

# Does low blood pressure increase the risk of stillbirth?

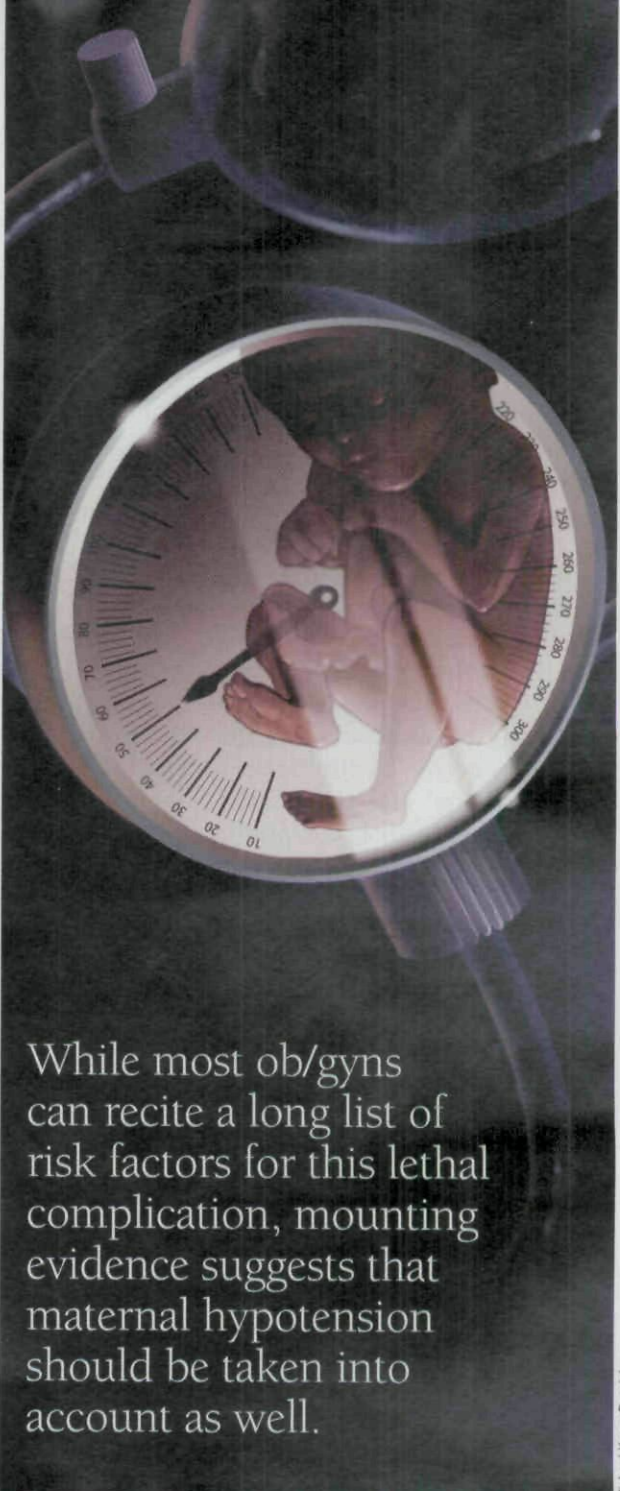
By Eric Hodgson, MD,  
and Errol Norwitz, MD, PhD

**C**linicians don't appreciate stillbirth as much as they should. Would it surprise you to learn, for instance, that antepartum stillbirths—defined as fetal demise after 20 weeks' gestation and before delivery—account for more perinatal deaths than either complications of prematurity or sudden infant death syndrome?<sup>1,2</sup> And despite intensive efforts, about half of all stillbirths remain unexplained.<sup>3-5</sup> While hypertensive disorders are well-known causes of adverse pregnancy outcome, including stillbirth, we'd like to consider the far more provocative question: Does low blood pressure increase the risk of this complication?

The perinatal mortality rate in the United States has decreased by 75% since 1950, due primarily to a drop in neonatal mortality. Although fetal deaths also decreased during that time, stillbirths continue to contribute disproportionately to perinatal mortality. In 1998, for example, the neonatal mortality rate in the US was 4.8 per 1,000 births, while the comparable fetal mortality rate was 6.7 per 1,000 births.<sup>6</sup>

## What causes stillbirth?

Many fetal deaths can be attributed to maternal disorders such as diabetes or hypertensive disease; fetal pathology, including congenital anomalies, multiple pregnancy, and intrauterine growth restriction (IUGR); placental abnormalities like placental abruption; or complications of labor and delivery. Despite intensive investigation, however, approximately 50% (range, 25%–60%) of antepartum deaths remain unexplained.<sup>3-5</sup> Recent studies have identified a number of risk factors for unexplained



While most ob/gyns can recite a long list of risk factors for this lethal complication, mounting evidence suggests that maternal hypotension should be taken into account as well.

stillbirth, including postterm pregnancy, advanced maternal age, maternal obesity, first births, smoking, infertility, low socioeconomic status, and unexplained elevations in maternal serum  $\alpha$ -fetoprotein (MSAFP), human chorionic gonadotropin (hCG), and pregnancy-associated plasma protein-A (PAPP-A).<sup>1,3,4,7-16</sup> Several studies have suggested that low blood pres-

DR. HODGSON is Chief Resident and DR. NORWITZ is Associate Professor and Director of Perinatal Research, and Co-Director, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Conn.

sure is an additional risk factor for unexplained stillbirth.<sup>17,18</sup>

Physiologic adaptations occur in the maternal cardiovascular system in response to the demands of pregnancy. In healthy normotensive women, blood pressure fluctuates significantly and in predictable ways throughout pregnancy. It falls in early pregnancy and is usually 10 mm Hg below baseline in the second trimester, declining to a mean of 105/60 mm Hg.<sup>19-21</sup> The fall in blood pressure is due primarily to a reduction in systemic vascular resistance. Both low resistance in the uteroplacental circulation and systemic vasodilatation contribute to the decline in vascular resistance. We don't fully understand the factors responsible for this vasodilatation but they include decreased vascular responsiveness to the pressor effects of angiotensin II and norepinephrine, increased release of endothelial prostacyclin, enhanced nitric oxide production, and a direct effect of estrogen, progesterone, prolactin, and related hormones.

Blood pressure reaches a nadir around 20 to 28 weeks and returns to baseline at term.<sup>22-24</sup> Keep in mind, however, that blood pressure measurements are subject to change depending on the technique and instrument used and positioning of the patient.<sup>24-26</sup> For the sake of consistency and standardization, measurements in pregnancy should always be taken from the brachial artery at the level of the heart with the patient in the sit-

## Conventional wisdom says prenatal low blood pressure is reassuring. Perhaps not.

ting position at rest for at least 5 minutes using an appropriately sized manual cuff and listening for the 5th Korotkoff's sound (disappearance, not muffling) to designate diastolic pressure.<sup>23,27,28</sup>

### Blood pressure abnormalities and adverse pregnancy outcomes

A sustained elevation in blood pressure of  $\geq 140$  mm Hg systolic,  $\geq 90$  mm Hg diastolic, or both should be regarded as abnormal at any stage of pregnancy, and may represent chronic hypertension, preeclampsia, or gestational non-proteinuric hypertension.<sup>26,29</sup> On the other hand, conventional wisdom suggests that low blood pressure in pregnancy is reassuring, despite the fact that the data supporting this view are limited. In fact, several studies suggest that low blood pressure in the third trimester increases the threat of both stillbirth and growth restriction.<sup>17,18,30-32</sup>

In 1978, researchers analyzed outcome data from over 38,000 pregnant women in an attempt to determine the best criteria for diagnosing pregnancy-associated hypertension.<sup>17</sup> When fetal mortality rates were analyzed by blood

pressure, the lowest stillbirth rate corresponded with a maximum diastolic pressure in the third trimester of 75 to 84 mm Hg. As expected, fetal mortality rates increased with increasing blood pressure. Surprisingly, maternal hypotension (defined in this study as a maximum diastolic blood pressure in the third trimester of less than 65 mm Hg) correlated with a threefold increased risk of stillbirth as compared with normotensive women. Moreover, this risk persisted after delivery with the offspring of pregnancies complicated by maternal hypotension at greater risk for subsequent neonatal death.<sup>17</sup>

To further study the link between stillbirth and blood pressure, investigators analyzed data collected prospectively from 210,814 first singleton births of babies weighing more than 200 g among mothers with no hypertension before 20 weeks and without proteinuria delivering between 24 and 43 weeks' gestation at 15 maternity units located in a single London health region between 1988 and 2000.<sup>18</sup> After 34 weeks' gestation, birthweight was highest and stillbirth rates lowest when the highest recorded diastolic blood pressure during pregnancy was between 70 and 90 mm Hg. The relationship between blood pressure and stillbirth was represented by an inverted U shaped curve, such that both higher and lower blood pressures were associated with higher stillbirth rates (Figure 1) and lower

Several studies suggest low blood pressure in the third trimester increases threat of stillbirth and growth retardation . . .

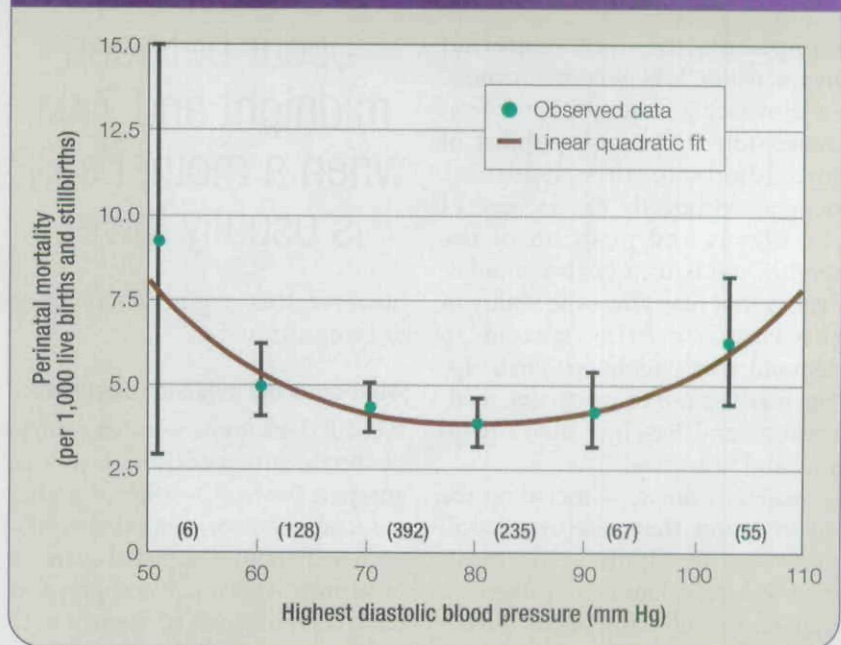
birthweights. These relationships persisted even after adjusting for maternal weight, height, chronic renal disease, and proteinuria. The authors estimated that 94.3 (11.4%) of the observed 825 perinatal deaths were attributable to mothers having diastolic blood pressures differing from the optimal pressure range (80–90 mm Hg). Most (91.2%) of these excess perinatal deaths (86.1 excess deaths) occurred among women with lower blood pressures, mainly in the ranges 70–79 mm Hg (51.2 excess deaths) and 60 to 69 mm Hg (30.9 excess deaths).<sup>18</sup>

These data are consistent with prior studies showing a relationship between low blood pressure and low birthweight and preterm birth.<sup>30–32</sup> However, these studies were all small and underpowered to evaluate the effect of maternal hypotension on perinatal mortality. Nevertheless, taken together, they suggest that the rise in blood pressure in the third trimester of pregnancy may represent a healthy physiologic response of the maternal cardiovascular system to the relative inability of the placenta to keep pace with fetal growth, and may be necessary to achieve optimal birthweight. Indeed, interventions designed to interfere with this increase in blood pressure in the second half of pregnancy (such as anti-hypertensive medications) have repeatedly been shown to be associated with low birthweight.<sup>33,34</sup>

#### Low blood pressure and stillbirth

The cause of low maternal blood pressure in pregnancy is not

FIGURE 1. Linking blood pressure to perinatal deaths



Perinatal mortality per 1,000 live births and stillbirths in relation to highest diastolic blood pressure in mothers and gestation between 24 and 43 weeks at delivery, including women with proteinuria and chronic hypertension. Values adjusted for calendar year and women's ethnic group, smoking status, height, weight, age at booking, and Carstairs' deprivation score.

Source: Steer PJ, et al.<sup>18</sup> (Reprinted with permission of *BMJ*.)

known, but likely represents a primary disorder of venous hemodynamic function rather than adrenal cortical insufficiency.<sup>35</sup> The mechanism by which low blood pressure leads to stillbirth is not well understood, but appears to be related to placental perfusion since the relation between low blood pressure and stillbirth largely disappears if corrected for birthweight (Figure 1).<sup>18</sup> One possible explanation is that there may be a threshold placental perfusion pressure below which the fetus cannot survive. In women with a low baseline blood pressure, a further drop in systemic pressure, such as may occur when a

woman rolls over onto her back during sleep with resultant supine hypotension, may result in a drop in placental perfusion below a critical threshold, resulting in fetal demise.

Supine hypotension syndrome (aortocaval compression syndrome) is a common complication of late pregnancy, and is provoked primarily by placing the patient supine. This causes mechanical compression of the inferior vena cava by the uterus and leads to a decrease in cardiac preload and a resultant precipitous drop in cardiac output and blood pressure. Symptoms range from unspecific

**The mechanism by which hypotension affects pregnancy outcomes remains unknown, but may involve placental hypoperfusion . . .**

complaints to severe maternal hypotension, loss of consciousness, cardiovascular collapse, and fetal depression.<sup>36</sup> The susceptibility of individuals to this syndrome depends primarily on the size of the uterus and position of the mother and fetus, but also on other factors that may affect the ability of the cardiovascular system to respond to a circulatory challenge (such as the use of vasoactive medications and baseline blood pressure and heart rate).<sup>36</sup>

Indirect evidence—including the observation that sleeping blood pressures are significantly lower than waking values in all trimesters, that most stillbirths occur during the mother's sleep cycle (12 midnight to 7 AM), and that a drop in blood pressure and corresponding fetal heart rate deceleration with maternal position change during sleep, can be demonstrated in select women—support this hypothesis. Although attractive,

## Most stillbirths occur between midnight and 7 AM, when a mother's BP is usually lower.

however, this hypothesis remains to be confirmed.<sup>37-40</sup>

### What does the evidence suggest?

We still don't know whether routine obstetric interventions (such as antepartum fetal testing or earlier induction of labor) can prevent stillbirth and improve perinatal outcome in women with low blood pressure. Early identification of women with hypotension (defined variably in the literature as a maximum diastolic blood pressure of 60 to 65 mm Hg or maximum blood pressure of 110/65 mm Hg and treatment with mineralocorticoids to expand intravascular volume and increase blood pressure has been recom-

mended by some investigators.<sup>41-43</sup> Although these studies had small numbers of subjects and, as such, were underpowered to evaluate the effect of this intervention on perinatal mortality, results suggest a significant improvement in placental perfusion as measured by radioisotope flow studies and an increase in birthweight by approximately 500 g.<sup>38-40</sup>

Despite conventional wisdom, low blood pressure in the third trimester of pregnancy may not be a reassuring observation. Indeed, recent studies suggest that it may be a risk factor for stillbirth. However, these data should be regarded as preliminary at this time and should not prompt a sudden change in the management of such patients. Further studies are needed to confirm these observations and to determine whether one or more obstetric interventions (such as antepartum fetal testing, earlier induction of labor, or mineralocorticoid administration) can improve perinatal outcome in this setting. □

### REFERENCES

1. Cotzias CS, Paterson-Brown S, Fisk NM. Prospective risk of unexplained stillbirth in singleton pregnancies at term: population-based analysis. *BMJ*. 1999;319:287-288.
2. Ventura SJ, Martin JA, Curtin SC, et al. Births: final data for 1998. *Natl Vital Stat Rep*. 2000;48:1-100.
3. Huang DY, Usher RH, Kramer MS, et al. Determinants of unexplained antepartum fetal deaths. *Obstet Gynecol*. 2000;95:215-221.
4. Frøen JF, Arnestad M, Frey K, et al. Risk factors for sudden intrauterine unexplained death: epidemiological characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol*. 2001;184:694-702.
5. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet*. 1987;1:1192-1194.
6. Martin JA, Hamilton BE, Ventura SJ. Births: preliminary data for 2000. *Natl Vital Stat Rep*. 2001;49:1-20.
7. Hilder L, Costelloe K, Thilaganathan B. Prolonged pregnancy: evaluating gestation-specific risks of fetal and infant mortality. *Br J Obstet Gynaecol*. 1998;105:169-173.
8. Rand L, Robinson JN, Economy KE, Norwitz ER. Post-

term induction of labor revisited. *Obstet Gynecol*. 2000;96:779-783.

9. Smith GC. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. *Am J Obstet Gynecol*. 2001;184:489-496.
10. Fretts RC, Schmittlidiel J, McLean FH, et al. Increased maternal age and the risk for fetal death. *N Engl J Med*. 1995;333:1002-1004.
11. Fretts RC, Usher RH. Causes of fetal death in women of advanced maternal age. *Obstet Gynecol*. 1997;89:40-45.
12. McDonald SD, Murphy K, Beyene J, et al. Perinatal outcomes of singleton pregnancies achieved by in vitro fertilization: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2005;27:449-459.
13. Spencer K. Second-trimester prenatal screening for Down syndrome and the relationship of maternal serum biochemical markers to pregnancy complications with adverse outcome. *Prenat Diagn*. 2000;20:652-656.
14. Smith GC, Stenhouse EJ, Crossley JA, et al. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intrauterine growth restriction, prema-

ture birth, preeclampsia, and stillbirth. *J Clin Endocrinol Metab*. 2002;87:1762-1767.

15. Chandra S, Scott H, Dodds L, et al. Unexplained elevated maternal serum alpha-fetoprotein and/or human chorionic gonadotropin and the risk of adverse outcomes. *Am J Obstet Gynecol*. 2003;189:775-781.
16. Smith GC, Crossley JA, Aitken DA, et al. First-trimester placentation and the risk of antepartum stillbirth. *JAMA*. 2004;292:2249-2254.
17. Friedman EA, Neff RK. Hypertension-hypotension in pregnancy. Correlation with fetal outcome. *JAMA*. 1978;239:2249-2251.
18. Steer PJ, Little MP, Kold-Jensen T, et al. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. *BMJ*. 2004;329:1312.
19. Clapp JF 3rd, Seaward BL, Sleamaker RH, et al. Maternal physiologic adaptations to early human pregnancy. *Am J Obstet Gynecol*. 1988;159:1456-460.
20. Lindheimer MD, Katz AI. Sodium and diuretics in pregnancy. *N Engl J Med*. 1973;288:891-894.
21. Brown MA, Whitworth JA. The kidney in hypertensive

**If the hypothesis stands up to scrutiny, antepartum fetal testing, earlier labor induction, or mineralocorticoids may improve outcomes.**

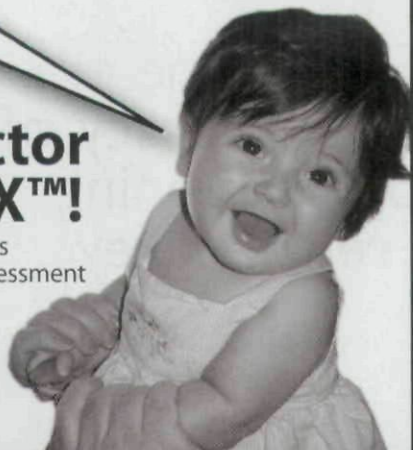
Did You  
Say Risk  
Assessment?

**LENETIX™**  
MEDICAL SCREENING LABORATORY, INC.

## My Mom's Doctor Chose LENETIX™!

The Laboratory That Specializes  
In First and Second Trimester Risk Assessment

- The Integrated Test\*
- The Contingent Test\*
- The Modified Sequential\*



\*As stated in the NEJM 10/05... "measurements of a combination of markers in both the first and second trimesters provides the best screening performance."

LENETIX™ Medical Screening Laboratory, Inc.  
174 Mineola Boulevard • Suite #1 • Dept COBG9  
Mineola, New York 11501-2513  
Tel: 516-248-0036 • Fax: 516-248-4436  
[www.lenetix.com](http://www.lenetix.com) • [testing@lenetix.com](mailto:testing@lenetix.com)

Call For  
FREE PATIENT  
Educational  
Flowcharts

For more information, circle 112 on RSVP card

## Your Complete Source for COLPOSCOPES

Seiler Precision Microscopes offers a colposcope that is ideal for all Ob/Gyn applications.

See our website or contact Seiler for more information.



SEILER 905  
COLPOSCOPE



SEILER 955  
COLPOSCOPE

A Commitment to  
Excellence  
Since 1945

**SEILER**  
PRECISION MICROSCOPES

[www.seilerinst.com](http://www.seilerinst.com) (314) 968-2282 • (800) 489-2282

For more information, circle 129 on RSVP card

## HYPOTENSION

pregnancies—victim and villain. *Am J Kidney Dis.* 1992; 20:427-442.

22. Hunyor SN. Vascular, volume, and cardiac response to normal and hypertensive pregnancy. *Hypertension.* 1984;6:129-132.

23. Norwitz ER, Robinson JN, Malone FD. Pregnancy-induced physiologic alterations. In: Dildy GA, Belfort MA, Saade GR, et al., eds. *Critical Care Obstetrics.* 4th ed. Boston, Mass: Blackwell Science Ltd.; 2004:19-42.

24. Wilson M, Morganti AA, Zervoudakis I, et al. Blood pressure, the renin-aldosterone system and sex steroids throughout normal pregnancy. *Am J Med.* 1980;68:97-104.

25. Ginsberg J, Duncan S. Direct and indirect blood pressure measurement in pregnancy. *J Obstet Gynaecol Br Commonw.* 1969;76:705-710.

26. Kirshon B, Cotton DB. Invasive hemodynamic monitoring in the obstetric patient. *Clin Obstet Gynecol.* 1987; 30:579-590.

27. Johenning AR, Barron WM. Indirect blood pressure measurement in pregnancy: Korotkoff phase 4 versus phase 5. *Am J Obstet Gynecol.* 1992;167:577-580.

28. De Swiet M, Shennan A. Blood pressure measurement in pregnancy. *Br J Obstet Gynaecol.* 1996;103:862-863.

29. American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin No. 33. Washington, DC: 2002.

30. Grunberger W, Leodolter S, Parschalk O. Maternal hypotension; fetal outcome in treated and untreated cases. *Gynecol Obstet Invest.* 1979;10:32-38.

31. Ng PH, Walters WA. The effects of chronic maternal hypotension during pregnancy. *Aust N Z J Obstet Gynaecol.* 1992;32:14-16.

32. Harsanyi J, Kiss D. Hypotension in pregnancy. *Zentralbl Gynaekol.* 1985;107:363-369.

33. Easterling TR, Brateng D, Schmucker B, et al. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. *Obstet Gynecol.* 1999;93:725-733.

34. von Dadelszen P, Ornstein MP, Bull SB, et al. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet.* 2000;355:87-92.

35. Goeschel K, Peters I, Schneider J. Hypotension in pregnancy, a sequela of adrenal cortex insufficiency? *Geburtshilfe Frauenheilkd.* 1987;47:854-858.

36. Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstet Gynecol.* 1994;83:774-788.

37. Siamopoulos KC, Papanikolaou S, Elisaf M, et al. Ambulatory blood pressure monitoring in normotensive pregnant women. *J Hum Hypertens.* 1996;10:S51-S54.

38. Collins JH. Umbilical cord accidents—time of death? *Am J Obstet Gynecol.* 1997;177:1566.

39. Hoppenbrouwers T, Hodgman JE, Harper RM, et al. Fetal heart rates in siblings of infants with sudden infant death syndrome. *Obstet Gynecol.* 1981;58:319-325.

40. Collins JH. Umbilical cord accidents—time of death: continued. *Am J Obstet Gynecol.* 1998;179:275-276.

41. Grunberger W, Leodolter S, Parschalk O. Maternal hypotension: fetal outcome in treated and untreated cases. *Gynecol Obstet Invest.* 1979;10:32-38.

42. Grunberger W, Parschalk O. Hypotension during pregnancy and premature delivery. *Wien Med Wochenschr.* 1980;130:210-213.

43. Grunberger W, Parschalk O, Fischl F. Treatment of hypotension complicating pregnancy improves fetal outcome. *Med Klin.* 1981;76:257-260.

Copyright of Contemporary OB/GYN is the property of Advanstar Communications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.