

Does low blood pressure increase the risk of stillbirth?

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Clinicians 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?^{1,2} And despite intensive efforts, about half of all stillbirths remain unexplained.³⁻⁵ 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.⁶

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.³⁻⁵ 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 α -fetoprotein (MSAFP), human chorionic gonadotropin (hCG), and pregnancy-associated plasma protein-A (PAPP-A).^{1,3,4,7-16} Several studies have suggested that low blood pres-

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sure is an additional risk factor for unexplained stillbirth.^{17,18}

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.¹⁹⁻²¹ 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.²²⁻²⁴ Keep in mind, however, that blood pressure measurements are subject to change depending on the technique and instrument used and positioning of the patient.²⁴⁻²⁶ 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.^{23,27,28}

Blood pressure abnormalities and adverse pregnancy outcomes

A sustained elevation in blood pressure of ≥ 140 mm Hg systolic, ≥ 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.^{26,29} 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.^{17,18,30-32}

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.¹⁷ 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.¹⁷

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 2000.¹⁸ 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

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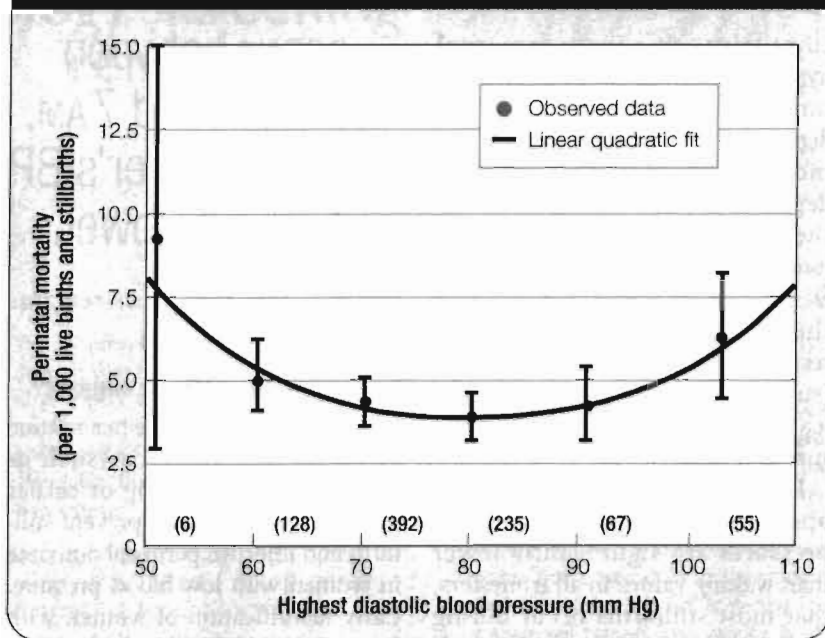
birthweights. These relationships persisted even after adjusting for maternal weight, height, chronic renal disease, and proteinuria. The authors estimated that 94.3 (11.4%) of the observed 825 perinatal deaths were attributable to mothers having diastolic blood pressures differing from the optimal pressure 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).¹⁸

These data are consistent with prior studies showing a relationship between low blood pressure and low birthweight and preterm birth.^{30–32} 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.^{33,34}

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.¹⁸ (Reprinted with permission of *BMJ*.)

known, but likely represents a primary disorder of venous hemodynamic function rather than adrenal cortical insufficiency.³⁵ 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).¹⁸ 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 (aorticaval 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 . . .

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

complaints to severe maternal hypotension, loss of consciousness, cardiovascular collapse, and fetal depression.³⁶ 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).³⁶

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,

however, this hypothesis remains to be confirmed.³⁷⁻⁴⁰

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.⁴¹⁻⁴³ 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 birth-weight by approximately 500 g.³⁸⁻⁴⁰

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. □

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