Published in final edited form as:

Biomed Pharmacother. 2005 October ; 59(Suppl 1): S86–S91.

Circadian rhythm of maternal blood pressure and fetal growth

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Abstract

This study aimed at examining any relation between the circadian variation in blood pressure (BP) in human pregnancy and fetal growth. A prospective study included 52 pregnant women monitored during the third trimester of pregnancy. There were 33 uncomplicated pregnancies with normal fetal growth (Group 1) and 19 pregnancies complicated by intrauterine growth retardation (IUGR), confirmed at birth (Group 2). Ten women (five in each group) had pregnancy-induced hypertension. All women were hospitalized and followed a similar daily routine. BP was recorded with an automatic wearable device. Measurements were obtained every 20 min for 24 ± 1 h. BP profiles were analyzed by conventional statistical methods and by cosinor, involving the least squares fit of cosine curves with an anticipated period (24 h) to the data. BP parameters, fetal outcome, demographic and obstetric characteristics were compared between the two groups. Logistic regression and multivariate analyses were used to assess factors putatively associated with fetal outcome. The circadian amplitude of diastolic BP was found to be larger in normotensive women with IUGR. As gauged by odds ratios (OR), the circadian amplitude of diastolic BP (OR = 1.7, 95% CI: 1.1–2.8; $P = 0.03$) and hematocrit (OR = 1.4, 95% CI: 1.0–1.9; $P = 0.04$) were the only variables positively and independently associated with IUGR. In the presence of maternal hypertension, the circadian amplitude of systolic BP was negatively associated with IUGR (OR = 0.7, 95% CI: 0.5–1.0; $P = 0.03$). A larger circadian variation in diastolic BP, rather than a difference in the mean value of systolic or diastolic BP, was found to be statistically significantly associated with IUGR. This study adds another condition in which the circadian BP amplitude constitutes a harbinger of elevated risk, apart from an association with a shortened lifespan in the absence or presence of malignant hypertension and with an increased risk of stroke and nephropathy reported earlier.

Keywords

Blood pressure; Circadian rhythm; Human pregnancy; Intrauterine growth retardation (IUGR); Pregnancy-induced hypertension

1. Introduction

In utero growth retardation (IUGR) is reportedly associated with raised blood pressure (BP) values in adulthood and with decreased arterial compliance in the trunk and legs [1,2]. During pregnancy, high maternal BP values are reported to adversely affect fetal growth and to be associated with an increased risk of intrauterine growth restriction, more so in the presence of pre-eclampsia than in the presence of gestational hypertension [3]. BP-lowering therapy could

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also negatively affect fetal growth, a larger treatment-associated decrease in BP corresponding to a higher odds ratio of impaired fetal growth [4].

The mechanism by which an elevated BP affects fetal growth has been related to changes in vascular resistance, but the BP coordination in idiopathic IUGR is not known. Since a compromised placental vasculature or blood volume reduction may be involved [5,6], any local vasoconstriction can be expected to affect the BP profile. Because BP is highly variable from moment to moment, a single BP measurement is neither accurate nor adequate in diagnosing normotension (or hypertension). With respect to monitoring for a single circadian cycle, as done herein, the same qualification applies to this study's results insofar as references for a given individual woman are concerned. With this limiting qualification, BP variability in itself may be a source of useful information. Circadian hyper-amplitude-tension (CHAT), defined as an excessive circadian BP variation (BP overswinging), has been associated with a large increase in cardiovascular morbidity, cerebral ischemic events and nephropathy in particular [7–9] and with higher values of the left ventricular mass index, reflecting an increased risk of target organ damage [10].

BP exhibits a circadian periodic variation with lower values during the night and higher values during the day [11–14]. This rhythmicity is also present throughout pregnancy [15–17]. An altered circadian pattern has been reported in pregnancy-induced hypertension [18] and in severe preeclampsia, where a complete reversal of the BP variation has been reported [19,20]. Single BP measurements are then only a poor indicator of the complex adaptation of the maternal circulation, while BP variability needs to be considered [7–11,13,21–24].

This study aimed at examining BP variability during pregnancy and at assessing any influence of maternal BP on fetal growth, accounting for parity, smoking, volume constriction, and diet.

2. Subjects and methods

Fifty-two women with a singleton pregnancy, who attended the prenatal clinic of the hospital volunteered to enter the study and all provided informed consent. Ten women were diagnosed as having pregnancy-induced hypertension (PIH), defined by an anamnestic evaluation negative for pre-pregnancy hypertension and a BP value at rest above 140/90 mmHg on two different occasions. The remainder had acceptable BP values at the time of testing and remained normotensive until delivery. Gestational age was determined by early ultrasound examination at less than 12 weeks. IUGR was diagnosed as a growth rate pattern monitored by ultrasonography in the lower 10th percentile, adjusted for gender, gestational age, and national standards [25], confirmed by a birth weight in the lower 10th percentile [26]. None of the fetuses had any malformations or diseases other than IUGR. None of the pregnant women was affected by medical diseases other than PIH. They did not receive any medications, except for iron and vitamins.

All patients were hospitalized for at least 2 days during which they were encouraged to follow the same daily routine. Lights were turned off from 22:00 to 06:00 h, and meals were served at 08:00, 12:00 and 19:00 h. On the second day, blood was taken for determination of hemoglobin (Hb) and hematocrit (Ht), and maternal BP and heart rate (HR) were recorded oscillometrically at 20-min intervals for 24 ± 1 h, using a portable automatic device (Space labs Holter PA 5200) [27].

BP and HR measurements were plotted as function of time and analyzed by single cosinor [28,29]. This approach consists of fitting by least squares a cosine function with a given period (24 h) to the data. Point and interval (95% confidence interval) estimates are thus obtained for the MESOR, a rhythm-adjusted mean, for the double circadian amplitude, an estimate of the predictable extent of change within a day, and for the acrophase, a measure of the timing of

overall high values recurring each day. Rhythm detection is established by means of the zero-amplitude test. Statistical significance is reached for a probability less than 5%. Results were summarized for each group by population-mean cosinor [28,29] and compared by parameter tests [30].

The Student *t*-test and/or the Mann–Whitney test were also used to compare continuous variables, depending on whether the normality of their distribution could be validated or not. Odds ratios (OR) were computed to assess the relationship between IUGR and categorical variables such as gender, smoking, PIH, gravidity, and parity. Both linear and logistic regression models [31] tested the association of fetal growth pattern with continuous and dichotomic variables, treating outcomes respectively as a continuous or as a dichotomic variable. Continuous independent variables were entered as such in the model or after categorization [32]. Analyses were carried out overall and after removing women with PIH. Multivariate analyses of variance were also performed, taking into consideration Ht, the presence of hypertension, and chronobiological end-points (MESOR, circadian amplitude and acrophase of BP), in order to obtain an “adjusted” estimation of their association with IUGR.

3. Results

All women were first compared between IUGR with AGA (appropriate size for gestational age) pregnancies, irrespective of the maternal obstetric history. Fetal growth pattern was within the reference range for gestation in 33 women (Group 1: AGA, 28 with normotension and five with PIH). It was below the 10th percentile in 19 women (Group 2: IUGR, 14 with normotension and five with PIH). Parity, gestational age at testing, pre-pregnancy weight, weight gain, body mass index, and the number of smokers were similar between the two groups, but Hb and Ht were statistically significantly higher in IUGR than in AGA pregnancies ($P < 0.01$), Table 1a. Cesarean sections were also more common among IUGR than among AGA pregnancies, Table 1b.

A statistically significant circadian BP rhythm could be demonstrated on an individualized basis for all normotensive women and for all but four women with PIH. Overall, the circadian amplitude of diastolic BP was found to be larger among IUGR, than among AGA pregnancies ($P < 0.01$ from Mann–Whitney test), whereas the circadian amplitude of systolic BP was slightly smaller among IUGR than among AGA pregnancies. Of all variables examined herein, multivariate logistic regression analyses only found Ht and the circadian amplitude of BP to be statistically significantly associated with IUGR, Table 2 (left).

After excluding women with PIH, the circadian amplitude of diastolic BP remained statistically significantly larger among IUGR, than among AGA pregnancies (mean $\pm$ S.D.: 9.3 ± 1.7 vs. 7.4 ± 3.2 mmHg, $P = 0.01$), Table 3. Multivariate logistic regression analyses on these 42 normotensive women find the circadian amplitude of diastolic BP and Ht to remain independently associated with IUGR, Table 2 (right). The relation with the circadian amplitude of systolic BP, however, is no longer statistically significant, Table 2 (right).

4. Discussion and conclusion

This study shows that the circadian amplitude of diastolic BP is related to fetal growth independently of Ht (and Hb). This association holds true and when women with PIH are excluded. No association was found, however, with the MESOR of BP. The circadian BP amplitude is a measure of the extent of oscillation in BP values around the MESOR. Despite an acceptable BP MESOR, pregnancies complicated by IUGR are characterized by increased deviations of the maternal BP from the MESOR as compared to uncomplicated pregnancies.

The mechanisms for an increase in BP during daytime are not known. It is possible that during the night the fluid re-absorption can compensate the low blood volume or that the pressure effect of vasoactive peptide is increased in a volume - depleted vasoconstrictive state. The latter is more likely to be present — or increased — during the day, when sympathetic activity is increased [33] and venous BP tone is low in relation to the standing position [34], than during the night. We recently found that ANF is increased in cases of IUGR with acceptable mean BP values [35]. Its vasodilatory action may have a compensatory effect, especially in the placental perfusion, where receptors for ANP have been found, thus preventing a further increase in vasoconstriction but also reducing the BP mean.

The loss of circadian BP rhythmicity and a paradoxical increase in BP during sleep has been reported in PIH patients until a complete reversal of the circadian pattern [15,19,36–39]. In this study, most of the women had an acceptable BP profile. The circadian amplitude of systolic BP amplitude was found to be positively associated with the presence of PIH but negatively associated with the diagnosis of IUGR. An increase in the circadian BP amplitude had been observed to occur before an increase in the MESOR of BP in the stroke-prone spontaneously-hypertensive Okamoto rat (handled for measurements) [40], perhaps reflecting an increased vascular reactivity. An increase in vascular responsiveness has been described in hypertensive pregnant patients [19], and it is possible that the circadian amplitude of systolic BP could become a useful marker in pregnancy, but the small sample size of this study does not allow us to draw definitive conclusions.

The circadian amplitude of SBP was negatively rather than positively related to IUGR in the presence of PIH. As suggested by Easterling [41,42], PIH patients move from a hyper-dynamic low-resistance state to a state of high resistance when fetal growth is compromised. The first stage may be reflected by an increase in the circadian amplitude of systolic BP, whereas the second stage may be associated with a decrease in the circadian amplitude of systolic BP. An increase in BP may allow placental perfusion to be maintained. Reportedly, in PIH patients the mean BP, cardiac output and ejection volume are lower in pregnancies complicated by IUGR [43,44]. In IUGR, the increase in maternal BP may stem from a compensatory mechanism that is jeopardized by anti-hypertensive treatment [45].

An increase in fetal and neonatal death rate associated with low diastolic BP during pregnancy has been reported [46]. The relation between mean diastolic BP values during the last 3 months of pregnancy and neonatal weight suggests that fetal growth is affected when the diastolic BP is above 90 or below 65 mmHg [46,47]. A lower birth weight associated with an extremely low BP has also been reported [48]. Most of these studies were not done chronobiologically, however, being based on BP spotchecks rather than on serial measurements taken during the night as well as during the day.

The absence of a decrease in hematocrit and in MAP is reportedly correlated with impaired fetal growth [49]. Doppler flow measurements show that the hypervolemic hemodilution is of advantage for the mother and the fetus, while a reduction in blood volume expansion during pregnancy is associated with a heightened risk of IUGR [50]. IUGR has already been reported to be associated with increased Hb and Ht values [51,52], in keeping with results herein.

It is well known that both pre-pregnancy weight and weight gain can strongly influence BP [53] and fetal growth [54,55]. In this study, however, there was no difference in either variable between women with uncomplicated pregnancies and women with pregnancies complicated by IUGR, or between normotensive women and women with PIH. It is possible that the quality of the food more than the total amount of weight increase can affect fetal growth, but the negative results have to be qualified by the small sample size of this study.

A relation between BP variability and target organ damage is another possible explanation. It is not known which component of the arterial pressure leads to vascular damage. It might be expected that individuals with increased BP variability may suffer more vascular damage. But animal studies indicate that increased BP variability, by sectioning the carotid sinus and aortic baroreceptor nerves, does not necessarily lead to accelerated vascular damage, although this question has received little attention. In clinical studies, the relationship of BP variability to cardiovascular disease risk was shown to be nonlinear: the circadian amplitude of BP has to exceed a threshold value for risk to be increased [56, see also 57]. Larger circadian amplitude of BP in children with a positive vs. negative family history of high BP and/or related cardiovascular disease was also observed [58]. And a larger circadian BP amplitude was found in patients with an intermediate value of the left ventricular mass index (LVMI) but no increase in BP MESOR, observed only at higher LVMI values [59]. Theoretically, the larger circadian amplitude of diastolic BP found herein in the presence of IUGR could reflect the pre-hypertension state observed in non-pregnant adults [60]. If so, it is conceivable that normotensive pregnancies complicated by IUGR may eventually evolve toward MESOR-hypertension if pregnancy would last long enough. The known influence of PIH on fetal growth would then be matched in reverse by an effect of IUGR on maternal BP.

In conclusion, of clinical interest is the finding herein that a larger circadian amplitude of diastolic BP is statistically significantly and independently associated with the presence of IUGR, irrespective of the maternal BP MESOR, whereas in presence of high BP, the circadian amplitude of systolic BP is inversely related to IUGR, suggesting opposite effects of IUGR and PIH on maternal BP variability. Hematocrit (and hemoglobin) was also found to be associated with fetal growth retardation, independently of BP. The reader is referred to the literature for associations of the circadian BP amplitude with lifespan [61–63] and for a comparison of the relative merits of assessing the circadian variation versus a classification into ‘dippers’ and non-dippers’ according to the day-night ratio [64,65].

Acknowledgements

GM-13981 (FH), Dr. h.c. mult. Earl Bakken Fund (GC, FH) and University of Minnesota Supercomputing Institute (GC, FH).

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Table 1

Table 1a. Comparison of demographic and clinical variables between AGA and IUGR pregnancies

	AGA (n = 33)		IUGR (n = 19)		Mann-Whitney
	mean	S.D.	mean	S.D.	
AGE (years)	31.15	5.37	30.58	4.05	NS
GESTATIONAL AGE (weeks)	33.48	5.93	33.73	2.64	NS
Pre-pregnancy	58.12	9.59	55.89	5.66	NS
MATERNAL WEIGHT (kg)	10.18	3.3	9.95	2.12	NS
WEIGHT INCREASE (kg)	22.11	4.12	21.05	2.01	NS
MATERNALBMI (kg/m ²)	11.25	1.15	12.07	1.13	0.01
Hb (g/dl)	33.68	2.77	35.95	3.11	0.01
Ht(%)	3072	954	1930	486	0.01
FETAL WEIGHT (g)					

Table 1b. Comparison of demographic and clinical variables between AGA and IUGR pregnancies

	AGA (n = 33)		IUGR (n = 19)		χ^2 (P); OR [95% CI]
	n	%	n	%	
smokers					
Yes	10	30.3	5	26.3	0.093 (0.760); 0.82 [0.23, 2.90]
No	23	69.7	14	73.7	
First pregnancy					
Yes	11	33.3	10	52.6	1.865 (0.172); 2.22 [0.70, 7.06]
No	22	66.7	9	47.4	
Pluriparae					
Yes	12	36.4	5	26.3	0.553 (0.457); 0.63 [0.18, 2.17]
No	21	63.6	14	73.7	
PIH					
Yes	5	15.1	5	26.3	0.968 (0.325); 2.00 [0.50, 8.08]
No	28	84.9	14	73.7	
Cesarean section					
Yes	14	42.4	16	84.2	8.626 (0.003); 7.24 [1.76, 29.7]
No	19	57.6	3	18.8	

AGA: Appropriate size for gestational age; IUGR: intrauterine growth retardation;

Hb: Hemoglobin; Ht: Hematocrit; OR: Odds Ratio;

CI: Confidence Interval; NS: Not statistically significant (P > 0.05).

Table 2

Results of multivariate logistic regression analyses

	All women (<i>n</i> = 52)		After removal of women with PIH (<i>n</i> = 42)	
	Adjusted OR (95%CI)	P	Adjusted OR (95%CI)	p
PIH	2.5 (0.2–26.8)	0.44	-	-
Hematocrit	1.3 (1.0–1.7)	0.03	1.4 (1.0–1.9)	0.04
SBP MESOR	1.0 (0.9–1.1)	0.76	1.0 (0.9–1.2)	0.83
DBP MESOR	1.1 (0.9–1.2)	0.28	1.0 (0.8–1.2)	0.99
SBP Amplitude	0.7 (0.5–1.0)	0.03	0.8 (0.6–1.1)	0.17
DBP Amplitude	1.8 (1.1–2.7)	0.01	1.7 (1.1–2.8)	0.03

OR: Odds ratio; PIH: Pregnancy-Induced Hypertension; CI: confidence interval;

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure;

MESOR: Midline Estimating Statistic Of Rhythm, rhythm-adjusted mean value;

Amplitude: Half the extent of predictable variation within a day.

Comparison of circadian BP rhythm characteristics between AGA and IUGR normotensive pregnancies (after removing women with PIH)

	AGA (n = 28)		IUGR (n = 14)	
	mean	S.D.	Mean	S.D.
SBP MESOR (mmHg)	115.08	22.41	114.83	9.13
DBP MESOR (mmHg)	76.11	11.31	72.69	8.87
SBP Amplitude (mmHg)	8.57	4.33	8.44	2.37
DBP Amplitude (mmHg)	7.43	3.19	9.29	1.73
SBP acrophase(degrees)	-218(14:40)	50	-222 (13:40)	64
DBP acrophase (degrees)	-220 (14:40)	44	-205 (13:40)	59

AGA: Appropriate for gestational age; IUGR: Intrauterine Growth Retardation

S.D.: standard deviation;

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure;

MESOR: Midline Estimating Statistic Of Rhythm, rhythm-adjusted mean value;

Amplitude: Half the extent of predictable variation within a day;

Acrophase: Timing of overall high values recurring each day, expressed in (negative) degrees, with 360° equated to 24 h, and 0° set to local midnight.