The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

The association between high-normal blood pressure and the development of preeclampsia in twin pregnancies

Nathan S. Fox, Melissa B. Hill, Courtney T. Connolly, Rebecca A. Klahr, Kelly B. Zafman & Andrei Rebarber

To cite this article: Nathan S. Fox, Melissa B. Hill, Courtney T. Connolly, Rebecca A. Klahr, Kelly B. Zafman & Andrei Rebarber (2019): The association between high-normal blood pressure and the development of preeclampsia in twin pregnancies, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2019.1601696

To link to this article: https://doi.org/10.1080/14767058.2019.1601696

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2019.1601696

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The association between high-normal blood pressure and the development of preeclampsia in twin pregnancies

Nathan S. Fox[a,b], Melissa B. Hill[a], Courtney T. Connolly[a], Rebecca A. Klahr[a], Kelly B. Zafman[a] and Andrei Rebarber[a,b]

[a]Department of Obstetrics, Gynecology, and Reproductive Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [b]Maternal Fetal Medicine Associates, PLLC, New York, NY, USA

ABSTRACT

Objective: We sought to determine if women with twin pregnancies and blood pressure (BP) above the 95th percentile but within normal ranges (i.e. less than 140 systolic and 90 diastolic) are at increased risk of hypertensive disorders of pregnancy.

Methods: Retrospective cohort study of all women with twin pregnancies being cared for by a single Maternal Fetal Medicine practice between 2012 and 2018. We identified all women who had a systolic blood pressure (SBP) or diastolic blood pressure (DBP) above the 95th percentile but less than 140 systolic and 90 diastolic at any point during pregnancy. Based on prior publications, the 95th percentile was defined as: a SBP 121–139 mmHg up to 30 weeks or 131–139 mmHg after 30 weeks, a DBP 81–89 mmHg up to 34 weeks or 85–89 mmHg after 34 weeks. We excluded women diagnosed with chronic hypertension either before or during pregnancy. The primary outcome was the development of preeclampsia. Chi-square and logistic regression were used.

Results: A total of 457 patients met the inclusion criteria, of whom 109 (23.9%) had either a systolic or diastolic BP above the 95th percentile (but normal) at any time during pregnancy. These women were significantly more likely to develop preeclampsia (30.3 versus 12.6%, $p < .001$, aOR 2.32 (1.31, 4.09)) and gestational hypertension without preeclampsia (16.5 versus 4.6%, $p < .001$, aOR 4.27 (2.01, 9.07)).

Conclusions: In women with twin pregnancies, a high-normal systolic or diastolic BP (above 120 systolic or 80 diastolic prior to 30 weeks, or above 130 systolic or 84 diastolic after 30 weeks) is associated with a significantly increased risk of gestational hypertension and preeclampsia.

ARTICLE HISTORY
Received 30 January 2019
Revised 19 March 2019
Accepted 27 March 2019

KEYWORDS
Blood pressure; high normal; preeclampsia; twin

Introduction

Pregnant women experience numerous anatomic and physiologic changes starting soon after conception and lasting until several weeks after delivery [1,2]. In singleton pregnancies, systolic blood pressure (SBP) and diastolic blood pressure (DBP) both decrease in the second trimester, followed by a return to baseline in the third trimester [1,2]. Prior research indicates that women with twin pregnancies have even more profound cardiovascular changes [3,4]. One longitudinal, study of 520 patients with twin pregnancies found that changes in blood pressure (BP) were evident at 6 weeks' gestation and persisted until 30 weeks, when the BP began to rise slowly [5].

Preeclampsia is defined as a SBP $\geq$140 mmHg or DBP $\geq$ 90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient and the new onset of either proteinuria, thrombocytopenia, elevated liver transaminases, elevated creatinine, pulmonary edema, or cerebral or visual symptoms [6]. Elevated BP without any other findings is referred to as gestational hypertension [6]. Women with twin pregnancies have an increased risk of preeclampsia with a relative risk of 2.9 [7]. However, the prediction of preeclampsia in singleton and twin pregnancies is difficult [6,8]. Serum marker screening algorithms [9] and Doppler assessment of the uterine circulation in the second trimester [10] have resulted in limited sensitivity and poor generalizability given their cost and the technical expertise required.

In singleton pregnancies, a SBP that is 30 mmHg above the baseline or a DBP that is 15 mmHg above the baseline are associated with an increased risk of

CONTACT Nathan S. Fox nfox@mfmnyc.com Maternal Fetal Medicine Associates, PLLC, 70 East 90th Street, New York, NY, USA

preeclampsia, but not diagnostic [6]. Additionally, revised recommendations for the diagnosis of hypertension in nonpregnant adults now consider a SBP 130–140 and a DBP 80–90 as stage-I hypertension [11]. Recent evidence suggests women with singleton pregnancies and BP in this range are at increased risk of preeclampsia, gestational diabetes, and preterm birth [12].

In twin pregnancies, prior research examining blood pressure across pregnancy defined the 95th percentile as: a SBP above 120 mmHg up to 30 weeks or above 130 mmHg after 30 weeks, a DBP above 80 mmHg up to 34 weeks or above 84 mmHg after 34 weeks [5]. The objective of this study was to determine if women with twin pregnancies and blood pressure above the 95th percentile (but normal, i.e. less than 140 SBP and 90 DBP) are at increased risk of preeclampsia, and if so, whether this could be used as a predictor for preeclampsia in twin pregnancies.

Materials and methods

After Biomedical Research Alliance of New York Institutional Review Board approval was obtained, the charts of all patients with twin pregnancies >22 weeks delivered by a single maternal–fetal medicine practice were reviewed. We included all women who delivered subsequent to our original publication of BP in twin pregnancies [5] such that there would be no overlap of patients in the studies. Therefore, we included women who delivered between May 2012 and May 2018. We excluded patients with chronic hypertension prior to pregnancy as well as those diagnosed with chronic hypertension during pregnancy, defined as a SBP $\geq$ 140 mmHg or a DBP $\geq$ 90 mmHg prior to 20 weeks [6].

Using our electronic medical record, we examined all BP measurements during pregnancy for all women and identified all women with a SBP or DBP above the 95th percentile at any time during pregnancy. The 95th percentile was defined as: a SBP above 120 mmHg up to 30 weeks or above 130 mmHg after 30 weeks, a DBP above 80 mmHg up to 34 weeks or above 84 mmHg after 34 weeks [5]. Once a woman had a SBP of 140 mmHg or greater or a DBP of 90 mmHg or greater, she was defined as having gestational hypertension or preeclampsia.

Over the course of the inclusion years, all BP measurements were taken by a physician, nurse, or medical assistant in the manner recommended by ACOG and the Task Force on Hypertension: using a manual cuff and mercury sphygmomanometer with the patient in the seated upright position, and defining the DBP as the pressure at which the sound disappears (Korotkoff phase V) [6]. All twin pregnancies in our practice undergo early ultrasound to confirm gestational age and chorionicity. If the pregnancy was the result of *in vitro* fertilization (IVF), gestational age was determined from the date of embryo transfer. Over the course of the study period, all women with twin pregnancies were advised to take 81 mg of aspirin daily [13].

We compared women with and without a BP measurement above the 95th percentile at any time in pregnancy. We compared baseline characteristics between the two groups including maternal age, body mass index (BMI), IVF, egg donation, chorionicity, use of anticoagulation (heparin or low molecular weight heparin), parity, multifetal pregnancy reduction, and race. Our primary outcome was the development of preeclampsia, as defined by the Task Force on Hypertension [6], either before or after delivery (up to 6 weeks postpartum). Our predefined secondary outcome was the development of gestational hypertension without preeclampsia. We used chi-square testing for the unadjusted analysis, and then binary logistic regression to control for any differences in baseline characteristics between the two groups with a p-values<.05. We performed three comparisons: (1) women with and without a SBP or DBP above the 95th percentile; (2) women with and without a SBP above the 95th percentile; (3) women with and without a DBP above the 95th percentile. We then calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the positive and negative likelihood ratios (LR) for a BP above the 95th percentile as a predictor of preeclampsia. We also calculated the area under the curve (AUC) and 95% confidence intervals to tests the significance of these tests as predictors of preeclampsia. Statistical tests were performed using IBM SPSS for Windows version 22.0 (IBM Corp.).

Results

There were 474 patients with twin deliveries >22 weeks over the course of the study period. We excluded 11 patients with a diagnosis of chronic hypertension (8 diagnosed prepregnancy, 3 diagnosed in pregnancy prior to 20 weeks), five patients who transferred to our practice late in the third trimester such that we did not have reliable BP measurements from earlier in pregnancy, and one patient who moved out of state at 26 weeks, leaving 457 patients in the analysis. Overall, 98 women (21.4%) had a SBP

Table 1. Baseline characteristics of women with twin pregnancies who did and did not have a blood pressure above the 95th percentile but within the normal range.

	Either SBP or DBP > 95% $N = 109$	No SBP or DBP > 95% $N = 348$	p
Advanced maternal age (≥35 years)	56 (51.4%)	149 (42.8%)	.117
Prepregnancy body mass index >30 kg/m^2	23 (21.1%)	22 (6.3%)	<.001
In vitro fertilization	64 (58.7%)	156 (44.8%)	.011
Egg donation	17 (15.6%)	21 (6.0%)	.002
Chorionicity			.909
Dichorionic	87 (79.8%)	276 (79.3%)	
Monochorionic	22 (20.2%)	72 (20.7%)	
Anticoagulation	5 (4.6%)	7 (2.0%)	.142
Nulliparous	81 (74.3%)	204 (58.6%)	.003
Multifetal pregnancy reduction from higher order pregnancy	2 (1.8%)	11 (3.2%)	.467
White race	89 (81.7%)	287 (82.5%)	.845

Data presented as *n* (%). SBP: systolic blood pressure; DBP: diastolic blood pressure.
95% SBP defined as: 121–139 mmHg up to 30 weeks or 131–139 mmHg after 30 weeks.
95% DBP defined as: 81–89 mmHg up to 34 weeks or 85–89 mmHg after 34 weeks.

Table 2. Maternal outcomes, based on the presence or absence of a blood pressure above the 95th percentile but within the normal range.

	Either SBP or DBP> 95% $N = 109$	No SBP or DBP > 95% $N = 348$	p	Adjusted OR (95% CI)[a]
Preeclampsia	33 (30.3%)	44 (12.6%)	<.001	2.32 (1.31, 4.09)
Gestational hypertension without preeclampsia	18 (16.5%)	16 (4.6%)	<.001	4.27 (2.01, 9.07)
	SBP > 95% $N = 98$	No SBP > 95% $N = 359$	p	Adjusted OR (95% CI)[a]
Preeclampsia	31 (31.6%)	46 (12.8%)	<.001	2.46 (1.38, 4.41)
Gestational hypertension without preeclampsia	17 (17.3%)	17 (4.7%)	<.001	4.43 (2.07, 9.47)
	DBP > 95% $N = 42$	No DBP > 95% $N = 415$	p	Adjusted OR (95% CI)[a]
Preeclampsia	18 (42.9%)	59 (14.2%)	<.001	3.31 (1.58, 6.95)
Gestational hypertension without preeclampsia	7 (16.7%)	27 (6.5%)	.017	2.92 (1.13, 7.57)

Data presented as *n* (%). SBP: systolic blood pressure; DBP: diastolic blood pressure.
95% SBP defined as: 121–139 mmHg up to 30 weeks or 131–139 mmHg after 30 weeks.
95% DBP defined as: 81–89 mmHg up to 34 weeks or 85–89 mmHg after 34 weeks.
[a]Adjusted for maternal prepregnancy obesity, *in vitro* fertilization, egg donation, nulliparity.

above the 95th percentile during pregnancy; 42 women (9.2%) had a DBP above the 95th percentile during pregnancy, and 109 women (23.9%) had either a SBP or DBP above the 95th percentile during pregnancy. Thirty-one women had both SBP and DBP above the 95th percentile during pregnancy. A total of 77 women (16.8%) developed preeclampsia and an additional 34 women (7.4%) developed gestational hypertensions without preeclampsia.

Baseline characteristics of the women with and without a SBP or DBP above the 95th percentile at any time in pregnancy are shown in Table 1. Women with a BP above the 95th percentile were significantly more likely to be nulliparous, obese and undergo *in vitro* fertilization, and egg donation. These four variables were therefore included in the logistic regression analysis to calculate adjusted odds ratios and 95% confidence intervals.

The incidence of preeclampsia and gestational hypertension without preeclampsia in women with and without a BP above the 95th percentile are shown in Table 2. Having a SBP or DBP above the 95th percentile was independently associated with the development of preeclampsia and gestational hypertension without preeclampsia. We found similar results when examining the 95th percentile of SBP alone as well as for DBP alone (Table 2).

Although the incidence of advanced maternal age did not differ between the two groups (Table 1), we repeated the regression analysis including this variable, as advanced maternal age is a known risk factor for hypertensive disorders in pregnancy. The addition of advanced maternal age to the regression analysis did not change the significance of any of the results in Table 2 (data not shown).

The test characteristics for a BP above the 95th percentile as a predictor of preeclampsia in twin pregnancies are shown in Table 3. Having a SBP or DBP above the 95th percentile was a significant predictor of preeclampsia (AUC 0.61, 95% confidence interval 0.54, 0.69). Similarly, a SBP above the 95th percentile, or a DBP above the 95th percentile were also significant

Table 3. Test characteristics of a blood pressure above the 95th percentile but within the normal range as a predictor of preeclampsia in twin pregnancies.

	Sensitivity	Specificity	PPV	NPV	+LR	−LR	AUC
Either SBP or DBP > 95%	43%	80%	30%	87%	2.2	0.71	0.61 (0.54, 0.69)
SBP > 95%	40%	82%	32%	87%	2.2	0.73	0.61 (0.54, 0.69)
DBP > 95%	23%	94%	43%	86%	3.8	0.82	0.59 (0.51, 0.66)

SBP: systolic blood pressure; DBP: diastolic blood pressure; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; AUC: area under curve (95% confidence interval).
95% SBP defined as: 121–139 mmHg up to 30 weeks or 131–139 mmHg after 30 weeks.
95% DBP defined as: 81–89 mmHg up to 34 weeks or 85–89 mmHg after 34 weeks.

predictors of preeclampsia. Positive likelihood ratios ranged from 2.2 to 3.8 and negative likelihood ratios ranged from 0.82 to 0.71.

Discussion

In this study, we found that in women with twin pregnancies a high-normal blood pressure above the 95th percentile was associated with a significantly increased risk of developing gestational hypertension and preeclampsia. For example, 30.3% of women with either a SBP or DBP above the 95th percentile developed preeclampsia, as compared to 12.6% in women without a blood pressure above the 95th percentile. There are two clinical considerations that might be gleaned from our data. First, the sensitivity of a SBP or DBP above the 95th percentile as a predictor of preeclampsia was only 43%, indicating that most women with twin pregnancies who develop preeclampsia will have no prior "borderline" blood pressure readings. Therefore, the development of preeclampsia in most women with twin pregnancies has a relatively sudden onset. In our practice, women with twin pregnancies undergo blood pressure testing in our office every 2 weeks from 24–32 weeks, and then every week thereafter. So, most women developed gestational hypertension or preeclampsia without any blood pressure warning 1 week earlier. Second, if a woman with a twin pregnancy does have a BP above 120/80 mmHg prior to 30 weeks or above 130/84 after 30 weeks, she is at significantly increased risk of developing gestational hypertension or preeclampsia. It is unclear what the ideal management should be in this situation, but we would suggest close monitoring either with more frequent office visits, enhanced patient education, and/or initiation of home BP monitoring.

In singleton pregnancies, a SBP that is 30 mmHg above the baseline or a DBP that is 15 mmHg above the baseline are associated with an increased risk of preeclampsia and warrant closer monitoring [6]. Also, in singleton pregnancies, women with a BP between 130/80 and 140/90 have an increased risk of preeclampsia [12]. We believe our study represents a similar phenomenon in twin pregnancies. Although not diagnostic of hypertension or preeclampsia, women with twin pregnancies and BP above the 95th percentile are at increased risk of developing gestational hypertension and preeclampsia. Given the increased risk of hypertensive disorders in twins and currently limited tools available clinically to predict this potentially serious complication, we propose our model has a significant advantage of availability. Universal assessment of uterine artery Dopplers is not easy to implement, is costly to perform, and appears to have some interobserver variability [14]. Regarding serum marker screening, it is not routinely performed in twin pregnancies, is costly to obtain, has limited sensitivities, and may not even be available in some countries.

Interestingly, in twin pregnancies, the 95th percentile for BP is only 120/80 mmHg until 30 weeks [5]. A BP slightly above this would most likely not trigger any significant concern among most providers as these BP readings are common in singleton pregnancies. However, twin pregnancies have more marked physiologic changes and BP readings above 120/80 prior to 30 weeks are abnormal and warrant close observation.

Strengths to our study include the large sample size and BP measurements as early as 6 weeks. We were able to exclude patients with chronic hypertension, which is important in defining the risk of preeclampsia. BP measurements were recorded in a standardized manner consistent with recommended guidelines [6]. We also had direct contact with these patients throughout pregnancy and did not simply rely on registry data or hospital discharge diagnoses. Therefore, we are confident the diagnoses of gestational hypertension and preeclampsia were as accurate as possible. Our study is limited by the demographics of our cohort. It is unknown if our findings would differ if our methods were applied to a different cohort of women, for example of different ethnicities, with lower rates of *in vitro* fertilization, or women with twin pregnancies not under the care of an MFM practice. Additionally, while we recommended low-dose aspirin

to all women with twin pregnancies, we were unable to reliably track compliance. Our study is also limited by its retrospective design in that all BP measurements were ones obtained in clinical practice, as opposed to a formal research protocol, and it is possible that there were differences in the number of BP measurements taken. We also do not typically use an average of several BP measurements. However, this latter point may allow for greater generalizability in clinical practice.

In conclusion, in women with twin pregnancies, a high-normal SBP or DBP that is above the 95th percentile is associated with a significantly increased risk of gestational hypertension and preeclampsia. Although the ideal follow-up for these women is not known, we suggest more frequent office visits for BP checks, enhanced patient education on the signs and symptoms of hypertensive disorders of pregnancy, or initiation of home BP monitoring.

Disclosure statement

None of the authors have any potential conflicts of interest to report.

ORCID

Nathan S. Fox http://orcid.org/0000-0001-5071-8182
Kelly B. Zafman http://orcid.org/0000-0001-6343-1973

References

[1] 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(1):97–104.
[2] Macdonald-Wallis C, Lawlor DA, Fraser A, et al. Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. Hypertension. 2012;59(6):1241–1248.
[3] Kametas NA, McAuliffe F, Krampl E, et al. Maternal cardiac function in twin pregnancy. Obstet Gynecol. 2003;102(4):806–815.
[4] Kuleva M, Youssef A, Maroni E, et al. Maternal cardiac function in normal twin pregnancy: a longitudinal study. Ultrasound Obstet Gynecol. 2011;38(5): 575–580.
[5] Fox NS, Roman AS, Hastings J, et al. Blood pressure changes across gestation in patients with twin pregnancies. J Matern Fetal Neonatal Med. 2014;27(9): 898–903.
[6] American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122(5):1122–1131.
[7] Bartsch E, Medcalf KE, Park AL, et al. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.
[8] Fox NS, Roman AS, Saltzman DH, et al. Risk factors for preeclampsia in twin pregnancies. Am J Perinatol. 2014;31(2):163–166.
[9] Svirsky R, Levinsohn-Tavor O, Feldman N, et al. First- and second-trimester maternal serum markers of preeclampsia in twin pregnancy. Ultrasound Obstet Gynecol. 2016;47(5):560–564.
[10] Geipel A, Berg C, Germer U, et al. Doppler assessment of the uterine circulation in the second trimester in twin pregnancies: prediction of pre-eclampsia, fetal growth restriction and birth weight discordance. Ultrasound Obstet Gynecol. 2002;20(6):541–545.
[11] Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19): e127–e248.
[12] Sutton EF, Hauspurg A, Caritis SN, et al. Maternal outcomes associated with lower range stage 1 hypertension. Obstet Gynecol. 2018;132(4):843–849.
[13] LeFevre ML, US Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(11):819–826.
[14] Steer CV, Williams J, Zaidi J, et al. Intra-observer, inter-observer, interultrasound transducer and intercycle variation in colour Doppler assessment of uterine artery impedance. Hum Reprod. 1995;10(2):479–481.