normotensive counterparts (Campbell & MacGillivray, 1999; Sibai et al., 2000). Review of two studies (Campbell & MacGillivray, 1999; Sibai et al., 2000) comparing hypertensive to normotensive twin pregnancies gives no clear evidence concerning differences in gestational age at delivery, mean twin birth weights, or low twin birth weights.



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## Uric Acid Levels as a Serum Marker

Uric acid, an end product of purine metabolism, is elevated in maternal serum during pregnancy (Seitchik, 1956). Increased maternal or fetal uric acid production, decreased breakdown by intestinal bacteria or decreased renal excretion are all postulated mechanisms for this increase. Elevation of uric acid in preeclamptic patients compared to normotensive patients was first observed in 1917 by Slemons and Bogert (1917) and subsequently by other investigators (Redman et al., 1976; Sagan et al., 1984; Voto et al., 1988). Uric acid levels are higher in twins compared to singleton pregnancies, regardless of the presence of hypertensive disorders (Fischer et al., 1995). One explanation for this difference is that the uric acid produced by two fetuses is greater than that produced by a single fetus, as suggested by the fact that uric acid levels are higher in the blood of the fetus compared to the mother, and that fetal uric acid is excreted in the maternal urine and stool (Hill, 1978). In 1995, Fischer et al., conducted the first study to determine the mean serum uric acid levels at the time of delivery (0.8 days ±1.3 days) in preeclamptic and normotensive twin compared with singleton pregnancies, while correcting for the differences in gestational age. The mean level of serum uric acid in normotensive twin pregnancies was 4.0 mg/dL at 24–28 weeks, 4.4 mg/dL at 29–32 weeks, 6.0 mg/dL at 33–36 weeks and 5.5 mg/dL at 37–40 weeks. The adjusted mean serum uric acid level (controlled for difference in gestational age at delivery) of preeclamptic twin pregnancies was 7.7 ± 1.3 mg/dL at the time of delivery compared to 5.4 ± 1.6 mg/dL in non-preeclamptic twin pregnancies. Using receiver operating characteristic curves, it was determined that a maternal serum uric acid level of 6.5 mg/dL at the time of delivery identified preeclampsia with a sensitivity of 94% and a specificity of 78%. In 1997, Koike et al. (1997) followed maternal serum uric acid levels in twin and singleton pregnancies, noticing that increased uric acid levels often occurred two weeks before the onset of preeclampsia (average onset at 33 weeks). A level of 5.5 mg/dL measured at week 30 to 31 of pregnancy was determined to be the optimal cutoff value in predicting the onset of preeclampsia, with a sensitivity of 73% and a specificity of 74% (See Figures 1 and 2). Given such observations, increased serum uric acid levels, considered a result of preeclampsia and not a primary cause of it, could be useful in predicting which patients are at risk for hypertensive disease and preeclampsia.

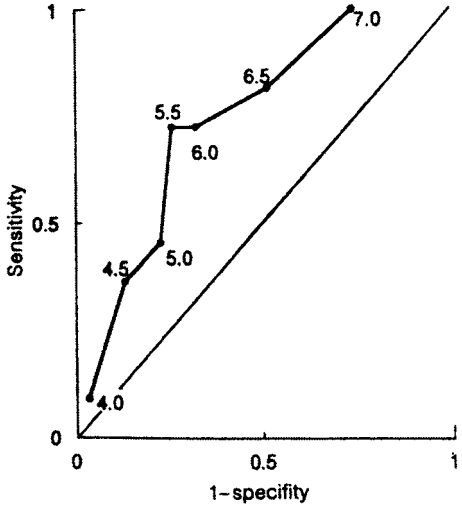


**Figure 1**

ROC curve used to determine optimal cutoff value for preeclampsia at weeks 31–32 (Koike et al., 1997).

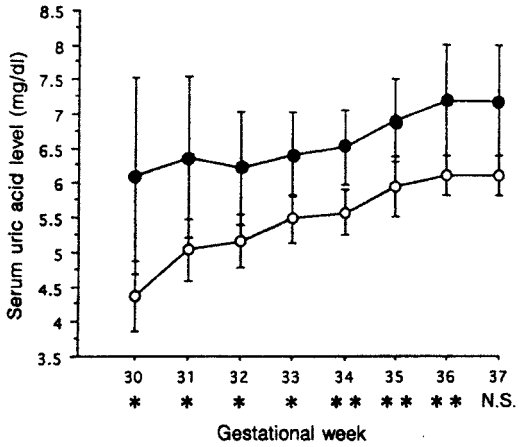


**Figure 2**

Average serum uric acid levels in normotensive (open circle) versus preeclamptic (closed circle) patients (Koike et al., 1997).

## Management

The clinical goals of management in all hypertensive disorders in pregnancy are to prevent or control convulsions, ensure survival of the mother with minimal or no morbidity, and deliver healthy infant(s) without sequelae. It is imperative to have a proper diagnosis based on clinical evidence to achieve the most appropriate therapy. As no authoritative literature concerning the treatment of hypertensive disorders in twins exists, clinical management is generally provided by practitioners as it would be in a singleton pregnancy.

### Chronic Hypertension

The management of pregnant patients with chronic hypertension is not uniform. Whereas it is considered beneficial to reduce the mother's blood pressure, this action may also decrease uteroplacental perfusion and thereby jeopardize fetal development (De Swiet, 2000; Von Dadelszen et al., 2000). The drug of choice for blood pressure reduction is methyldopa, as it maintains stable uteroplacental blood flow and fetal hemodynamics (Montan et al., 1993). If contraindications to its use such as drug-induced liver damage are present, or if it results in somnolence, an alternative drug such as labetalol can be administered (National High Blood Pressure Education Program Working Group, 2000). Despite its rapid absorption and short half-life, the



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peak effect of methyldopa is delayed for 6 to 8 hours, even after intravenous administration, and the duration of action of a single dose usually lasts about 24 hours if once or twice daily dosing is used (Write et al., 1982).

A woman whose blood pressure is well controlled by antihypertensive therapy before pregnancy may continue the medications; however, drugs that inhibit angiotensin-converting enzyme are contraindicated during pregnancy, owing to their association with fetal growth retardation, oligohydramnios, congenital malformations, neonatal renal failure, and neonatal death (Hansen et al., 1991; Rosa et al., 1989).

Diuretic therapy is useful in pregnant women with salt-sensitive hypertension or with left ventricular dysfunction but should be discontinued if preeclampsia develops (National High Blood Pressure Education Program Working Group, 1990), as it is known that preeclampsia is associated with a reduction of plasma volume (Hays et al., 1985), and fetal outcome is worse among women with chronic hypertension who do not have expansion of plasma volume (Arias & Zamora, 1979). Diuretics should also be stopped if there is evidence of reduced fetal growth (National High Blood Pressure Education Program Working Group, 1990). Experience with calcium antagonists is limited and their effects on the fetus and neonate are presently unknown (Sibai, 1996).

#### Hypertension and Lactation

Little information is available regarding excretion of antihypertensive drugs in breast milk and the potential effects of these drugs on neonates of a woman with mild hypertension who wish to breast-feed. In these cases, blood pressure should be monitored closely. Among women with more severe hypertension who take one medication, the dosage must be reduced and the mother and the infant(s) closely observed. If a β-blocker is indicated, the best options are definitely propanolol or labetalol, as they do not appear to be concentrated in breast milk (National High Blood Pressure Education Program Working Group, 2000).

#### Preeclampsia

The management of preeclampsia basically consists of three important points: early diagnosis, close medical supervision, and timely delivery. The first priority in treatment of preeclampsia is maternal safety; the second is delivery of a healthy infant who does not require intensive and prolonged neonatal care (Barton et al., 1994; Gilstrap et al., 1978; Sibai, 1996; Sibai et al., 1987; Sibai et al., 1992). Prevention of preeclampsia can be accomplished through close evaluation of the risk factors mentioned above. Among investigations assessing the efficacy of low-dose aspirin to prevent preeclampsia, some conclude that aspirin is beneficial, whereas others claim there is no benefit. An important study conducted in 1998 by the U.S. National Institute of Health determined that the incidences of preeclampsia, perinatal death, preterm delivery, and fetal growth restriction are the same among patients who received low-dose aspirin prophylactically and patients who did not (Caritis et al., 1998).

In women who have already developed the preeclampsia, hospitalization is the initial recommendation. Management should include close monitoring of the mother's blood pressure, weight, urinary protein excretion, and serial determination of platelet count, serum liver enzymes and fetal well-being, either assessed by nonstress testing or biophysical profile (National High Blood Pressure Education Program Working Group, 1990). Therapeutic efforts outside of delivery are primarily palliative. Although these efforts may slow progression of the disorder and permit continuation of pregnancy, none has reversed it. For that reason, women with mild preeclampsia at 38 weeks and a cervix favorable for induction (Bishop's score, > 6) or women with severe preeclampsia beyond 32 to 34 weeks of gestation should be induced to avoid possible maternal and fetal complications (National High Blood Pressure Education Program Working Group, 1990). At 33 to 34 weeks of gestation, the fetus may benefit from corticosteroid administration (National High Blood Pressure Education Program Working Group, 2000).

In some cases, preeclampsia improves after hospitalization and treatment with magnesium sulfate and acutely administered antihypertensive agents (Odendaal et al., 1990; Sibai et al., 1990; Sibai et al., 1994). The initial antihypertensive drug of choice is intravenous hydralazine administered as a 5mg bolus (National High Blood Pressure Education Program Working Group, 1990). The dose may be repeated as needed every 20 minutes for a cumulative total dose of 20mg. If 20mg of hydralazine does not achieve the desired therapeutic response, or if the mother experiences sides effects such as tachycardia, headache, or nausea, 20mg of intravenous labetalol or 10mg of PO nifedipine may be given (Sibai, 1996). Such management may allow prolongation of pregnancy with a decrease in perinatal morbidity and mortality (National High Blood Pressure Education Program Working Group, 2000). As women with preeclampsia are at increased risk of convulsions, magnesium sulfate should be given prophylactically during labor and postpartum to all woman with a history of preeclampsia (Lucas et al., 1995; Sibai, 1996; Sibai & Ramanathan, 1992).

#### Eclampsia

Patients with eclampsia must be treated either in the intensive care unit or in a location in which skilled nursing or medical attention can be provided. A protocol similar to that for preeclampsia is advised, with the addition of magnesium sulfate to control convulsions. A 4–6 g intravenous loading dose of magnesium sulfate is given, followed by intravenous infusion of 1.5–2.0 grams/hour to attain a therapeutic level of 4.8–8.4 mg/dL (Pernoll, 2001). Magnesium sulfate is to be continued during labor and delivery, and for at least 24 hours postpartum (Cunningham et al., 1993; Sibai, 1990). Other options to treat convulsions are available, but according to the Collaborative Eclamptic Trial (The Eclampsia Trial Collaborative Group, 1995), magnesium sulfate is superior to both phenytoin and diazepam for the treatment and prevention of recurrent convulsions in women with eclampsia.



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## Conclusion

Mothers with twin gestations are at increased risk for hypertensive disorders of pregnancy compared to their singleton counterparts. Factors such as race and young age increase the likelihood of development of hypertensive disorders in twin gestations, whereas income level, smoking, zygosity and heritability have a negligible effect. Serum uric acid levels are a useful predictor for the onset of hypertensive disease in twin gestations at weeks 31–32 of pregnancy, but the utility of this marker is uncertain in the absence of curative management protocols for hypertensive disease in pregnancy other than delivery. Current management recommendations of hypertensive diseases in twin gestations are the same as those for singleton pregnancies. Because multiple gestations lead to an increased risk of preeclampsia and eclampsia, and thus an increased risk of maternal mortality (Blickstein, 1997), these gravida are at high risk and deserve close attention.

## Footnote

1 A recently published paper from India (Nobis, 2001) details the mortality and morbidity associated with eclampsia. Among 1,706 cases of eclampsia treated between 1976 and 1998 at two medical colleges, mortality was 11.54% and morbidity 42.96%. Causes of death included pulmonary edema (19.3%), heart failure (14.7%), shock (14.2%), renal failure (12.7%), hyperpyrexia (11.6%), CVA (7.6%), and pneumonia (10.6%). Deaths were least common after treatment with magnesium sulfate (3.7%) compared to phenytoin sodium (4.6%) and diazapam (9.0%).

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