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Acute improvement in hemodynamic control after osteopathic manipulative treatment in the third trimester of pregnancy☆

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KEYWORDS
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Summary
Objectives: The physiological changes that occur during pregnancy, including increased blood volume and cardiac output, can affect hemodynamic control, most profoundly with positional changes that affect venous return to the heart. By using Osteopathic Manipulative Treatment (OMT), a body-based modality theorized to affect somatic structures related to nervous and circulatory systems, we hypothesized that OMT acutely improves both autonomic and hemodynamic control during head-up tilt and heel raise in women at 30 weeks gestation.
Design: One hundred subjects were recruited at 30 weeks gestation.
Setting: The obstetric clinics of UNTHealth in Fort Worth, TX.
Intervention: Subjects were randomized into one of three treatment groups: OMT, placebo ultrasound, or time control. Ninety subjects had complete data ($N = 25$, 31 and 34 in each group respectively).
Main outcome measures: Blood pressure and heart rate were recorded during 5 min of head-up tilt followed by 4 min of intermittent heel raising.
Results: No significant differences in blood pressure, heart rate or heart rate variability were observed between groups with tilt before or after treatment ($p > 0.36$), and heart rate variability was not different between treatment groups ($p > 0.55$). However, blood pressure increased significantly ($p = 0.02$) and heart rate decreased ($p < 0.01$) during heel raise after OMT compared to placebo or time control.

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Conclusions: These data suggest that OMT can acutely improve hemodynamic control during engagement of the skeletal muscle pump and this was most likely due to improvement of structural restrictions to venous return.

Introduction

Many changes occur in the cardiovascular system of a pregnant woman. Some of these changes begin as early as the first trimester. There is a decrease in mean arterial pressure and systemic vascular resistance coupled with an increase in circulating volume, heart rate, and cardiac output, resulting in a physiologic stress to the mother.[1] Although the basic physiology of pregnancy is generally understood, the effects of structural changes and altered autonomic function on hemodynamic control have not been systematically studied. Moreover, there have been no studies on the effect of Osteopathic Manipulative Treatment (OMT) on autonomic function or hemodynamic control during pregnancy.

Stress to the human system is manifested commonly as an increase in sympathetic activity and a shift of autonomic balance to a more sympathetic dominant state, which could increase the risk of adverse long-term health conditions. Similar autonomic changes, including increased sympathetic activity, commonly occur in pregnancy. In some patients, other factors may combine with an increased sympathetic tone, leading to pregnancy-induced hypertension[2] and preeclampsia.[3] In addition, enhanced maternal stress has been linked to preterm labor.[4,5] It is unknown whether these changes in autonomic function can also manifest as altered hemodynamic control. Limited literature suggests that hemodynamic control does change throughout the course of pregnancy.[6–11] The control of blood pressure in the third trimester appears to be somewhat impaired in many women as evidenced by a greater tendency for hypotension during a Valsalva maneuver after epidural block of the sympathetic-mediated vasoconstrictor responses.[6] The hemodynamic response to standing has been studied more extensively.[7–11] Although not a prevalent problem, orthostatic hypotension during pregnancy may be a concern in part because of these reduced compensatory responses as well as structural limitations of venous return imparted by the size and position of the uterus. In addition, the reflex sympathetic response needed to maintain blood pressure with orthostatic challenge may add to the overall increased maternal stress, and lead to some of the outcomes described above.

OMT may affect hemodynamic control in pregnancy by two theorized mechanisms: (1) removing structural restrictions on the circulation, and (2) direct effects on the autonomic nervous system. Improvement of pelvic mobility and structural restrictions by OMT can theoretically impact hemodynamic control, particularly when the skeletal muscle pump is engaged. During pregnancy, restrictions within the pelvic girdle can be significant due to the presence of the large uterus during the third trimester of pregnancy. The anterior rotation to the pelvis, combined with the ball-valve effect of the enlarged uterus in the pelvis, can compress lymphatic and venous vessels and impede fluid return to central circulation.[12] This impedance may be exacerbated in the presence of somatic dysfunction in the pelvis. In addition, OMT is theorized to affect autonomic tone and control in part by altering the tone of connective tissues and musculoskeletal structures around nerves along the spinal column, thus reducing any pressure on the nerves themselves, and optimizing the function of the system. If indeed OMT enhances the reflex responses to a stressor, then it would be expected that hemodynamic control would be optimized and the net stress on the system would be reduced. In this study, we hypothesized that OMT improves the hemodynamic control during an orthostatic challenge head-up tilt when engagement of the skeletal muscle pump occurs and improves autonomic function by enhancing heart rate variability and decreasing resting heart rate.

Methods

Subjects

All subjects were enrolled in a larger clinical trial on OMT and low back pain in pregnancy (the PROMOTE study). As part of that study, they were approached for their interest in participating in these additional measures. One hundred volunteers (age 18–34) at the 30th week of pregnancy were recruited for this study. The primary exclusion criteria included: (1) self-reported history of syncopal episodes, (2) patients deemed to be high risk by the obstetrical care provider (including but not limited to: abruptio placenta, placenta previa, pre-eclampsia, eclampsia, pregnancy-induced hypertension, vaginal bleeding, gestational diabetes), and (3) patients with a lower extremity injury sprain or fracture after screening for inclusion/exclusion criteria, volunteers were accepted into the study and provided written informed consent to participate. The protocol was approved by the local Institutional Review Board at the University of North Texas Health Science Center, and is registered at www.clinicaltrials.gov (NCT00426244). All subjects were familiarized with the procedures prior to the experimental day.

Upon arrival to the laboratory on the experimental day, the subject was non-invasively instrumented for measurements of heart rate (standard limb-lead electrocardiography) and beat-to-beat arterial pressure using a Finapres plethysmographic monitor (Finapres Medical Systems, Amsterdam, Netherlands). The subject was positioned in the left lateral recumbent position and in a slight head-up position (10° head-up tilt) on a circular-frame bed (Stryker Corporation, Kalamazoo, Michigan) that allows for tilting to specific angles. After a period of 20 min of quiet rest, baseline data were collected. These included baseline heart rate, blood pressure, and assessment of heart rate variability as determined from a 5 min period of continuous heart rate measurement during quiet uncontrolled breathing. All measures were recorded on a computerized data acquisition system (WINDAQ®, Akron, OH) for analysis.

After the baseline period, the patient was tilted to 60° head-up tilt for 5 min followed by 4 min of intermittent calf muscle tension (heel raises) in a cadence of 2 s up and 3 s down. The heel raise was performed such that the heel rose to approximately 1 in. of the base of the bed. Following the heel raises, the subject recovered for an additional 5 min The 5 min period of tilting was adequate to obtain a clear steady-state period and obtain sufficient data to estimate heart rate variability measures. Likewise, the 4 min period of heel raising allowed for steady-state measures to be obtained for all variables and was tolerable for all subjects. No adverse reactions were experienced during any of the procedures.

Treatments

Subjects were randomized into one of three treatment groups: OMT, placebo ultrasound (PLAC), or time control (TC). Each OMT group participant received a 20—30 min standardized set of hands-on treatments to her head, neck, abdominal diaphragm, back, pelvis, sacrum, and pelvic diaphragm. Techniques used included soft tissue, articulatory, myofascial release, and muscle energy. The techniques are commonly taught at Osteopathic medical schools, and are described in detail at http://www.hsc.unt.edu/Sites/OsteopathicManipulativeMedicine/index.cfm?pageName=Research Placebo ultrasound group participants received a 20 min sub-therapeutic ultrasound systematically administered over the same major body regions as addressed by the OMT. Both the OMT and PLAC treatments were performed with the subjects fully clothed. Subjects in the time control group received no treatment, but instead had 20 min of quiet time between measurements.

Measurements

Arterial pressure was measured non-invasively (photoplethysmography), by use of a Finometer monitor placed around the middle finger. Heart rate variability was estimated using both time-domain (SDNN) and frequency-domain (power spectra) measures by obtaining beat-to-beat values of R—R interval which were recorded digitally into a data acquisition system (WINDAQ®, Akron, OH). The data were then linearly interpolated and re-sampled at 2 Hz to create an equidistant time series for spectral analysis. The time series was detrended with a 3rd order polynomial fit and divided into 256 point epochs. Each epoch was Hanning-window filtered and Fast Fourier transforms were implemented to generate autospectra for each variable. These data analyses sequence conform to the recommendations of the international consensus panel for the assessment of cardiovascular variability.[13] High frequency (HF) power of RR interval (0.2—0.4 Hz), similar to normal respiratory rhythm, was used as an index of parasympathetic control as supported by a number of studies in dogs and humans[14] utilizing parasympathetic blockade and nerve stimulation. The ratio of low to high frequency power of R—R interval is widely recognized to be an index of the balance between the sympathetic and parasympathetic systems and was used for this purpose.[15,16]

Statistical analyses

Baseline data prior to the first physiologic interventions along with pretreatment responses to the head-up tilt and heel raise interventions were compared across treatment groups and time (pre-post treatment) with a two-way analysis of variance (ANOVA). For significant main effects, a group × time interaction effect was performed *post hoc* to determine specific differences. For the tilt and heel raise response data, a change variable was estimated to use for illustration in the figures. An (lower case Greek alpha) level of 0.05 was set for significance.

Results

Baseline data comparisons

Complete data sets were obtained in 90 subjects (25 OMT, 31 placebo and 34 time control). The difference in group size is an effect of the random agreement of subjects to participate. The loss of 10 subjects from the total enrolled 100 subjects was due to technical issues that arose with the instrumentation, and thus prevented the acquisition of complete data sets. The demographic distribution of the subjects within each group is summarized in Table 1. CONSORT diagram showing subject flow through the study is Fig. 1.

There were no significant differences in baseline blood pressure, heart rate or indices of heart rate variability between any groups as shown in Table 2 ($p > 0.05$). In addition, no significant differences between the pre- and post-treatment baseline periods were observed for any of the groups ($p > 0.05$).

Tilt stimulus (treatment effects)

The responses to head up tilt before and after treatment are summarized in Fig. 2. Illustrated in this figure are the group mean changes from baseline to steady-state of the head-up tilt position for mean arterial pressure (ΔMAP) and heart rate (ΔHR). Small increases in MAP were observed during tilt for all conditions pre- and post-treatment ($p < 0.05$), but no significant differences between treatment groups, within treatment groups or pre-post treatment were observed ($p > 0.05$). Similarly, heart rate was increased significantly during all tilt conditions ($p < 0.01$), but no differences between treatment groups or between pre- to post-treatment ($p > 0.05$) were observed. The heart rate variability responses were not significantly difference between groups for either the initial response to tilt or between pre-post treatment responses to tilt as seen in Fig. 3 ($p > 0.05$). There were no group versus treatment time (pre-post) significant interactions ($p > 0.05$) (Fig. 4).

Heel raise condition (treatment effects)

The change in the responses from the tilt steady-state to the heel raise steady-state is shown for all treatment groups both pre- and post-treatment in Fig. 3. During heel raise (combined with tilt), MAP increased slightly (1—8 mmHg

Table 1 Demographic table.

	OMT (%)	US (%)	SC (%)
N	30	34	36
Race			
Black/African American	9 (34.6)	11 (39.3)	8 (29.6)
White	13 (50)	15 (53.6)	15 (55.6)
Other	4 (15.4)	2 (7.1)	4 (14.8)
Ethnicity			
Hispanic/Latino	9 (30.0)	8 (23.5)	14 (41.2)
Non-Hispanic/non-Latino	21 (70.0)	26 (76.5)	20 (58.8)
Primigravida	7 (26.9)	8 (27.6)	10 (31.3)
Multigravida	19 (73.1)	21 (72.4)	22 (66.8)
Median BMI	28.38	31.28	31.82
Mean BMI	29.74	32.18	32.96
Median age	22.29	24.22	22.00
Mean age	22.53	23.73	23.14

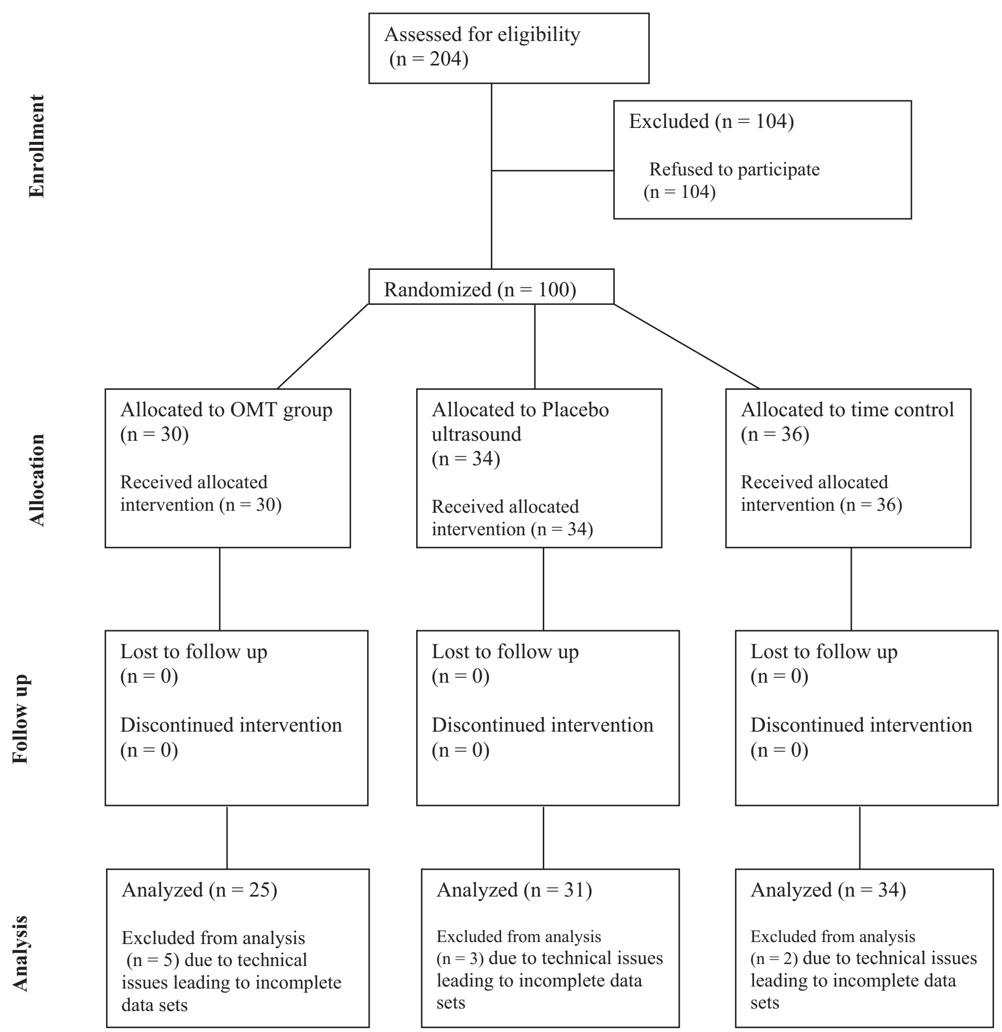

Figure 1 CONSORT diagram showing the flow of participants through each stage of the study.

Table 2 Baseline data for each group.

	Time control	Sham	OMT
Heart rate (b/min)	82 ± 3	78 ± 3	83 ± 2
Blood pressure (mmHg)	117 ± 4/72 ± 3	123 ± 5/69 + 3	116 ± 3/74 ± 2
Heart rate variability indices			
SDNN (ms)	124 ± 17	116 ± 13	112 ± 22
HF power (ms^2/Hz)	32 ± 9	44 ± 10	41 ± 8
LF power (ms^2/Hz)	168 ± 35	202 ± 50	237 ± 44

No significant difference among groups was found for baseline heart rate, blood pressure or indices of heart rate variability ($p > 0.05$).

among groups) and this was associated with a modest decrease in HR (3—10 bpm) in all groups. No significant difference was observed from pre- to post-treatment for either the time control or placebo groups ($p > 0.05$). However, a main effect for treatment time was observed for both the change in MAP and HR ($p < 0.05$), and a significant group versus treatment time interaction was observed that demonstrated a significantly greater increase in ΔMAP and decrease in ΔHR during the OMT treatment condition when compared to time control and placebo ($p < 0.05$). Finally, no significant differences in the heart rate variability responses were observed between groups or between the pre-post differences between groups as shown in Fig. 5 ($p > 0.05$).

Discussion

This study is the first to address the effects of osteopathic manipulative treatment (OMT) on the autonomic and hemodynamic control in healthy women in their third trimester of pregnancy. The primary finding was that OMT can improve the hemodynamic response associated with engagement of the skeletal muscle pump via heel raising and this was associated with an increased MAP and associated decreased heart rate during the heel raise maneuver. There was no effect of OMT on basal measures of heart rate variability or on the response to head-up tilt alone; thus it appears that the OMT benefit observed during heel raising was due to improvement in the support of venous return during the heel raising maneuver. These findings suggest that OMT directed to relieve structural restrictions can provide enhanced hemodynamic regulation as discussed below, and this appears to be independent of any changes in autonomic control of heart rate.

Pregnancy is accompanied by significant changes in the hemodynamic state of a woman, autonomic balance and function, and the ability to respond to physiological and

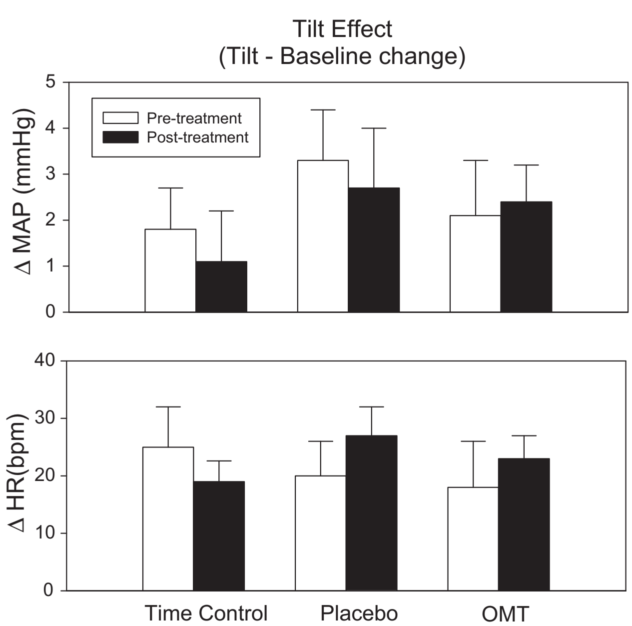

Figure 2 The effect of tilt (as change from baseline to steady-state of head-up tilt) for mean arterial pressure (ΔMAP) and heart rate (ΔHR) are illustrated for pre-treatment (open bars) and post-treatment (solid bars) for each treatment group. No significant mean effects for group or pre-post treatment and there was not a significant group-treatment interaction observed ($p > 0.05$).

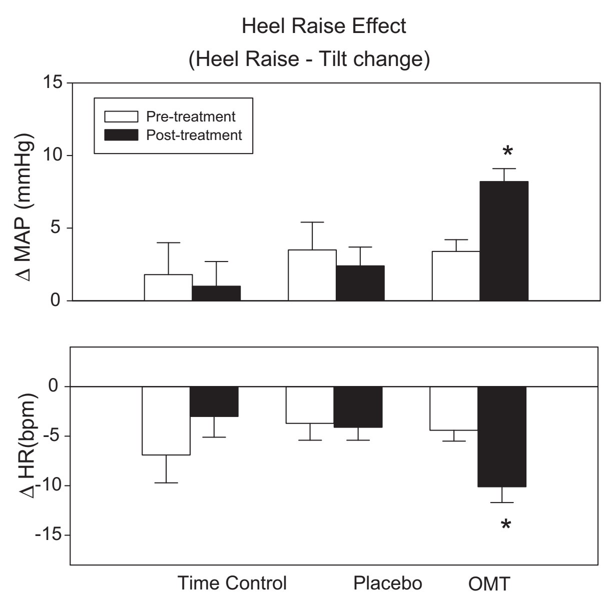

Figure 3 The effect of heel raising (as change from steady-state tilt to steady-state of heel raising) for mean arterial pressure (ΔMAP) and heart rate (ΔHR) are illustrated before (open bars) and after (solid bars) treatment for each treatment group. A significant group-treatment interaction was observed for both ΔMAP ($p < 0.01$) and ΔHR ($p < 0.05$) and these differences were specific to the pre-post treatment responses with OMT.

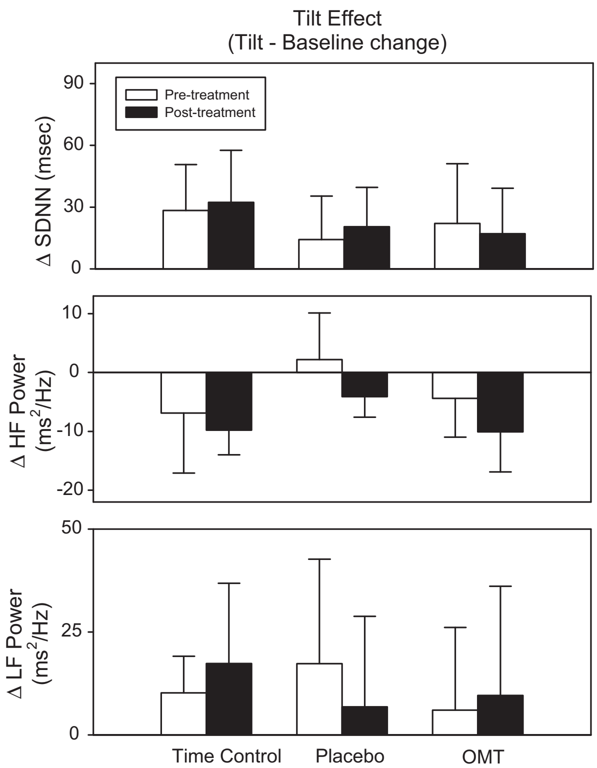

Figure 4 The effect of tilt (as change from baseline to steady-state of head-up tilt) for time-domain (ΔSDNN) and frequency domain (ΔHF power and ΔLF power) heart rate variability measures are illustrated. Data are illustrated for pre-treatment (open bars) and post-treatment (solid bars) for each treatment group. No significant mean effects for group or pre-post treatment and there was not a significant group-treatment interaction observed ($p > 0.05$).

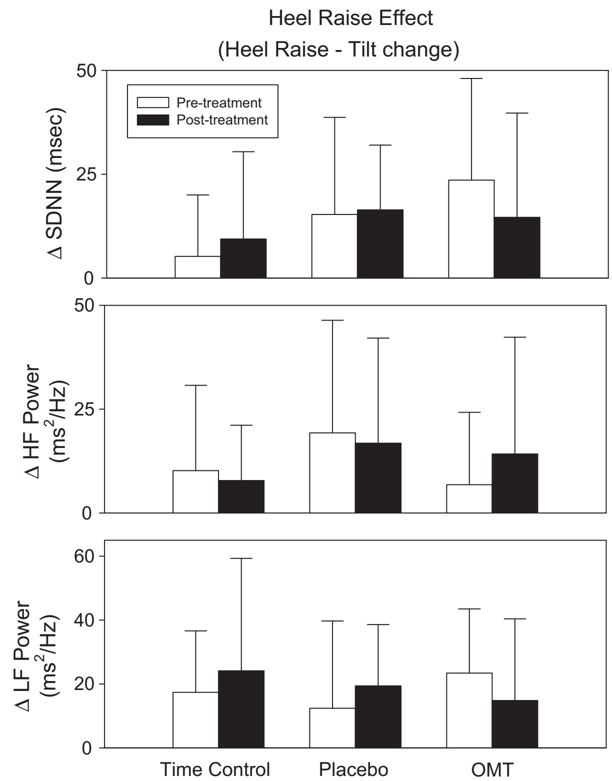

Figure 5 The effect of heel raising (as change from steady-state tilt to steady-state of heel raising) for time-domain (ΔSDNN) and frequency domain (ΔHF power and ΔLF power) heart rate variability measures are illustrated. Data are illustrated for pre-treatment (open bars) and post-treatment (solid bars) for each treatment group. No significant mean effects for group or pre-post treatment and there was not a significant group-treatment interaction observed ($p > 0.05$).

anatomical stressors. The normal changes in hemodynamic and autonomic function are significant alone in pregnancy, and complications of maladaptive cardiovascular control are a serious problem when it occurs in pregnant women and may create a further risk for the patient.[17–20] Hemodynamic changes accompanying pregnancy include an impairment of neural control of blood pressure as evidenced by reduced pressor responses to Valsalva's maneuver and exercise.[6,21–24] The changes in heart rate variability suggest that pregnancy is accompanied by a generalized blunting of vagal control as evidenced by reduced time-domain measures reduced high frequency power of the power spectrum of heart rate.[22,25,26] Collectively, these data suggest that both autonomic and hemodynamic control may be blunted in pregnancy, and thereby may represent a condition in which a pregnant woman may not respond as effectively to physiological stressors. In this study, we address potential benefits of OMT on hemodynamic and autonomic regulation during the third trimester of pregnancy in the setting of an orthostatic stress.

Effects on the response to tilt

A consistent response to the 60° head-up tilt position was adequate support of arterial pressure and a modest increase in heart rate, albeit with considerable variability among patients. Nevertheless, these data demonstrate good hemodynamic support independent of the treatment groups, as the normal response to tilt often involves a modest decrease in arterial pressure. This is likely due in part to the typical increase in cardiac output and expanded blood volume which accompanies pregnancy.[27–29] It has been shown that the response to tilt in earlier states of pregnancy can be associated with a modest blunting of the responses, and syncopal symptoms were reported to be increased particularly in the second trimester of pregnancy.[7,30] This appears to be due in part to a reduction in cardiac output.[7,9] Perhaps more importantly is a reduction in the reflex autonomic responses leading to compensatory tachycardia and vasoconstriction.[7,11] The heart rate responses also tend to be reduced during an orthostatic challenge,[11,30,31] however, other studies suggest that the heart rate response can be unchanged or somewhat enhanced.[6,9,10,32] So the responses appear to be variable in healthy women. In addition, there is limited data to suggest that in mid- to late pregnancy the catecholamine response to orthostasis is reduced.[11,33] In this study a modest head-up tilt of 60° was used for 5 min and there were no significant differences in the response to tilt with any of the treatment conditions. The lack of the OMT effect suggests that there was not a direct effect of

OMT on the normal hemodynamic effects of gravity associated with the upright position or on the basal autonomic state and its control. We have recently shown that certain OMT techniques can enhance vagal control of heart rate.[34] In this study the lack of direct effect on autonomic function was also observed as the baseline indices of heart rate variability were unchanged after OMT. These findings suggest that either there was no direct effect, or that the process of moving from the treatment room into the experimental room reversed any subtle changes in autonomic balance that may have accompanied the immediate OMT treatment.

Effects on the response to heel raising

There have been no studies on the effectiveness of the muscle pump in regulating venous return in pregnancy. This study was the first to assess the effectiveness of OMT on the heel raising effects on hemodynamic regulation in the third trimester of pregnancy, and the most significant finding in this study was an improvement in the blood pressure response to heel raising. The normal response to engagement of the skeletal muscle pump is an increase in venous return which in turn results in increased cardiac output and blood pressure.[35–37] This was observed in each of the pretreatment conditions; however, after treatment, only the OMT produced an alteration in this response. The OMT lead to an enhanced blood pressure increase during the heel raising maneuver which was accompanied by a reduction in heart rate. The response was associated with an enhanced systolic blood pressure response as well; this suggests that cardiac output was improved rather than the vasoconstrictor response, and that this was mediated by a substantial increase in stroke volume. This is also consistent with an enhanced venous return. Therefore, it follows that the primary improvement was mediated by an improvement in the venous return during the heel raising maneuver and that the decreased heart rate was secondary to the improved arterial pressure support during the heel raising maneuver. The latter would be expected due to a baroreflex-mediated response to the improved blood pressure maintenance during the heel raising.

Application of osteopathic reasoning supports OMT enhancement of venous return. During pregnancy, the weight and size of the uterus compresses on venous and lymphatic vessels, especially in the pelvis, creating a ball-valve effect, which increases the pooling of blood in the lower extremities. OMT is theorized to improve peripheral circulation by treating the fascial planes through which the blood vessels travel. These fascial planes also surround the muscles, and when there is dysfunction in a region of the body, the fascia becomes strained. This strain may be very small, but significant enough to impede blood flow in blood vessels, particularly in low-pressure vessels, and therefore contribute to restricted venous drainage and tissue congestion, resulting in greater pooling. Releasing this fascial strain can increase venous return to central circulation.[38]

Strengths and limitations

Although these data suggest that OMT can have some acute benefits for hemodynamic regulation in pregnant women, it does not address the duration of any benefits relating to these effects. Further research is needed to evaluate the potential benefits on pregnancy-related hemodynamic conditions such as lower leg edema, varicose veins, and hemorrhoids. The duration of effect and frequency of treatment required to elicit significant reduction in these pregnancy-related conditions is needed. This study was part of a larger clinical trial of patient outcomes that involved 9 weeks of OMT on a weekly or biweekly basis. Report of these findings is forthcoming and may provide some further insight into the longer-term benefits of OMT during pregnancy.

The data in this study did not demonstrate a positive effect on autonomic regulation. The assessment of autonomic function involved indirect measures and thus may not have provided the sensitivity to determine a clear effect on autonomic function. However, the primary finding was an effect on blood pressure and heart rate associated with the heel raise maneuver which suggests that cardiovascular stress is diminished due to enhanced hemodynamic control after OMT.

Clinical significance and conclusion

The hemodynamic effects of OMT described in this paper may have significant clinical implications for pregnant women. There is growing evidence that dysfunction of maternal venous hemodynamics is part of the pathophysiology of preeclampsia. The effects of abnormal cardiovascular adaptation to pregnancy including decreased venous capacitance[39] and distensibility[40] and a decreased cardiac output[41] may be blunted by OMT during pregnancy.

As noted above, decreased lower extremity blood pooling could impact the incidence or severity of common complaints in pregnancy such as lower extremity edema, varicose veins, and hemorrhoids. Few medications or procedures are approved to effectively treat these conditions in pregnancy due to potential risk to the fetus. OMT is a safe, non-pharmacologic intervention that may provide unique benefits. Additionally, if venous return and blood pressure control are enhanced, pregnant women may experience less cardiovascular stress during many daily activities. Less cardiovascular stress would be expected to lead to a reduced overall sympathetic tone, and therefore also reduced incidence of associated potential complications of increased sympathetic activity. Any intervention which can positively impact the incidence of pregnancy complications is of great importance to healthcare. If efficacious in decreasing pregnancy complications, OMT could be advocated as a low cost, low-tech adjunctive treatment for decreasing pregnancy complications in places where high technology and high cost interventions are unavailable.

Conflict of interest statement

No conflict of interest exists for the authors of this manuscript.

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References

1. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv* 1994;**49**(12 Suppl.):S1—14.
2. Greenwood JP, Stoker JB, Walker JJ, Mary DA. Sympathetic nerve discharge in normal pregnancy and pregnancy-induced hypertension. *J Hypertens* 1998;**16**(5):617—24.
3. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia — a state of sympathetic overactivity. *New Engl J Med* 1996;**335**(20):1480—5.
4. Hobel C, Culhane J. Role of psychosocial and nutritional stress on poor pregnancy outcome. *J Nutr* 2003;**133**(5 Suppl. 2):1709S—17S.
5. McLean M, Smith R. Corticotrophin-releasing hormone and human parturition. *Reproduction* 2001;**121**(4):493—501.
6. Castren O, Saarikoski S, Siimes A. Vascular reactivity in normal pregnancy and in pregnancies complicated by hypertension. *Int J Gynecol Obstet* 1973;**11**:236—46.
7. Pyorala T. Cardiovascular response to the upright position during pregnancy. *Acta Obstet Gynecol Scand* 1966;**45**(Suppl. 5):1—116.
8. Easterling TR, Schmucker BC, Benedetti TJ. The hemodynamic effects of orthostatic stress during pregnancy. *Obstet Gynecol* 1988;**72**(4):550—2.
9. Clark SL, Cotton DB, Pivarnik JM, et al. Position change and central hemodynamic profile during normal third-trimester pregnancy and post partum. *Am J Obstet Gynecol* 1991;**164**(3):883—7.
10. Droste S, Sorensen T, Price T, et al. Maternal and fetal hemodynamic effects of autologous blood donation during pregnancy. *Am J Obstet Gynecol* 1992;**167**(1):89—93.
11. Nisell H, Hjemdahl P, Linde B, Lunell NO. Sympatho-adrenal and cardiovascular reactivity in pregnancy-induced hypertension. I. Responses to isometric exercise and a cold pressor test. *Br J Obstet Gynaecol* 1985;**92**(7):722—31.
12. Stone C. *Visceral and obstetric osteopathy*. Edinburgh; New York: Churchill Livingston/Elsevier; 2007. Projected Date: 0701.
13. Heart rate variability: standards of measurement, physiological interpretation and clinical, use., task force of the European society of cardiology and the north American society of pacing and, electrophysiology. *Circulation* 1996;**93**(5):1043—65.
14. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension* 1995;**25**(6):1276—86.
15. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986;**59**(2):178—93.
16. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: A tool to explore neural regulatory mechanisms. *Br Heart J* 1994;**71**(1):1—2.
17. Lewinsky RM, Riskin-Mashiah S. Autonomic imbalance in preeclampsia: evidence for increased sympathetic tone in response to the supine-pressor test. *Obstet Gynecol* 1998;**91**(6):935—9.
18. Kimpinski K, Iodice V, Low PA. Postural tachycardia syndrome associated with peripartum cardiomyopathy. *Auton Neurosci* 2010;**155**(1—2):130—1.
19. Metsaars WP, Ganzevoort W, Karemaker JM, Rang S, Wolf H. Increased sympathetic activity present in early hypertensive pregnancy is not lowered by plasma volume expansion. *Hypertens Pregnancy* 2006;**25**(3):143—57.
20. Pal GK, Shyma P, Habeebullah S, Shyjus P, Pal P. Spectral analysis of heart rate variability for early prediction of pregnancy-induced hypertension. *Clin Exp Hypertens* 2009;**31**(4):330—41.
21. Eckberg DL. Parasympathetic cardiovascular control in human disease: |a critical review of methods and results. *Am J Physiol* 1980;**239**(5):H581—93.
22. Ekholm EM, Piha SJ, Antila KJ, Erkkola RU. Cardiovascular autonomic reflexes in mid-pregnancy. *Br J Obstet Gynaecol* 1993;**100**(2):177—82.
23. Airaksinen KE, Hartikainen JE, Niemela MJ, Huikuri HV, Mussalo HM, Tahvanainen KU. Valsalva manoeuvre in the assessment of baroreflex sensitivity in patients with coronary artery disease. *Eur Heart J* 1993;**14**(11):1519—23.
24. Matthews KA, Rodin J. Pregnancy alters blood pressure responses to psychological and physical challenge. *Psychophysiology* 1992;**29**(2):232—40.
25. Ekholm EM, Erkkola RU, Piha SJ, Jalonen JO, Metsala TH, Antila KJ. Changes in autonomic cardiovascular control in mid-pregnancy. *Clin Physiol* 1992;**12**(5):527—36.
26. Van Hoogenhuyze D, Weinstein N, Martin GJ, et al. Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1991;**68**(17):1668—76.
27. Smith ML, Raven PB. Cardiovascular responses to lower body negative pressure in endurance and static exercise-trained men. *Med Sci Sports Exerc* 1986;**18**(5):545—50.
28. Carter 3rd R, Watenpaugh DE, Wasmund WL, Wasmund SL, Smith ML. Muscle pump and central command during recovery from exercise in humans. *J Appl Physiol* 1999;**87**(4):1463—9.
29. Ogoh S, Volianitis S, Nissen P, Wray DW, Secher NH, Raven PB. Carotid baroreflex responsiveness to head-up tilt-induced central hypovolaemia: effect of aerobic fitness. *J Physiol* 2003;**551**(Pt 2):601—8, http://dx.doi.org/10.1113/jphysiol.2003.
30. Ihrman K. A clinical and physiological study of pregnancy in a material from northern Sweden. VI. The arterial blood pressures at rest and in orthostatic test during and after pregnancy. *Acta Soc Med Ups* 1960;**65**:314—25.
31. Widlund GG. The cardio-pulmonal function during pregnancy a clinical-experimental study with particular respect to ventilation and oxygen consumption among normal cases in rest and after work tests. *Acta Obstet Gynecol Scand* 1945;**25**(s1):7—125.
32. Ekholm EM, Piha SJ, Erkkola RU, Antila KJ. Autonomic cardiovascular reflexes in pregnancy. A longitudinal study. *Clin Auton Res* 1994;**4**(4):161—5.
33. Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. *Am J Obstet Gynecol* 1986;**154**(1):80—4.
34. Giles PD, Hensel KH, Pacchia CF, Smith ML. Sub-occipital decompression enhances heart rate variability indices of cardiac control in healthy subjects. *J Altern Complement Med* 2013;**19**(2):92—6.
35. Laughlin MH. Skeletal muscle blood flow capacity: role of muscle pump in exercise hyperemia. *Am J Physiol* 1987;**253**(5 Pt. 2):H993—1004.
36. Shepherd JT. *Physiology of the circulation in human limbs in health and disease*. Philadelphia: Saunders; 1963.
37. Stegall H. Muscle pumping in the dependent leg. *Circ Res* 1966;**19**(1):180.

38. Kuchera ML, Kuchera WA. *Osteopathic considerations in systemic dysfunction*. Columbus, OH: Greyden Press; 1994.
39. Goodlin RC. Venous reactivity and pregnancy abnormalities. *Acta Obstet Gynecol Scand* 1986;**65**(4):345—8.
40. Sakai K, Imaizumi T, Maeda H, Nagata H, Tsukimori K, Takeshita A, Nakano H. Venous distensibility during pregnancy. Comparisons between normal pregnancy and preeclampsia. *Hypertension* 1994;**24**(4):461—6.
41. Rang S, van Montfrans GA, Wolf H. Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol* 2008;**198**(5):519.e1—9.