

Maternal Blood Pressure in Pregnancy and Stillbirth: A Case-Control Study of Third-Trimester Stillbirth

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ABSTRACT

An immense body of literature on the effects of hypertension on perinatal morbidity and mortality exists, but only a handful of studies have reported adverse outcomes associated with low maternal blood pressure during pregnancy. This study aimed to investigate if there is an increased risk of fetal loss associated with hypotension during pregnancy. A matched case-control study of stillbirth and maternal blood pressure was conducted in which maternal blood pressures for a total of 124 pregnancies culminating in stillbirth were compared with maternal blood pressures in 243 (matched) pregnancies resulting in a liveborn infant. Women whose diastolic blood pressures fell in a borderline range (60 to 70 mm Hg) were consistently at greater risk of stillbirth relative to normotensive pregnancies. Women who had three or more mean arterial pressure values ≤ 83 mm Hg during the course of their pregnancy were at nearly twice the risk of stillbirth (odds ratio 1.78; 95% confidence interval [CI] 1.06 to 2.99; $p = 0.03$). Systolic hypotension was not significantly associated with stillbirth, but proportionately more control women were noted to have systolic hypertension (SBP ≥ 130 mmHg) than cases, and the adjusted odds of stillbirth in women who were hypertensive at either their first or last antenatal visit or whose antenatal average SBP was ≥ 130 mm Hg were all very close to 0.4 (95% CI 0.37 to 0.43; $p = 0.02$ to 0.03) relative to normotensives. We concluded that maternal hypotension, particularly borderline hypotension, may be a contributory risk factor for stillbirth. Women with hypertension in pregnancy may now be at a decreased risk of stillbirth as a result of the close care and treatment they receive.

KEYWORDS: Hypotension, hypertension, stillbirth, pregnancy outcome

BACKGROUND

Variations in blood pressure, to either extreme, are known to influence both perinatal morbidity and mortality. There is much published on the negative impact of hypertension on both the fetus and the mother. It is also well known that when maternal blood pressure suddenly

drops, for whatever reason, it can have a short-term harmful affect on both the mother and her unborn infant.¹⁻⁴ However, there has been little research undertaken on the effect of persistent maternal hypotension during pregnancy, even though the results of that research suggest that low maternal blood pressure may be

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as dangerous to the fetus as the well-known influence of hypertension.

A study conducted in the early 1960s⁵ reported that women with very low diastolic (DBP) and systolic blood pressure (SBP) at an antenatal booking are at increased risk of perinatal mortality. This finding has been supported in large population-based studies^{6,7} as well as in smaller cohort studies reported in German research literature.⁸⁻¹¹ There have been two studies reporting the influence of persistent maternal hypotension on fetal growth and/or premature birth,^{12,13} and there has also been several papers examining the effect of treating hypotension on improving fetal outcome.^{10,14-17} However, only one recently published study⁶ has specifically examined the possible significance of persistent maternal hypotension on the risk of stillbirth. This was a large British study in which over 210,000 nulliparous women with singleton pregnancies were followed throughout their pregnancy. After each birth, the attending midwives recorded the initial DBP as well as the highest DBP observed during pregnancy. They found that "perinatal mortality was lowest when the highest diastolic maternal blood pressure during pregnancy was between 70 and 90 mm Hg" (p. 5).

Here we present the findings from a case-control study comparing women whose pregnancy resulted in a stillbirth with women whose infant was liveborn. The purpose of this study was to ascertain if hypotension in pregnancy is associated with an increased risk of third-trimester stillbirth.

SUBJECTS AND METHODS

Population

Two large Australian tertiary referral obstetric hospitals participated in this study. Both these hospitals provide a comprehensive range of antenatal, birthing, and postpartum care.

Ethics Approval

Ethics approval was applied for from each hospital's institutional Human Research Ethics Committee. Because this study involved retrospective audit of medical records, the main ethical issue these committees considered was the balance between protecting the participant's rights to privacy and the public's interest in research. Patient consent would ordinarily be required to obtain access to an individual's case notes, however we considered that a formal letter asking for this consent might engender psychological distress. Therefore, we applied for and were granted access to participants' case notes without patient consent under section 95 and 95a of the Australian Commonwealth Privacy Act 2001.

Case Selection

All women with a discharge diagnosis of stillbirth (from whatever attributed cause) over a 5-year period ranging from April 1, 1997, to March 31, 2002, at the two participating hospitals were identified and considered as cases for inclusion in the study. This time period yielded 646 potential cases.

A woman was excluded from the study if she:

- Had a multiple pregnancy (20 pregnancies excluded).
- Had not attended at least three antenatal visits prior to the stillbirth (53 excluded).
- Had no ultrasound examination (3 were excluded) (this was an exclusion criterion for another arm of the study examining placental position).
- Had a fetus weighing ≤ 1000 g (413 excluded; the vast majority of these were around 20 weeks of gestation, making matching to a liveborn infant impossible).
- Had scant, absent, or large amounts of indecipherable data (24 excluded).

The number of cases from both the participating hospitals after all exclusions was 133.

Control Selection

The control group for this study consisted of women who gave birth to a liveborn infant at the same hospital as the cases. As the outcome of interest was stillbirth; neonatal deaths were not eligible. The next-in-time birth that met the matching criteria was selected from the database. These criteria included the following:

- Maternal age (within 5 years of a case mother)
- Infant gender (exact match to case infant)
- Gestational age (within 2 weeks of the case infant's stated gestational age)
- Year of birth (within 2 years of case infant's birth).

An attempt was made to match two controls with every case, but for five cases only one matched control could be identified, and on nine occasions no control could be selected. Cases with no controls were discarded, but those with one matched control were included. This made the total number of cases 124, controls 243, and an entire sample of 367 women.

Data Collection

Because the blood pressures for each antenatal visit were not recorded electronically by the participating hospitals, these observations were collected by retrospective audit of case notes. All blood pressures (systolic and diastolic) recorded over the course of the pregnancy were extracted, together with various demographic, obstetric, and medical data.

Defining Blood Pressure Categories

Studies reporting an association between hypotension and poor pregnancy outcome have used a variety of definitions of hypotension. For that reason we felt it was necessary to use several alternative definitions to examine which readings were the more likely predictors of stillbirth. Table 1 lists the definitions we used.

All the blood pressure recordings collected were used either singly or in combination. Single recordings of the SBP, DBP, and mean arterial pressure (MAP) at the initial (booking) visit as well as at the last visit prior to the birth were used; we also used all of the blood pressures recorded during the pregnancy to calculate the average systolic and diastolic readings. Rather than calculate an average MAP, three or more readings were used from the MAP definition to categorize the women (e.g., if a woman had three or more MAP readings ≤ 83 mm Hg during the pregnancy, she was categorized as “borderline hypotensive”; but if she had three or more values ≤ 73 mm Hg she was classified as “extremely hypotensive.” Although these MAP categories are not strictly mutually exclusive, none of the women in our study fell into more than one category. Because of the method of calculating MAP, each category could include several differing BP readings, and we created a “ready reckoner” to demonstrate the relationship among SBP, DBP, and calculated MAP (Fig. 1).

Analysis

The analysis for this study involved comparing exposures (to maternal blood pressure) in stillborn cases with the corresponding exposure in matched controls. All variables were examined using conditional logistic regression in the statistical software package Egret for Windows, version 2.0.31 (Cytel Software, Cambridge, MA). This software was chosen for the facility with which it handles variable numbers of matched controls per case.

The results are expressed in terms of odds ratios (OR), 95% confidence intervals (CI), and probability

		Systolic Blood Pressure										
		90	95	100	105	110	115	120	125	130		
Diastolic Blood Pressure	40	57	58	60	62	63	65	67	68	70	68	70
	45	60	62	63	65	67	68	70	72	73	72	73
	50	63	65	67	68	70	72	73	75	77	75	77
	55	67	68	70	72	73	75	77	78	80	78	80
	60	70	72	73	75	77	78	80	82	83	82	83
	65	73	75	77	78	80	82	83	85	87	85	87
	70	77	78	80	82	83	85	87	88	90	88	90
	75	80	82	83	85	87	88	90	92	93	92	93
	80	83	85	87	88	90	92	93	95	97	95	97
	85	87	88	90	92	93	95	97	98	100	98	100
90	90	92	93	95	97	98	100	102	103	102	103	
95	93	95	97	98	100	102	103	105	107	105	107	
100	97	98	100	102	103	105	107	108	110	108	110	

Key:

Extreme Hypotension
Borderline Hypotension
Normotension	
Hypertension

Figure 1 Mean arterial pressure ready reckoner (all figures rounded to the nearest whole number).

values (p), corresponding to the likelihood of the observed differences arising by chance. A p value of < 0.05 was considered statistically significant. Demographic variables that may have confounded the association of stillbirth with low maternal blood pressure were identified, and the OR was adjusted by these factors in the conditional regression analysis. These variables were not chosen as matching variables because once matching has occurred, it is impossible to assess the matching variable’s impact on stillbirth risk, and we wanted to be free to assess this association. Therefore, adjustment was made for nonwhite race (including African, Southeast Asian, and Australian Aboriginal), multigravidity, (more than one pregnancy), multiparity (more than one birth), and small for gestational age (< 10 th percentile for gestational age). Although we had hoped to adjust for low body mass index (BMI), in the time period that the study

Table 1 Definitions of Hypo- and Hypertension for Each of the Summary Measures of Blood Pressure (mm Hg)

Blood Pressure Measure	Extremely Hypotensive	Borderline Hypotensive	Normotensive	Hypertensive
Single (time-specific) values				
MAP	≤ 73	73–83	83–103	≥ 103
DBP	≤ 60	60–70	70–90	All values ≥ 90
SBP	≤ 100	100–110	110–130	All values ≥ 130
Composite values				
3 values of MAP	3 or more readings ≤ 73	3 or more readings ≤ 83 , but not all ≤ 73	All others	3 or more readings ≥ 103
Average of all recorded DBP values	≤ 60	60–70	70–90	Average ≥ 90
Average of all recorded SBP values	≤ 100	100–110	110–130	all values ≥ 130

MAP, mean arterial pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

was conducted maternal height was not recorded as a matter of routine at the first antenatal visit.

RESULTS

Systolic Blood Pressure (SBP)

When examining SBP readings, proportionately more control women were hypertensive than case women. In women whose SBP was > 130 mm Hg at their initial visit to the antenatal clinic and at their last visit, the (adjusted) ORs for stillbirth were 0.36 (95% CI 0.14 to 0.90; $p = 0.03$) and 0.43 (95% CI 0.20 to 0.94; $p = 0.03$), respectively, relative to women who were normotensive (110 to 130 mm Hg). For women whose average SBP was > 130 mm Hg throughout the entire pregnancy, the adjusted OR of a stillbirth was 0.37 (95% CI 0.16 to 0.84; $p = 0.02$). No statistically significant differences were seen in women who had any degree of systolic hypotension (i.e., SBP ≤ 110 mm Hg). However, we did notice a slightly raised (albeit not statistically significant) risk of stillbirth in women whose SBP fell in the borderline range (100 to 110 mm Hg) at booking (adjusted OR 1.43; 95% CI 0.84 to 2.43; $p = 0.18$).

Diastolic Blood Pressure (DBP)

The adjusted odds ratios of stillbirth in women with borderline diastolic hypotension (60 to 70 mm Hg) were 2.1 (95% CI 1.17 to 3.66; $p = 0.01$) and 1.8 (95% CI 1.1 to 3.0; $p = 0.03$) relative to normotensive women at their first and last antenatal clinical visits, respectively. When the average DBP was borderline during the course of the pregnancy, the adjusted OR estimate was 1.8 (95% CI 1.1 to 3.0; $p = 0.01$). Women with a final-visit DBP > 90 mm Hg were more prevalent in the control group (40 controls, 9 cases), indicating again that hypertension at the end of the pregnancy was associated with a lower risk of stillbirth (adjusted OR 0.2 95%; CI 0.05 to 0.78; $p = 0.02$).

Mean Arterial Pressure

Neither borderline nor extreme hypotensive single MAP values at either the booking or final visits to the antenatal clinic were significantly associated with stillbirth. However, women whose MAP consistently fell in the borderline category during pregnancy were more prevalent in the case group than the control group (adjusted OR 1.8; 95% CI 1.0 to 3.1; $p = 0.03$).

Women whose MAP was classified as hypertensive at either their first or last antenatal clinic visits (MAP ≥ 103 mm Hg) were at less risk of stillbirth on

both occasions (adjusted OR at first visit 0.18 95%; CI 0.03 to 1.05; $p = 0.05$; and adjusted OR at last visit 0.30; 95% CI 0.13 to 0.70; $p = 0.005$).

When adjustment was made for other putative risk factors for stillbirth, the ORs were largely unchanged (Tables 2 and 3); therefore it can be assumed the association between hypotension and stillbirth is largely independent of other risk factors for stillbirth.

DISCUSSION

This study is the first of its kind to specifically examine a stillborn group to determine if hypotension is a risk factor for stillbirth.

It is certainly problematic that previously published studies have defined hypotension differently. With no standard definition to guide them, previous investigators have made a somewhat arbitrary definition of hypotension focusing on either the SBP,¹⁸ the DBP,^{5,7,13} readings for both SBP and DBP,⁶ or a specific blood pressure reading (e.g., 110/70 mm Hg¹² or combined low readings).^{8,9} This makes comparison among the findings of these studies difficult, and it also may explain some of the inconsistencies in the reported results. For example, Wolff et al¹⁸ examined only systolic hypotension and found, as we did, that there was little correlation between maternal systolic hypotension and stillbirth, whereas studies by Steer et al⁵ and Friedman and Neff,⁷ who examined only DBP, agree that diastolic hypotension is associated with an increased incidence of stillbirth.

Some studies have attracted criticism for examining only one blood pressure measure, and a strength of our work is that we examined a range of different measures of hypotension throughout pregnancy. Our study has found a consistent level of risk of stillbirth associated with borderline diastolic hypotension as well as consistently low MAP.

When choosing which definitions to use, we delineated a borderline hypotensive category. This is because two of the German studies^{8,9} had identified a "light," or borderline, category, and we wanted to replicate this in our study. Our research substantiates the findings of these earlier studies. Women whose blood pressure falls in the borderline hypotensive range appear to be at higher risk of stillbirth than those women in the extremely hypotensive group.

A possible explanation may be that women in the extremely low hypotensive group may be attracting attention and extra care not because of their extreme hypotension per se but for some other reason linked to it. For example, it is known that women who are underweight in pregnancy are at increased risk of poor pregnancy outcome.¹⁹ These women may also be more likely to fall into the extremely hypotensive range

Table 2 Estimated Odds Ratio of Stillbirth by Blood Pressure Category

Predictor	Case/Controls (n = 124/243)	Unadjusted Odds Ratio	Adjusted Odds Ratio
Average Diastolic Blood Pressure			
Severe hypotension	3/10	0.66 (0.17–2.57)	0.87 (0.20–3.74)
Borderline hypotension	67/102	1.6 (1.02–2.60)	1.91 (1.14–3.20)
Normotension	52/121	1 (ref)	1 (ref)
Hypertension	2/10	0.40 (0.08–1.98)	0.35 (0.07–1.75)
Diastolic Blood Pressure at Booking			
Severe hypotension	29/61	1.35 (0.73 – 2.52)	1.37 (0.71–2.65)
Borderline hypotension	64/93	2.0 (1.17–3.43)	2.1 (1.19–3.70)
Normotension	31/86	1 (ref)	1 (ref)
Hypertension	0/3	Inadequate numbers for analysis	
Diastolic Blood Pressure at Last Visit			
Severe hypotension	23/39	1.42 (0.74–2.74)	1.79 (0.86–3.70)
Borderline hypotension	53/76	1.57 (0.98–2.53)	1.77 (1.05–2.97)
Normotension	39/88	1 (ref)	1 (ref)
Hypertension	9/40	0.23 (0.06–0.84)	0.20 (0.05–0.76)
Average Systolic Blood Pressure			
Severe hypotension	2/4	0.96 (0.17–5.30)	0.86 (0.14–5.27)
Borderline hypotension	29/55	0.90 (0.53–1.53)	0.97 (0.54–1.74)
Normotension	82/142	1 (ref)	1 (ref)
Hypertension	11/42	0.42 (0.2–0.91)	0.37 (0.17–0.85)
Systolic Blood Pressure at Booking			
Severe hypotension	13/31	0.83 (0.39 – 1.75)	0.77 (0.34–1.73)
Borderline hypotension	53/78	1.34 (0.82–2.19)	1.45 (0.85–2.46)
Normotension	51/99	1 (ref)	1 (ref)
Hypertension	7/35	0.38 (0.16 – 0.91)	0.36 (0.14–0.90)
Systolic Blood Pressure at Last Visit			
Severe hypotension	11/23	0.85 (0.37–1.92)	0.93 (0.37–2.34)
Borderline hypotension	35/58	1.03 (0.60–1.75)	1.10 (0.62–1.93)
Normotension	63/108	1 (ref)	1 (ref)
Hypertension	15/54	0.42 (0.20–0.88)	0.43 (0.20–0.94)
Overall MAP			
Severe hypotension	8/18	1.17 (0.47 – 2.93)	1.08 (0.40–2.89)
Borderline hypotension	60/86	1.83 (1.09–3.08)	1.80 (1.04–3.11)
Normotension	51/120	1 (ref)	1 (ref)
Hypertension	5/19	0.55 (0.19–1.62)	0.46 (0.15–1.42)
MAP at Booking			
Severe hypotension	7/13	1.04 (0.41–2.65)	0.99 (0.37–2.65)
Borderline hypotension	33/61	1.0 (0.59–1.69)	0.97 (0.55–1.71)
Normotension	82/149	1 (ref)	1 (ref)
Hypertension	2/20	0.19 (0.04 – 0.83)	0.16 (0.04–0.75)
MAP at Last Visit			
Severe hypotension	2/6	0.56 (0.11–2.95)	0.54 (0.09–3.00)
Borderline hypotension	27/41	1.25 (0.70–2.24)	1.50 (0.80–2.84)
Normotension	86/153	1 (ref)	1 (ref)
Hypertension	9/43	0.36 (0.16–0.78)	0.30 (0.13–0.70)

MAP, mean arterial pressure.

because of their low body weight. Thus, even though they are currently not recognized to be at increased risk due to their extreme hypotension, they may be attracting extra care and attention due to their low body weight. It is therefore unfortunate that

BMI could not be included in multiple regression analyses.

This study is the first to use MAP readings when determining the risk of stillbirth in hypotensive women. We found that low MAP readings at the beginning or

Table 3 Estimated Odds Ratio of Stillbirth in Hypotensive Women by Covariates/Confounding Factors

		Case/Controls (n = 124/243)	Unadjusted Odds Ratio	Adjusted Odds Ratio
Hypotensive	N	68/104	1 (ref)	1.78 (1.06–2.99)
(3 or more MAP \leq 83)	Y		1.8 (1.09–2.92)	
Nonwhite	N	26/41	1 (ref)	1.35 (0.74–2.46)
	Y		1.28 (0.73–2.26)	
Multigravid	N	73/160	1 (ref)	0.85 (0.43–1.66)
	Y		0.73 (0.47–1.16)	
Multipara	N	22/44	1 (ref)	0.80 (0.40–1.59)
	Y		0.68 (0.43–1.08)	
SGA	N	41/44	1 (ref)	2.73 (1.60–4.66)
	Y		2.72 (1.62–4.56)	

MAP, mean arterial pressure; SGA, small for gestational age.

end of the pregnancy did not reflect increased risk of stillbirth; however, when blood pressure was persistently at borderline low levels (between 73 and 83 mm Hg) on three or more occasions during pregnancy, this approximately doubled the risk of stillbirth. This may be because MAP is a measure of tissue perfusion, and persistently low MAP levels therefore may be indicative of poor placental perfusion.

Of interest was the finding that hypertensive women are *not* at increased risk of stillbirth. The most likely explanation for this is the close monitoring and management that these women now receive during pregnancy.

Limitations of the Findings

There are several potential limitations to this study that should be taken into consideration when interpreting results. Blood pressures were collected from case-notes retrospectively, and thus the blood pressures were not taken in controlled conditions (same operator, same sphygmomanometer) but as part of routine antenatal care. Furthermore standard antenatal care is aimed at detecting hypertension and thus there may be some inaccuracy in those blood pressure recordings that were considered to be in the normal range. Another limitation was the relatively small number of case notes able to be reviewed. This prevented detailed analysis on some of the findings. The method of participant selection meant that a substantial number of stillbirths that occurred prior to the age of viability were unable to be used.

Generalizability of Results

This study's data were collected from regular antenatal attendees who birthed at urban tertiary referral centers. Generalizability to a pregnant population attending level two, one, or community maternity care providers cannot be inferred. Neither can these results be generalized to

those women who intend to birth in those settings. Furthermore, the study population was chiefly white women living in a developed nation, and so little can be said about whether these results are generalizable to a nonwhite population or pregnant women from developing nations.

CONCLUSIONS

This study's findings, along with the work of Steer et al,⁶ lends some credence to the findings of the earlier German studies^{8,9,20} that maternal hypotension in pregnancy increases the risk of stillbirth. Furthermore, it appears that results from our research support active management of hypertensive disease in pregnancy and that such management is reducing the risk of stillbirth in this group.

Recommendations

Further research is required to understand the extent of the effect of hypotension on poor pregnancy outcome and effective management strategies for hypotension.

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