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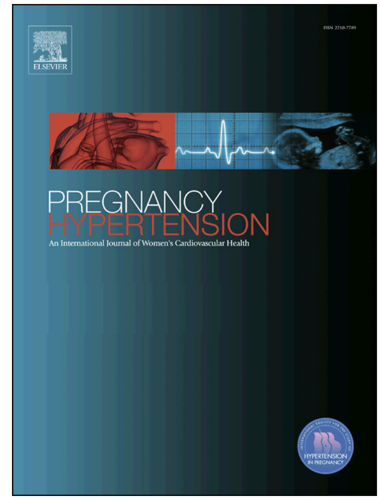

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Protocol for measurement of mean arterial pressure at 10-40 weeks' gestation

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Running title: Protocol for measurement of MAP

Abstract

The study aimed to identify the simplest protocol for the measurement of mean arterial pressure (MAP) across 10-40 weeks' gestation. 2,726 women with uncomplicated singleton pregnancy attending for their routine hospital visit between 10-40 weeks' gestation were recruited prospectively. The blood pressure (BP) was measured according to the National Heart Foundation of Australia (NHFA) protocol using automated devices. Linearizing regression models were determined for MAP derived from single, repeat and average measurements taken in the left and right arms using the same polynomial power of the best fit model determined using the NHFA protocol. Z-scores were used to compare the differences between the smoothed 50th percentiles. The first measurements taken in the left and right arms were on average 0.15SD and 0.12SD, respectively, higher than those obtained from the NHFA protocol. The second measurements taken in the left and right arms were both 0.26SD lower than the first measurement taken in the same arm and these values were lower than those from the NHFA protocol. The median MAP determined by the protocol of the average of two measurements taken in both arms was similar to the median MAP determined using the NHFA protocol (Z-score 0.0194SD). MAP derived by the average of two measurements in both arms had a quadratic relationship with gestation, with the measurement being the lowest in the mid-trimester. In conclusion, our study has demonstrated that at 10-40 weeks' gestation, BP recordings can be obtained by a simpler protocol using the average of two measurements in both arms.

Keywords: Protocol, Mean arterial pressure, Blood pressure, Pregnancy, Hypertension, Preeclampsia, Reference range

Introduction

In preeclampsia, hypertension develops as a result of vasoconstriction and reduced peripheral vascular compliance (1). Although hypertension is only a secondary sign of preeclampsia, it is an important one as it is an early indication of the condition. This highlights the importance of regular accurate monitoring of blood pressure during antenatal care. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) has recommended that blood pressure measurement should be carried out at each antenatal visit to screen for preeclampsia (2). Within this recommendation, the protocol for blood pressure measurement is specific for the use of mercury sphygmomanometer (2). However, the use of mercury sphygmomanometers has been banned or phased out because mercury is toxic (3). There are also considerable errors associated with the use of the mercury sphygmomanometer. These errors range from a malfunctioning manometer to observer errors such as digit preference and threshold avoidance (4, 5).

The introduction of automated blood pressure monitoring allows simple, standardized and repeated measurements to be taken. It has addressed many of the errors associated with the conventional sphygmomanometer. However, accurate assessment of blood pressure remains hindered by the considerable variability that blood pressure exhibits within each individual. The National Heart Foundation of Australia (NHFA) has therefore recommended that a minimum of two recordings should be made at 1-minute intervals until variations between consecutive readings fall to within 10 mmHg in systolic blood pressure and 6 mmHg in diastolic blood pressure (6). When this point of stability is reached, the average of the last two stable measurements of the left and right arms is calculated and it is recommended that the highest of these two measurements from the two arms should be used (6). Whether blood pressure should be taken on the left or right arm remains a subject of discussion. A difference between the two arms in the systolic and/or diastolic blood pressure of $\geq$10 mmHg was first reported in 1920 (7).

In the first-trimester of pregnancy, a significant inter-arm difference of $\geq$10 mmHg has been observed in a significant proportion of a healthy pregnant population and its prevalence increases with increasing blood pressure (8). For accurate risk assessment of preeclampsia at 11-13 weeks' gestation, a standardized protocol has been established that two measurements of mean arterial pressure (MAP) should be taken in both arms simultaneously (9). Such standardized protocol for the measurement of MAP throughout pregnancy has not been established.

The objective of this study is to identify the simplest protocol for the measurement of MAP across 10-40 weeks' gestation that could achieve comparable recordings to that obtained according to the NHFA protocol.

Materials and methods

This was a prospective cross-sectional study for establishing a protocol for MAP measurement in women with singleton pregnancy attending for their routine hospital visit between 10-40 weeks' gestation at King's College Hospital, London. Gestational age (GA) was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 20-24 weeks (10, 11). The blood pressure was measured according to the NHFA protocol (6) and we recorded maternal characteristics and medical history. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the Ethics Committee of King's College Hospital, London.

We prospectively examined 3,002 singleton pregnancies. We excluded 276 (9.2%) because they had missing outcome data (n=77), loss follow up (n=73), there was a major fetal defect (n=3), the pregnancies resulted in fetal death or miscarriage before 24 weeks' gestation (n=30), the women underwent termination of pregnancy (n=3), the women developed preeclampsia (n=55), pre-gestational diabetes (n=9), and chronic hypertension (n=26). Therefore, a total of 2,726 pregnant women were included in this study.

Measurement of blood pressure

Blood pressure was taken by validated automated devices (3BTO-A2, Microlife, Taipei, Taiwan), which were calibrated before and at regular intervals during the study (11). The recordings were made by doctors who had received appropriate training on the use of these machines. The women were in the sitting position, their arms were supported at the level of their heart and either a small (<22 cm), normal (22-32 cm) or large (33-42 cm) adult cuff was used depending on the mid-arm circumference (6). After rest for five minutes blood pressure was measured in both arms simultaneously and a minimum of two recordings were made at 1-minute intervals. When the last two blood pressure measurements in either arm differed by more than 10 mmHg in systolic and 6 mmHg in diastolic blood pressure, more recordings were made in both arms until variations between consecutive readings fell to within 10 mmHg in systolic and 6 mmHg in diastolic blood pressure. When this point of stability was reached, the MAP measurement of each arm was calculated as the average of the last two stable measurements, and as recommended, the highest final MAP from either arm was used (6).

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs), cigarette smoking during pregnancy (yes or no), medical history of chronic hypertension (yes or no), diabetes mellitus (yes or no), systemic lupus erythematosus or anti-phospholipid syndrome, family history of preeclampsia in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at ≥24 weeks' gestation), and previous pregnancy with preeclampsia (yes or no). The maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The definitions of non-proteinuric gestational hypertension and preeclampsia were those of the International Society for the Study of Hypertension in Pregnancy (12). The obstetric records of all women with pre-existing or pregnancy associated hypertension were examined to confirm if the condition was chronic hypertension, preeclampsia or gestational hypertension. The newborn was considered to be small for GA if the birth weight was less than the 5^{th} percentile after correction for GA at delivery (13).

Statistical Analysis

Paired samples t-test with Bonferroni adjustment was used to detect differences between measurements of systolic blood pressure, diastolic blood pressure, and mean arterial pressure taken in the left and right arms as well as between arms. Differences were considered significant if the adjusted p value was <0.05 / number of paired comparisons performed.

The MAP derived from the NHFA protocol was used as a reference to determine the potential differences in MAP obtained using single, repeat and average measurements. The Generalized Additive Models for Location, Scale and Shape (GAMLSS package version 5.0, 'R' statistical software package version 3.3.2) was used to generate linearizing regression models as a function of GA (polynomial or second degree fractional power) in order to estimate the expected MAP. The best fit model was determined for MAP derived using the NHFA protocol after measurements had been transformed to their natural log equivalent. Goodness of fit was assessed by inspecting residuals using quantile-quantile (Q-Q) plots and detrended Q-Q plots whilst the generalized Akaike information criterion was used to compare between different models (14, 15). The final model to estimate the mean MAP using the NHFA protocol was chosen as a balance between goodness of fit and model simplicity.

Linearizing regression models were determined for MAP derived from single, repeat and average measurements taken in the left and right arms using the same polynomial power of the best fit model determined using the NHFA protocol. It was assumed that MAP had the same temporal relationship with gestation irrespective of measurement protocol. Z-scores were used to compare the differences between the smoothed 50th percentiles using the method described by Salomon *et al* (16). Expected gestation specific MAP from single, repeat and average measurements protocols were expressed as z-scores using the expression $Z = ((X_{GA}/\mu_{GA})^{1/\upsilon} -1)/\upsilon_{GA}\sigma_{GA}$ where X_{GA} is the 50th percentile of MAP at a known GA determined using each protocol and υ_{GA}, μ_{GA}, and σ_{GA} are the Location, Mean and Scale values at any GA determined from the NHFA protocol. Results were presented graphically across the GA range to allow visual inspection. A z-score of 1 indicated a difference of 1 SD at that GA. Centiles were determined using the expression $\mu\times(1+z_p\upsilon_{GA}\sigma_{GA})^{1/\upsilon GA}$ where z_p is the centile of interest.

Results

Characteristics of the study population

The MAP measurements were available for analysis from 2,726 women without pregnancy complications. The median (interquartile range; IQR) number of MAP recordings performed per gestational week was 48 (IQR: 34-68). There were 2,221 (81.5%) women requiring two recordings, 354 (13.0%) requiring three recordings, and 151 (5.5%) requiring four or more recordings. Clinical characteristics of the study population are demonstrated in Table 1.

Intra- and Inter-arm measurement differences

Table 2 reports the mean difference between the last two consecutive measurements taken in the left and right arms. The mean intra-arm differences were ≈3 mmHg for systolic blood pressure and 1 mmHg for diastolic blood pressure, whilst inter-arm differences were ≈-0.5 mmHg for systolic blood pressure and ≈0.5 mmHg for diastolic blood pressure. Mean differences were statistically significant after Bonferroni adjustment. Absolute difference in consecutive systolic blood pressure measurements was ≥10 mmHg in 362 (13.5%) in the left arm and 357 (13.3%) in the right arm. Absolute difference in consecutive diastolic blood pressure measurements in the corresponding arms was ≥6 mmHg in 314 (11.7%) and 370 (13.7%), respectively. A significant inter-arm difference of ≥10 mmHg in the first measurements of systolic and diastolic blood pressure was observed in 352 (13.1%) and 101 (3.8%) cases, respectively. The respective values for the second measurements were 319 (11.9%) and 72 (2.7%).

Mean arterial pressure reference range across gestation compared to the NHFA protocol

The SD of MAP determined using the NHFA protocol, irrespective of gestation, was 7.31 mmHg. Modelling indicated that MAP by the NHFA protocol exhibited a quadratic relationship with gestation, with the MAP being at its lowest in the mid-trimester. The best fit model for median MAP as a function of GA in days determined from blood pressure taken using the NHFA protocol was given by the expressions median MAP:

Log μ(GA) = 4.52355 – 0.00169796 × GA + 00000537401 × GA^2; coefficient variation σ (GA) = $e^{-3.962356}$ and skewness υ (GA) = 0.5111683 – 0.0272428 × GA

Figure 1 displays the comparison of the gestational medians determined by the average of the first measurements, the average of the second measurements and the average of the first two measurements from both arms, relative to the median obtained using the NHFA protocol.

Relative to the expected median value determined using the NHFA protocol, the first measurements taken in the left and right arms were on average 0.15SD and 0.12SD higher, respectively. The second measurements taken in the left and right arms were both lower than those obtained using the NHFA protocol as well as being 0.26SD lower than the first measurement taken in the same arm. The average of the first measurements from both arms was consistently higher than the NHFA median and the average of the second measurements was consistently lower than the NHFA median throughout pregnancy. The mean differences in Z-scores relative to the NHFA median of the average of the first and second measurements from both arms were 0.13 and -0.13, respectively. There was a constant relationship between the median MAP determined by the protocol of the average of two consecutive measurements taken in both arms and the median MAP determined using the NHFA protocol (Figure 2). The mean difference in Z-scores between the two protocols (the average of both arms vs. the NHFA protocol) was 0.0194SD.

Mean arterial pressure reference range across gestation according to the new protocol

The SD of MAP determined using the protocol of the average of two measurements in both arms, irrespective of gestation, was 7.29 mmHg. Modelling indicated that MAP by this protocol exhibited a quadratic relationship with gestation, with the MAP being at its lowest in the mid-trimester (Table 3; Figure 3). The best fit model for median MAP as a function of GA in days determined from blood pressure taken using this protocol was given by the expressions median MAP:

$$\text{Log } \mu(GA) = 4.52594 - 0.00170796 \times GA + 0.00000539256 \times GA^2\text{; coefficient variation } \sigma(GA) = e^{-3.9659578} \text{ and skewness } \upsilon(GA) = 0.5175562 - 0.0274941 \times GA$$

Relative to the expected median value determined using the new protocol, the first measurements taken in the left and right arms were on average 0.13SD and 0.10SD higher, respectively. The second measurements taken in the left and right arms were 0.14SD and 0.16SD lower than those obtained using this protocol.

Discussion

Principal findings of the study

The study has demonstrated that in establishing a protocol for MAP measurement at 10-40 weeks' gestation: (i) a single measurement in either the left or right arm deviates the most from that of the NHFA protocol, (ii) the average of the first measurements from both arms was consistently higher than the NHFA median and the average of the second measurements was consistently lower than the NHFA median throughout pregnancy, (iii) the MAP recorded according to the protocol of the average of two measurements in both arms is effectively clinically equivalent to that determined using the NHFA protocol for purposes of screening, and (iv) the MAP exhibits a quadratic relationship with gestation, with the MAP being at its lowest in the mid-trimester. Our results suggest that, at 10-40 weeks' gestation, blood pressure recordings can be obtained by a simpler protocol using the average of two measurements in both arms.

Guidelines of blood pressure measurement

There is increasing awareness of the need for specific guidelines for blood pressure measurement in pregnancy. In order to address the inter-arm difference in blood pressure, the updated guidelines from several professional bodies have advised that blood pressure should be measured in both arms and the arm with the higher blood pressure value should be chosen for subsequent blood pressure measurements throughout pregnancy (17-21). In particular, the updated NHFA guideline now recommends that blood pressure should be measured at least three times in both arms and the average of the last two recordings should be used (20). Moreover, blood pressure between both arms should vary by <10 mmHg. If the blood pressure between both arms is ≥10 mmHg, one to two additional measurements should be taken and the average of these repeated recordings should be used (18, 19). Currently, these recommendations are not implemented worldwide. They have not addressed the issue of blood pressure variability exhibited within each individual and they do not provide explicit guidance on whether blood pressure should be measured repeatedly until a necessary point of stability is achieved.

Our group has strictly followed the guideline proposed by the NHFA (6). We have previously confirmed that in first trimester screening for preeclampsia by MAP, the best performance is provided by following the NHFA protocol (9). However, a new first trimester protocol, which utilizes a simpler approach of using the average of two recordings in each arm, has been developed because, in order to achieve the necessary point of stability in blood pressure according to the NHFA protocol, it is necessary to perform a minimum of two measurements in both arms in about 50% of cases, three measurements in 25% of cases and four measurements in 25% (9). The respective figures observed in this study were 81%, 13% and 6%.

Blood pressure profile

The findings that there is a quadratic relationship between MAP and gestation, with the MAP being at its lowest in the mid-trimester (22-24), and that there is a significant inter-arm difference in blood pressure, are in agreement with previous studies (8, 25, 26). Although a large difference in blood pressure between the two arms is a common finding in certain pathological conditions, such as dissection or coarctation of the aorta, peripheral vascular disease and unilateral neurological and musculoskeletal abnormalities (27), it is also found in normal healthy individuals (28, 29). Possible explanations for an inter-arm blood pressure difference in healthy individuals include anatomical variations such as the angulation and branching of aorta, differences in vascular resistance (30), and compression of the subclavian artery that supplies the arm by surrounding muscles or structures (31). The inter-arm blood pressure difference has also been shown to be an indicator of long-term cardiovascular risk (32, 33) and mortalities (34, 35). With pregnancy being a window of opportunity for a healthcare system to screen most women of reproductive age for risk factors of cardiovascular disease, it is therefore essential to measure blood pressure in both arms as part of routine antenatal care.

Strengths and weaknesses

The strengths of the study include the measurement of blood pressure in both arms simultaneously using validated automated devices across 10-40 weeks' gestation in a large normal pregnancy population using a standardized protocol. To date, there are no reference range studies that have simultaneously measured blood pressure in both arms and repeatedly until the blood pressure becomes stable. The main limitation of the study is that due to the nature of antenatal care it was not possible to recruit more cases before 10 weeks and after 40 weeks' gestation.

Conclusion

Measurement of blood pressure remains an important component of routine antenatal care. In our study, appropriately trained doctors have used validated automated devices to measure MAP in a large population of pregnant women at 10-40 weeks' gestation. As the NHFA protocol is considered complex and time consuming, this study has established that the measurement of MAP can be obtained by a simpler protocol using the average of two measurements in both arms.

Disclosure of interests

LR, PC, DSS, KHN, LCP have no conflict of interest

Contribution to authorship

LR and PC-article conception, statistic analysis, DSS-statistical analysis

KHN and LCP-design study, collection of data, article conception

Figure legends

Figure 1. Comparisons of the expected 50th percentile of mean arterial pressure (MAP) of the first left and right average (_._._), second left and right average (_.._.._), and the average of the first and second measurements in both arms (-----), relative to the expected 50th percentile of MAP derived from the National Heart Foundation of Australia protocol (NHFA; ___).

Figure 2. Comparisons of the expected 50th percentile of mean arterial pressure (MAP) of the average of the first two measurements in the left arm (…..), right arm (_.._) and both arms (**-----**) relative to the expected 50th percentile of MAP derived from the National Heart Foundation of Australia protocol (NHFA; ___).

Figure 3. Reference range of mean arterial pressure by the protocol of the average of the first two measurements in both arms across 10-40 weeks' gestation.

Table 1. Maternal characteristics in the study population.

Maternal characteristic	**n=2,726**
Maternal age in years, median (IQR)	31.2 (26.8-35.2)
Body mass index in Kg/m^2, median (IQR)	25.7 (22.9-28.9)
Racial origin	
Caucasian, n (%)	1,213 (44.50%)
Afro-Caribbean, n (%)	957 (35.10%)
South Asian, n (%)	295 (35.11%)
East Asian, n (%)	89 (3.26%)
Mixed, n (%)	172 (6.31%)
Parity	
Nulliparous, n (%)	954 (35.0%)
Parous – no previous preeclampsia, n (%)	542 (19.88%)
Parous – previous preeclampsia, n (%)	1,230 (45.12%)
Cigarette smoker, n (%)	206 (45.12%)
Family history of preeclampsia – Mother (n, %)	67 (2.46%)
Conception	
Spontaneous, n (%)	2,664 (97.43%)
Ovulation drugs, n (%)	43 (1.54%)
In-vitro fertilization, n (%)	19 (0.70%)

Table 2. Intra- and Inter-arm blood pressure measurement differences

Blood pressure parameter	Mean Difference ± SD (mmHg)	P[#]
Systolic blood pressure		
Left first vs second	2.970 ± 5.952	<0.001
Right first vs second	3.022 ± 6.192	<0.001
Left first vs right first	-0.573 ± 6.988	<0.001
Left second vs right second	-0.521 ± 6.513	<0.001
Diastolic blood pressure		
Left first vs second	1.123 ± 3.525	<0.001
Right first vs second	1.044 ± 3.759	<0.001
Left first vs right first	0.610 ± 4.445	<0.001
Left second vs right second	0.529 ± 4.124	<0.001
Mean arterial pressure		
Left first vs second	1.781 ± 3.278	<0.001
Right first vs second	1.693 ± 3.403	<0.001
Left first vs right first	0.264 ± 4.061	<0.001
Left second vs right second	0.177 ± 3.851	0.017
Left mean vs right mean	0.211 ± 3.464	0.002

P-value considered significant if p< (0.05/13) after Bonferroni adjustment.

Table 3. Reference range of mean arterial pressure using the protocol of the average of the first two measurements taken in both arms.

Gestational Week	n	Mean arterial pressure percentile				
		3rd	10th	50th	90th	97th
≤10	88	72.3	75.8	84.2	94.1	99.3
11	326	71.9	75.4	83.6	93.5	98.7
12	354	71.6	74.9	83.2	92.9	98.2
13	373	71.2	74.6	82.7	92.5	97.7
14	149	70.9	74.2	82.3	92.0	97.2
15	101	70.7	74.0	82.0	91.6	96.9
16	68	70.4	73.7	81.7	91.3	96.6
17	52	70.3	73.5	81.4	91.0	96.3
18	45	70.1	73.3	81.2	90.8	96.1
19	32	70.0	73.2	81.0	90.6	95.9
20	32	69.9	73.1	80.9	90.5	95.8
21	28	69.9	73.0	80.8	90.4	95.8
22	107	69.9	73.0	80.7	90.4	95.8
23	229	69.9	73.0	80.7	90.4	95.9
24	38	70.0	73.0	80.8	90.5	96.0
25	30	70.1	73.1	80.8	90.6	96.1
26	60	70.2	73.3	81.0	90.8	96.4
27	40	70.4	73.4	81.1	91.0	96.6
28	34	70.6	73.6	81.3	91.3	97.0
29	41	70.8	73.9	81.6	91.6	97.4

30	46	71.1	74.1	81.9	92.0	97.8
31	30	71.4	74.5	82.2	92.4	98.3
32	54	71.8	74.8	82.6	92.9	98.8
33	34	72.2	75.2	83.1	93.4	99.5
34	53	72.6	75.7	83.5	94.0	100.1
35	61	73.1	76.1	84.1	94.6	100.9
36	67	73.6	76.7	84.6	95.3	101.7
37	46	74.1	77.2	85.3	96.1	102.5
38	46	74.7	77.8	85.9	96.9	103.5
39	40	75.4	78.5	86.7	97.8	104.5
≥40	23	76.0	79.2	87.4	98.7	105.5

Percentiles determined using the following mean, coefficient of variation and skewness

Log $\mu(GA) = 4.52594 - 0.00170796 \times GA + 0.00000539256 \times GA^2$

coefficient variation $\sigma\ (GA) = e^{-3.9659578}$

skewness $\upsilon\ (GA) = 0.5175562 - 0.0274941 \times GA$

where GA is gestational age in days

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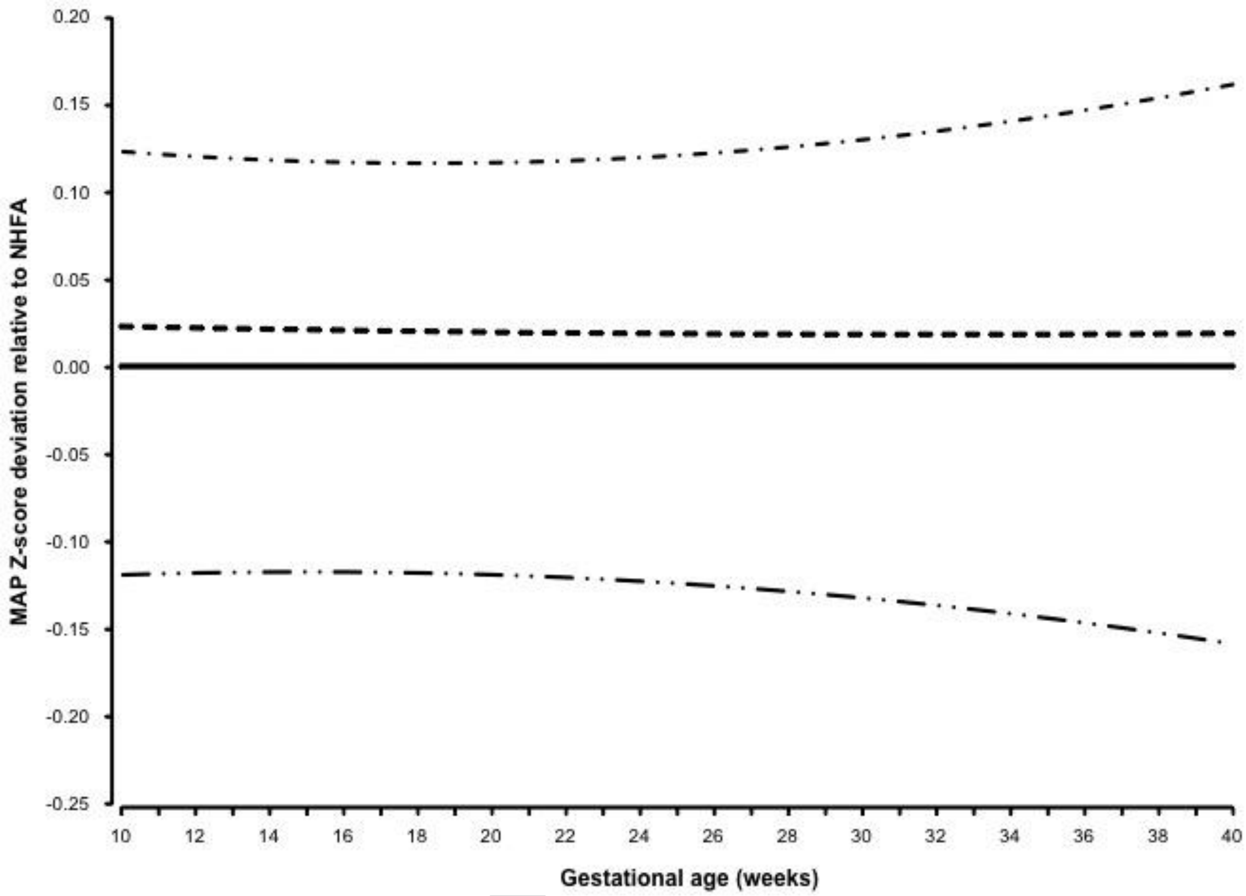
0.20
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MAP Z-score deviation relative to NHFA
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36
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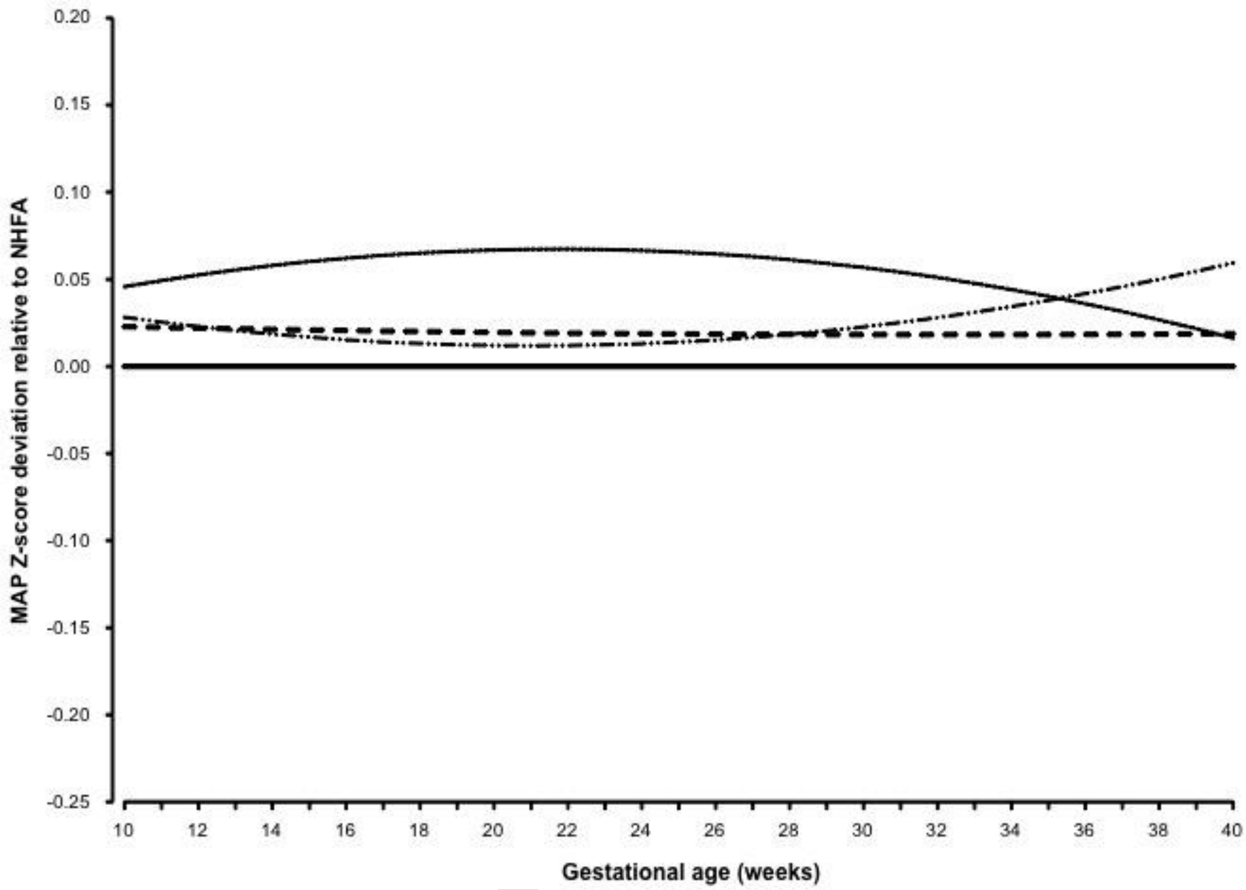
Gestational age (weeks)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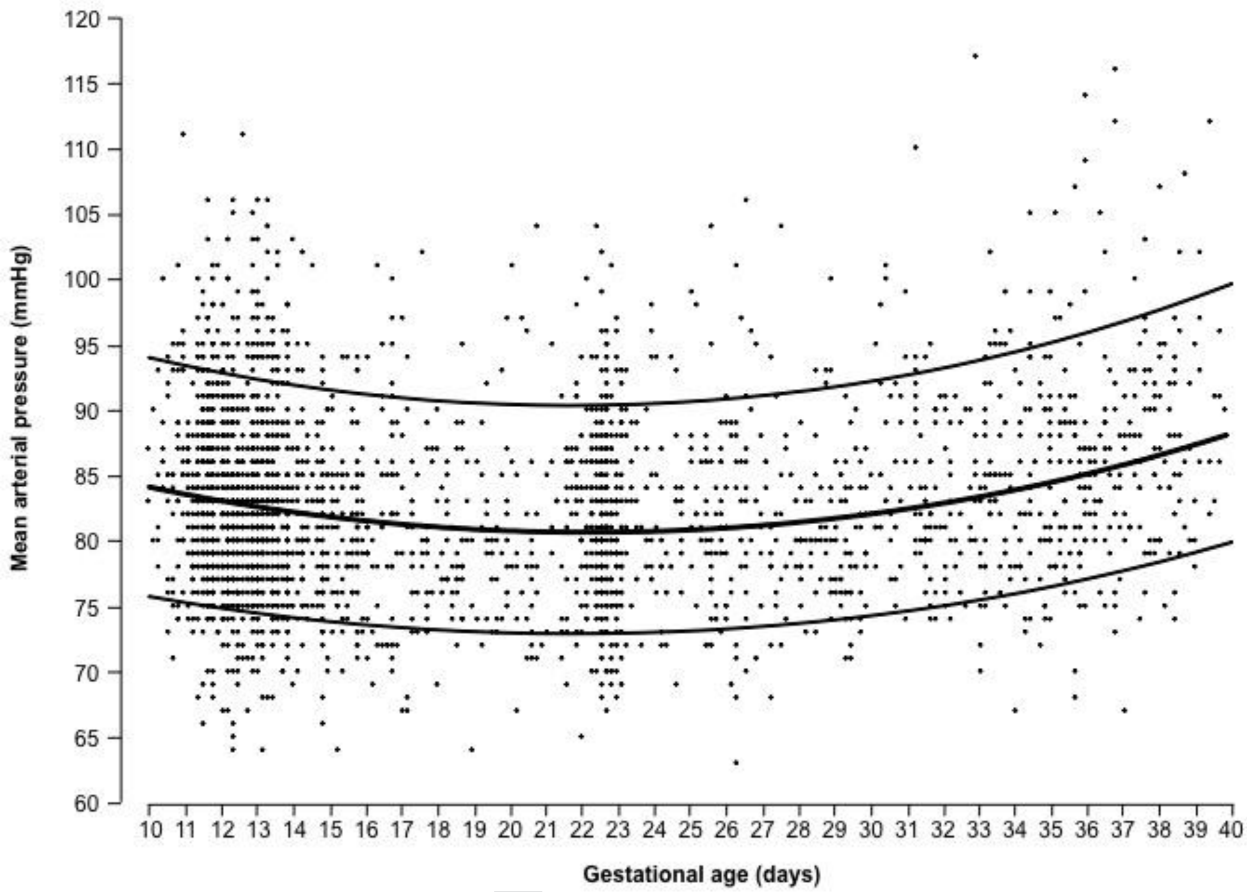
Gestational age (weeks)


Mean arterial pressure (mmHg)
120
115
110
105
100
95
90
85
80
75
70
65
60
10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Gestational age (days)

Highlight

- Hypertension is an important sign of preeclampsia, therefore accurate blood pressure monitoring during antenatal care is essential

- Due to considerable variability of blood pressure within each individual, National Heart Foundation of Australia (NHFA) has recommended to measure blood pressure until the variations between consecutive readings fall to within 10 mmHg in systolic blood pressure and 6 mmHg in diastolic blood pressure for both arms.

- There is no standardized protocol for the measurement of blood pressure throughout pregnancy.

- The mean arterial pressure (MAP) obtained from the average of two measurements in both arms is effectively clinically equivalent to that determined using the NHFA protocol.

- At 10-40 weeks' gestation, blood pressure recordings can be obtained by a simpler protocol using the average of two measurements in both arms instead of following the NHFA protocol, which is complex.