ABSTRACT

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Introduction

During pregnancy, a woman's body is challenged by significant physiological and biomechanical changes which can adversely affect normal function, mobility and quality of life. These changes may also contribute to co-morbid conditions accompanying pregnancy. Osteopathic manipulative medicine (OMM) is theorized to facilitate the body's adjustment to the physiological and biomechanical demands of pregnancy and improve the outcomes of pregnancy, labor and delivery. Thus, this dissertation research was designed to examine the possible effects of an acute regimen of OMM on the autonomic and hemodynamic control mechanisms and gait and mobility function in women during the third trimester of pregnancy.

Methods: Two studies were performed with 60 women at the 30^{th} week of pregnancy. Study 1: The hemodynamic and autonomic (heart rate variability) responses to head-up tilt with and without engagement of the muscle pump via toe raising were assessed before and after a regimen of either randomly assigned OMM, sub-therapeutic placebo ultrasound, or a time-control. Study 2: Assessment of a cadre of gait parameters and functions was performed before and after application of the same randomized treatment regimens.

Results: In Study 1, the response to tilt was not affected by OMM or placebo ultrasound, however, the systolic blood pressure response to toe raising was increased after OMM and was

accompanied by a lower heart rate and enhanced vagal control of heart rate. In study 2, there were no statistically significant differences between groups at baseline. In addition, there were no statistically significant differences between pre-and post-treatment values for any spatiotemporal gait parameters. However, improvements in stride width and base of support trended toward significance.

Conclusions: These data suggest that OMM improved hemodynamic control during engaging of the skeletal muscle pump that was most likely due to improvement of structural impediments to venous return. The gait data fail to elucidate a significant effect of OMM on gait parameters during the third trimester of pregnancy.

OSTEOPATHIC MANIPULATIVE MEDICINE IN PREGNANCY: ACUTE PHYSIOLOGICAL AND BIOMECHANICAL EFFECTS

DISSERTATION

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DOCTOR OF PHILOSOPHY

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"My grace is sufficient for you, for my power is made perfect in weakness…For when I am weak, then I am strong."

2 Corinthians 12:9-10

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CHAPTER 1

INTRODUCTION

The osteopathic philosophy of health is built on a model in which basic body functions are coordinated and integrated by the musculoskeletal system. Osteopathic medical students are taught to consider all of these aspects in assessing, diagnosing, and treating the individual patient. As a treatment method that reflects the osteopathic philosophy, osteopathic manipulative medicine (OMM) is a body-based modality in which the patient is evaluated and treated as a whole to improve physiologic functioning and remove impediments to optimal health and functioning.

During pregnancy, a woman's body is challenged by significant and extensive physiological and biomechanical changes. Some physiological changes, such as increased fluid volume and sympathetic tone, may lead to consequences such as edema, preterm labor, and meconium-staining of the amniotic fluid. The biomechanical state of the woman's body is also drastically affected; as the fetus grows and the uterus expands, the center of gravity shifts forward, rotating the pelvis anteriorly and increasing the lordosis of the low back, and may also affect the motion of the hips and legs. These postural changes also have consequences such as low back pain, decreased functional status, and altered gait. Both these physiologic and biomechanical consequences can have a potential long-term impact on the health of the mother and child.

OMM is theorized to facilitate the body's adjustment to the physiological and biomechanical demands of pregnancy and improve the outcomes of pregnancy, labor and delivery. Clinical case studies report reduced back pain, shorter labor, and fewer incidences of peripartum complications in patients who receive prenatal OMM. However, to date we have found no published systematic investigations of the efficacy of OMM in managing the adverse effects that pregnancy has on a woman's musculoskeletal system, nor have we found any published systematic studies to investigate the theoretical mechanisms of action of OMM in managing pain, edema, or gait in pregnant patients.

Thus, the overall question that guides this research project is: to what extent and by what physiological mechanisms does Osteopathic Manipulative Medicine (OMM) affect selected conditions related to pregnancy, labor and delivery? Based on the principles and theories of OMM and the limited previous studies, I am directing an ongoing clinical trial in which I hypothesize that OMM improves clinical outcomes including low back pain, functional status, incidence of meconium-stained amniotic fluid, and complications of labor and delivery. The two studies of this dissertation are substudies of this clinical trial and were designed to determine1) the potential benefits of OMM on hemodynamic and autonomic control and 2) the biomechanical function related to gait in the third trimester of pregnancy.

The Clinical Trial is an ongoing clinical study of the effects of OMM on selected outcomes in the third trimester of pregnancy. This parent study overarches and provides a framework for the two studies described in this dissertation:

Study One Hypothesis: OMM affects physiological measurements related to improved autonomic and peripheral hemodynamic regulation as assessed by the response to an orthostatic challenge.

Aim: To examine how OMM acutely affects autonomic balance during pregnancy,

Aim: To determine how OMM impacts lower extremity hemodynamic regulation during engagement of the skeletal muscle pump in the third trimester of pregnancy.

Study Two Hypothesis: OMM improves function related to gait in the third trimester of pregnancy.

For this dissertation, two studies are proposed to test the above hypotheses: Study One collects data from a sub-group of the Clinical Trial participants, and Study Two will assess the biomechanics from the same sub-group of Clinical Trial participants.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

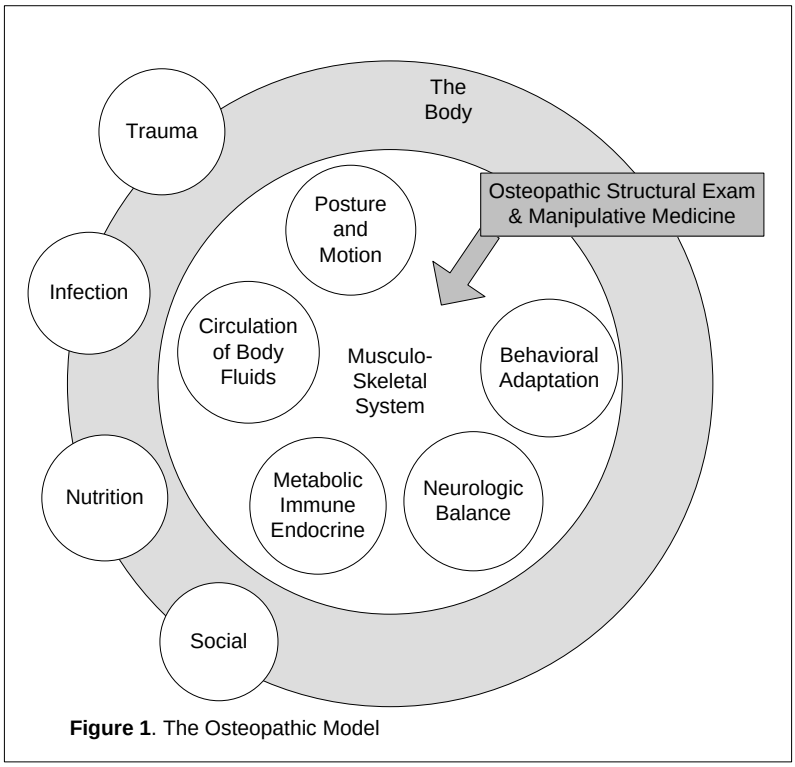


Figure 1. The Osteopathic Model

Despite decades of theory development and practice of osteopathic manipulative medicine (OMM), there are few rigorously controlled mechanistic studies of how OMM impacts the human body.

Osteopathic physicians are trained to use examination of the musculoskeletal system in the diagnosis and treatment of many conditions. Figure 1 provides a model of this approach to patient care. OMM treatments are used to help the body adjust to environmental stressors to maintain or restore optimum health. Environmental stressors include trauma, infection, nutrition, and social experiences. OMM is a body-based modality in which the patient is evaluated and treated as a whole to improve physiologic functioning and remove impediments to recovery from illness.

For this research plan, OMM is defined as a collection of manual techniques that are theoretically linked through assessment, diagnosis and treatment to an array of musculoskeletal disorders, systemic illnesses and other dysfunctional conditions of the human body. OMM aims to reduce or eliminate impediments to proper structure and function to assist the body's self-healing mechanisms. More specifically, Osteopathic physicians use OMM to identify restrictions of motion, tenderness, tissue changes, and asymmetry (somatic dysfunction), and to aid in repairing injured, damaged, or compromised tissue.

BACKGROUND

The remainder of this background section is organized around each of the outcome measures of interest.

Low Back Pain

For this clinical study, low back pain is defined as self-reported chronic and/or acute low back and posterior pelvic pain. Back pain is especially prevalent during pregnancy, with incidence rates varying between 48-90%. The pain can be mild or severe enough to interfere with daily activities. For example, up to 30% of 950 pregnant women reported in a survey that they had to stop performing at least one daily activity because of low back pain, thus negatively impacting their quality of life and that of their children(1). As a gravid uterus grows, its increasing size and weight tilts the pelvis forward, which increases the lordosis in the lumbar region of the spine(2) .This alteration in posture strains the ligaments, muscles, and joints of the surrounding areas, which can cause pain. In addition, hormonal influences, especially of

relaxin(3) contribute to structural instability of the pelvis by allowing the sacroiliac joints(4) and pubic symphysis to widen(5). Because of the bony instability and strain, the muscles frequently become hypertonic to add some support, and hypertonic muscles contribute to the feeling of pain and stiffness. Other musculoskeletal factors that have been shown to relate to the development of low back pain in pregnancy are depth of lumbar lordosis,(6) sacroiliac subluxation,(4) sacral shearing,(7) and muscle fatigue(8). For many years, these conditions have been treated by osteopathic physicians using Osteopathic Manipulative Medicine (OMM). Due to the potential risk to mother and child, many of the treatments commonly used for low back pain, such as muscle relaxants and pain medication, are not recommended for use during pregnancy. Pregnant women frequently are left to endure the pain until the end of their pregnancy(9).

Manipulation has been shown to affect some of these musculoskeletal dysfunctions common in pregnancy. Daly *et al.*, (4)in a small pilot study (n=11), demonstrated that pregnant women with low back pain and sacroiliac subluxation responded well to manipulation of their sacroiliac joints, and 91% had significant relief of their low back pain. These results were supported by a similar small study (n=20) by McIntyre in 1996 with 75% of those patients reporting elimination of their pain(10). Brady *et al.* reported a statistically significant decrease of their pregnant patients' perception of pain after OMM (n=97)(11). Chiropractic manipulation, which tends to primarily use High Velocity-Low Amplitude (HVLA) or thrust techniques, has also been shown to decrease or relieve back pain during pregnancy(12, 13). Manipulation is widely considered to be safe; after a thorough OVID Medline search of both the osteopathic and chiropractic literature, I found no reported negative outcomes as a result of manipulation during pregnancy.

In a recent study, Licciardone *et al.* found that patients who received OMM reported less pain and greater satisfaction with their back care. The treatment group also reported better physical functioning and mental health at one month into the trial(14). Other studies have shown that subjects who receive OMM use less medication for their back pain,(15) and improve sooner(16) than subjects who do not receive manipulation. In general, there is an argument in the literature that manipulation has not been unequivocally proven to be of statistically significant benefit, and must be studied more to reach a decisive conclusion(17). However, manipulation has been shown repeatedly to be of some benefit in many clinical applications, and is widely considered safe(18).

Functional status

Low back pain can be a source of significant disability during pregnancy. In 2004, Wang *et al.* reported that of 950 women that responded to a survey, 57% complained that low back pain interfered with their daily activities, 46.7% avoided some activity because of pain, 30.5% avoided exercise, and 10.6% had missed work because of low back pain(1). This amount of disability can impact quality of life, and make it difficult for women to care for themselves, their other children, or to work outside of the home.

In a pilot study conducted at UNTHSC, an OMM protocol very similar to that presented in this dissertation was used to study the effect of OMM on low back pain and functional status in pregnant women. Results from that study indicate that OMM lessens or halts the deterioration in back-specific functioning that often characterizes the third trimester of pregnancy and thereby provides an important clinical benefit(19).

Autonomic Tone

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(20). These changes are a physiologic stress to the mother. Maternal stress can have significant implications for the fetus. Increased resting sympathetic output has been linked to pregnancy induced hypertension,(21) and preeclampsia(22). In addition, corticotrophin-releasing hormone, which is elevated in situations of increased maternal stress, has been linked to preterm labor(23, 24). 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, and this is known to adversely affect long-term health.

Heart rate variability (HRV) has been shown to be a marker of autonomic tone. HRV measures fluctuations in autonomic input to the heart by the vagus nerve from the parasympathetic system and the effects of epinephrine and norepinephrine by the sympathetic system(25). The use of heart rate variability (HRV) to mathematically assess cardiac sympathetic and parasympathetic modulation was introduced in the 1970s and developed extensively over the subsequent 20 years(26-30). Considerable evidence now supports that these tools can provide quantitative insight into autonomic control in both experimental and clinical settings.

It has been demonstrated that the state of sympathovagal balance can be assessed from frequency domain analyses of cardiac rhythms. Heart rate or heart period (R-R interval) can be

assessed in either the time domain or the frequency domain, where it is quantified as the sum of the amplitude of oscillating elements across a range of frequencies. In the frequency domain analysis, the signal series of a period of consecutive heart beats can be represented by the sum of sinusoidal components of different amplitude, frequency and phase values. Many different methods have been described and their utility and application was previously reviewed (25) The fast Fourier transformation (FFT) has been the standard approach or some variation of this mathematical approach. The FFT employs an *a priori* selection of the frequency ranges as discussed below for this study(25, 28).

Traditionally, the spectra of HRV are analyzed in three frequency ranges: 0.00-0.05 Hz (VLF = very low frequency), 0.05-0.15 Hz (LF = low frequency), and 0.15-0.40 Hz which is associated with the respiratory rate (HF = high frequency). The amplitude of LF and HF components is assessed by the area (i.e. power) of each component and, therefore, squared units are used for its absolute value. In many analyses, a normalized unit can be obtained by dividing the power of a given frequency range by the total power and multiplying by 100.

Finally, the quantization of sympathovagal balance has been substantiated from a series of studies. Importantly, it is clear that the respiratory rhythm of HRV in the HF frequency range is an index of vagal modulation(28, 29, 31). These studies also demonstrated that LF frequency ranges are a function of both the sympathetic and vagal control of heart rate and last, the relation or proportion between these two frequency ranges appears to represent a measurement of sympathovagal balance(32).

In a landmark study by Montano and colleagues, HRV was used to assess the changes in sympathovagal balance during graded orthostatic tilt. This study demonstrated a strong relationship between the tilt stimulus and changes in the LF, HF and LF to HF ratio consistent with the expected changes in sympathetic and vagal activity during this physiological stress(31).

One of the theoretical mechanisms of OMM is that it affects autonomic balance through improving the tissues around the nervous system, thus optimizing its function. Study Two will examine the effects of OMM on autonomic balance by comparing the HRV before and after OMM treatments. Despite the theory, very little research has addressed this question, and this study will investigate this theory in the setting of the increased stress associated with pregnancy. A recent study from this laboratory demonstrated that OMM can reduce directly-measured sympathetic neural activity in healthy individuals(33).

If OMM treatments significantly decrease sympathetic tone and allow the mother to more readily adapt to the stresses of pregnancy, this study could impact these common and potentially severe complications.

Meconium-stained Amniotic Fluid and Preterm Labor

Meconium-stained amniotic fluid (MSAF) and preterm labor occur in approximately 12.5-14% and 11.6%, respectively (34, 35)of all births. Both of these are considered complicating factors of labor and delivery, and both have been linked to increased maternal stress. One source of information indicates that MSAF usually occurs in term or near-term pregnancies, and is linked with peripartum intrauterine stress and hypoxia. The same source

indicates that in about 5-10% of infants born through MSAF, Meconium Aspiration Syndrome occurs, with the development of respiratory distress, pneumonitis, and an associated death rate of about 12%(36). Stress has also been implicated as a major risk factor in preterm labor and delivery(35). MSAF and preterm delivery carry with them significant risks to the newborn, such as meconium aspiration syndrome as already mentioned, respiratory distress syndrome, congenital heart disease, infection, and other complications that can impact their survival rate and health.

Why would OMM affect the incidence of meconium-staining? Although the exact mechanism of this interaction is not known, it can be theorized based on the principles of osteopathic medical philosophy. As stated, pregnancy is a time of significant physiological and biomechanical change. The body, in its need to maintain an efficient state of homeostasis, must adapt to those changes. Anything that impedes the body's adaptation will decrease its efficiency, resulting in increased stress. Osteopathic philosophy states that structure and function are reciprocally interrelated, thus as structure is altered, so is function, and by improving the structure, the function improves as well. Therefore, decreasing the structural/postural stress may improve the body's ability to adjust to the physiological demands of pregnancy.

Pain itself is a stressor, and can increase the sympathetic tone within the autonomic nervous system. One small pilot study (n=20) in this laboratory investigated this relationship by applying a cold pressor stimulus. The cold pressor was effective at increasing pain and also sympathetic tone. Inhibitory OMM was applied to the thoracic paraspinal region of the healthy subjects with the aim of impacting the sympathetic chain ganglia which lies just anterior to the

rib heads. Using a measure of heart rate variability, results indicated that the inhibitory mode of paravertebral manipulation was effective in shifting the autonomic balance to a greater parasympathetic predominance. This is consistent with a reduction in net sympathetic neural tone. However, the subjects' pain perception did not change with OMM, indicating that there may be a more direct effect(37).

The second study (n=19) showed a similar effect on heart rate variability, but the OMM in this study was directed at the upper cervical spine, where it would be theorized to have more effect on the vagus nerve(38).

Therefore OMM may impact maternal stress in two ways: one, by decreasing low back pain, and indirectly impacting sympathetic tone; and two, by addressing the anatomical structures related to the sympathetic or parasympathetic nervous system and more directly decrease the sympathetic tone.

Maternal-fetal Outcomes of Labor and Delivery

Manipulation offers more to the expectant mother than reduction of her back pain. Anecdotal and empirical reports of the benefit of prenatal OMM have been around for as long as osteopathy. Many DOs have surveyed their practices, and compared outcomes of patients treated and not treated with OMM with national averages. For example, Lillian Whiting, D.O. reported an average labor time of 9 hours, 54 minutes in 99 cases that received OMM, an average of 21 hours, 6 minutes for 24 cases without OMM, and a national average at the time (1911) of 15 hours, 29 minutes(39). Similar results have been found by other osteopathic physicians, while

other reported findings include decreased labor pain, less use of pain medication during delivery, less use of forceps, and less nausea and vomiting during pregnancy. In addition, the finding of decreased labor times has been corroborated in several studies using chiropractic manipulative techniques(40-48).

More recently, two retrospective studies were completed by King et al.(48). The first of these reports reviewed records of 155 women who received OMM during pregnancy at four different sites and then compared the incidence of certain outcomes with the national averages. They found a lower incidence of meconium-stained amniotic fluid (7.1% versus the national average of 14.6%), preterm delivery (3.2% versus a national average of 10.0%), and use of forceps (6.4% versus a national average of 19.5%)(48). King expanded this study in 2003, increasing the number of reviewed charts to 321, with a control (no OMM) group at each of the four sites. Results were similar, with a statistically significant reduction in the incidence of meconium-stained amniotic fluid and preterm delivery, while a marginally significant reduction (P=.07) in the use of forceps was reported(49).

These findings are significant because of the serious consequences that can accompany meconium-staining or preterm delivery. There is a huge economic impact in that almost half of all neonatal hospital charges are for premature infants(35). The cost of an uncomplicated delivery averaged about $6,400, while a complicated delivery ranged from $20,000 to $400,000(50). It is not uncommon for these babies to have long-term complications, which adds to the cost of their care. Therefore, if OMM provides a low-risk intervention that could reduce the number of infants that are born prematurely or through meconium stained amniotic fluid, it

would make sense to incorporate it into standard prenatal care. Importantly, the long-range implication could mean a significant decrease in health care costs and improved maternal and fetal health.

Gait

Gait analysis has been used to study disease and treatment effects on parameters of gait, including multiple sclerosis, cerebral palsy, stroke, and post-orthopedic surgery(51). Gait analysis using the GAITRite has been validated in numerous studies as an objective and reliable measure to examine temporospatial parameters of gait(51-53).

In pregnancy, the postural changes already described begin to affect the gait. As the uterus enlarges and rotates the pelvis anteriorly, the strain is transferred into the hip joints and contributes to an external rotation of the lower extremities(54). This can widen the stance of gait, increasing the work of standing and walking, and possibly contributing to increased strain and discomfort. The exact changes of gait that develop with pregnancy have not been well documented. Application of the osteopathic model, though, would suggest that relieving some of the biomechanical strains of advancing pregnancy would improve gait. The effects of OMM have been studied in patients with gait disorders relating to Parkinson's disease, with good outcomes(55, 56). Improvements of several parameters of gait were noted after as little as one OMM treatment,(57) and persisting after a series of treatments ceased(58). Just as specific gait changes in pregnancy have not been well documented, the impact on any of those changes by OMM has also not been documented.

SIGNIFICANCE

The economic and health impact for the described consequences of complicated pregnancy, labor and delivery are significant. Recent perinatal statistics indicate that over four million babies were born in 2000. Of these, 11.6% were born prematurely. These premature infants account for almost half of all neonatal hospital charges(35). Infants born through meconium-stained amniotic fluid (MSAF) are at risk for meconium-aspiration syndrome, which can lead to respiratory distress and the need for extensive medical intervention. MSAF occurs in between 5.6 – 24.6% (median 14%) of all births, and meconium-aspiration syndrome occurs in 1.7 – 35.8% (median 10.5%) of this group(34). In the retrospective study by King, *et al.* a significant decrease in the incidence of pre-term labor and MSAF was found in patients who received OMM(49). Therefore, if OMM provides a low-risk intervention that could reduce the number of infants that are born prematurely or through meconium stained amniotic fluid, it would make sense to incorporate it into standard prenatal care. The long-range implication could mean decreased health care costs and improved maternal-fetal health.

As stated, the prevalence of low back pain in pregnancy has been reported to be between 48-90%,(59) with up to 30% of pregnant women ceasing some daily activity because of pain(1). However, estimates of the number of workdays lost or economic impact of low back pain in pregnancy has not been reported. One survey found that 10.6% of pregnant women took time off from work because of low back pain(1) and since manipulation has been shown to have a significant impact on low back pain in pregnancy (4, 10, 12, 13) it follows that OMM during pregnancy may improve functionality of these women.

In summary, if a low-risk intervention, such as osteopathic manipulation, can improve pain, functional status, and outcomes of labor and delivery in pregnant women, it would be reasonable and preferred to incorporate it into prenatal care. The goals of this proposal are to systematically test hypotheses related to this tenet.

References

1. Wang SM, Dezinno P, Maranets I, Berman MR, Caldwell-Andrews AA, Kain ZN. Low back pain during pregnancy: Prevalence, risk factors, and outcomes. Obstetrics & Gynecology. 2004 Jul;104(1):65-70.

2. Franklin ME, Conner-Kerr T. An analysis of posture and back pain in the first and third trimesters of pregnancy. Journal of Orthopaedic & Sports Physical Therapy. 1998 Sep;28(3):133-8.

3. Kristiansson P, Svardsudd K, von Schoultz B. Serum relaxin, symphyseal pain, and back pain during pregnancy. American Journal of Obstetrics & Gynecology. 1996 Nov;175(5):1342-7.

4. Daly JM, Frame PS, Rapoza PA. Sacroiliac subluxation: A common, treatable cause of low-back pain in pregnancy. Fam Pract Res J. 1991 Jun;11(2):149-59.

5. Lynch F. The pelvic articulations during pregnancy, labor, and the puerperium: An X-ray study. In: George Gray Ward JMD, editor. Transactions of the American Gynecological Society. Philadelphia: American Gynecological Society; 1919. p. 136.

6. Ostgaard HC, Andersson GB, Schultz AB, Miller JA. Influence of some biomechanical factors on low-back pain in pregnancy. Spine. 1993 Jan;18(1):61-5.

7. Treadwell RC, Magnus WW. Sacral shear: Review and a new treatment method for obstetrical patients. . 1996(Spring):16-18.

8. Perkins J, Hammer RL, Loubert PV. Identification and management of pregnancy-related low back pain. J Nurse. 1998 Sep-Oct;43(5):331-40.

9. Heckman JD, Sassard R. Musculoskeletal considerations in pregnancy.[see comment]. Journal of Bone & Joint Surgery - American Volume. 1994 Nov;76(11):1720-30.

10. McIntyre IN, Broadhurst NA. Effective treatment of low back pain in pregnancy. Aust Fam Physician. 1996 Sep;25(9 Suppl 2):S65-7.

11. Brady RE, Rottman J, Kappler RE, Veith EK. Osteopathic manipulation to treat musculoskeletal pain associated with pregnancy. JAOA. 1997;97(8):479.

12. Diakow PR, Gadsby TA, Gadsby JB, Gleddie JG, Leprich DJ, Scales AM. Back pain during pregnancy and labor. Journal of Manipulative & Physiological Therapeutics. 1991 Feb;14(2):116-8.

13. Guadagnino MR. Spinal manipulative therapy for 12 pregnant patients suffering from low back pain. Chiropractic technique (1992). 1999;11:108.

14. Licciardone JC, Stoll ST, Fulda KG, Russo DP, Siu J, Winn W, et al. Osteopathic manipulative treatment for chronic low back pain: A randomized controlled trial. Spine. 2003 Jul 1;28(13):1355-62.

15. Andersson GB, Lucente T, Davis AM, Kappler RE, Lipton JA, Leurgans S. A comparison of osteopathic spinal manipulation with standard care for patients with low back pain. N Engl J Med. 1999 Nov 4;341(19):1426-31.

16. MacDonald RS, Bell CM. An open controlled assessment of osteopathic manipulation in nonspecific low-back pain. Spine. 1990 May;15(5):364-70.

17. Koes BW, Assendelft WJ, van der Heijden GJ, Bouter LM. Spinal manipulation for low back pain. an updated systematic review of randomized clinical trials. Spine. 1996 discussion 2872-3; Dec 15;21(24):2860-71.

18. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. Ann Intern Med. 2003 Jun 3;138(11):898-906.

19. Stoll ST, Buchanan S, Hensel KL, King HH, Fulda KG, Licciardone JC. Osteopathic manipulative treatment of back pain and related symptoms during pregnancy: A randomized controlled trial. In press .

20. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv. 1994 Dec;49(12 Suppl):S1-14.

21. Greenwood JP, Stoker JB, Walker JJ, Mary DA. Sympathetic nerve discharge in normal pregnancy and pregnancy-induced hypertension. J Hypertens. 1998 May;16(5):617-24.

22. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia -- a state of sympathetic overactivity. N Engl J Med. 1996 Nov 14;335(20):1480-5.

23. McLean M, Smith R. Corticotrophin-releasing hormone and human parturition. Reproduction. 2001 Apr;121(4):493-501.

24. Hobel C, Culhane J. Role of psychosocial and nutritional stress on poor pregnancy outcome. J Nutr. 2003 May;133(5 Suppl 2):1709S-17S.

25. 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 Mar 1;93(5):1043-65.

26. Hyndman BW, Kitney RI, Sayers BM. Spontaneous rhythms in physiological control systems. Nature. 1971 Oct 1;233(5318):339-41.

27. Sayers BM. Analysis of heart rate variability. Ergonomics. 1973 Jan;16(1):17-32.

28. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science. 1981 Jul 10;213(4504):220-2.

29. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, 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 Aug;59(2):178-93.

30. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation. 1991 Aug;84(2):482-92.

31. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation. 1994 Oct;90(4):1826-31.

32. Malliani A. Principles of cardiovascular neural regulation in health and disease. Norwell, Mass: Kluwer Academic; 2000.

33. Cutler MJ, Holland BS, Stupski BA, Gamber RG, Smith ML. Cranial manipulation can alter sleep latency and sympathetic nerve activity in humans: A pilot study. Journal of Alternative & Complementary Medicine. 2005 Feb;11(1):103-8.

34. Cleary GM, Wiswell TE. Meconium-stained amniotic fluid and the meconium aspiration syndrome. an update. Pediatr Clin North Am. 1998 Jun;45(3):511-29.

35. Perinatal overview [homepage on the Internet]. . Available from: http://marchofdimes.com/peristats/.

36. Klingner MC, Kruse J. Meconium aspiration syndrome: Pathophysiology and prevention. Journal of the American Board of Family Practice. 1999 Nov-Dec;12(6):450-66.

37. Kinzler D. Sustained inhibitory rib-raising and microneurographic measurement of sympathetic nerve activity under cold-pressor stress. Thesis University of North Texas Health Science Center Unpublished. 2007.

38. Giles PD. Effects of cervical manipulation on cardiac autonomic control. 2006.

39. Whiting LM. Can the length of labor be shortened by osteopathic treatment. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1911;11:917.

40. Whiting L. The osteopathic management of pregnancy, and the reduction of obstetrical mortality. J Am Osteopath Assoc ; JAOA. 1934;33(8):531-533.

41. Dooley W. Osteopathy's contribution to prenatal care. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1946;46(1):6-7.

42. Guthrie RA. Lumbar inhibitory pressure for lumbar myalgia during contractions of the gravid uterus at term. J Am Osteopath Assoc. 1980 Dec;80(4):264-6.

43. Guthrie RA, Martin RH. Effect of pressure applied to the upper thoracic (placebo) versus lumbar areas (osteopathic manipulative treatment) for inhibition of lumbar myalgia during labor. J Am Osteopath Assoc. 1982 Dec;82(4):247-51.

44. Hart LM. Obstetrical practice. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1918:609.

45. TAYLOR GW. The osteopathic management of nausea and vomiting of pregnancy. J Osteopath (Kirksville). 1948 Apr;55(4):14-6.

46. Troyanovich S. Pregnancy and the chiropractic advantage. Today's Chiropractic. 1992;21(6):46-48.

47. Still E. Osteopathic obstetrics. Journal of Osteopathy. 1897;4(4):203-204.

48. King HH. Osteopathic manipulative treatment in prenatal care: Evidence supporting improved outcomes and health policy implications. AAO Journal. 2000(10):25-33.

49. King HH, Tettambel MA, Lockwood MD, Johnson KH, Arsenault DA, Quist R. Osteopathic manipulative treatment in prenatal care: A retrospective case control design study. J Am Osteopath Assoc. 2003 Dec;103(12):577-82.

50. Laman J, King M. Promoting healthy babies. Feb. 1994.

51. Publications referencing GAITRite [homepage on the Internet]. . Available from: http://www.gaitrite.com/index-new.html.

52. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. Gait Posture. 2005 Dec;22(4):317-21.

53. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. Gait Posture. 2003 Feb;17(1):68-74.

54. Stone C. Visceral and obstetric osteopathy. Edinburgh ; New York: Churchill Livingston/Elsevier, Projected Date: 0701; 2007.

55. Smutny CJ, Wells MR, Bosak A. Osteopathic considerations in parkinson's disease. J Am Osteopath Assoc. 1998;98(7):389.

56. Wells MR, Giantinoto S, D'Agate D, Areman RD, Fazzini EA, Dowling D, et al. Standard osteopathic manipulative treatment acutely improves gait performance in patients with parkinson's disease. J Am Osteopath Assoc. 1999 Feb;99(2):92-8.

57. D'Agate D, Areman RD, Fazzini EA, Giantinoto S, Wells M, Bosak A. Osteopathic manipulative treatment improves functional gait performance in patients with parkinson's disease. J Am Osteopath Assoc. 1997;97(8):485.

58. Wells MR, McCarty CL, Smutny CJ, Scandalis TA, Dittrich F, Fazzini EA. Osteopathic manipulation in the management of parkinson's disease: Preliminary findings [meeting abstracts]. J Am Osteopath Assoc. 2000;100(8):522.

59. Kristiansson P, Svardsudd K, von Schoultz B. Back pain during pregnancy: A prospective study. Spine. 1996 Mar 15;21(6):702-9.

CHAPTER 3

EXPERIMENTAL DESIGN AND METHODS

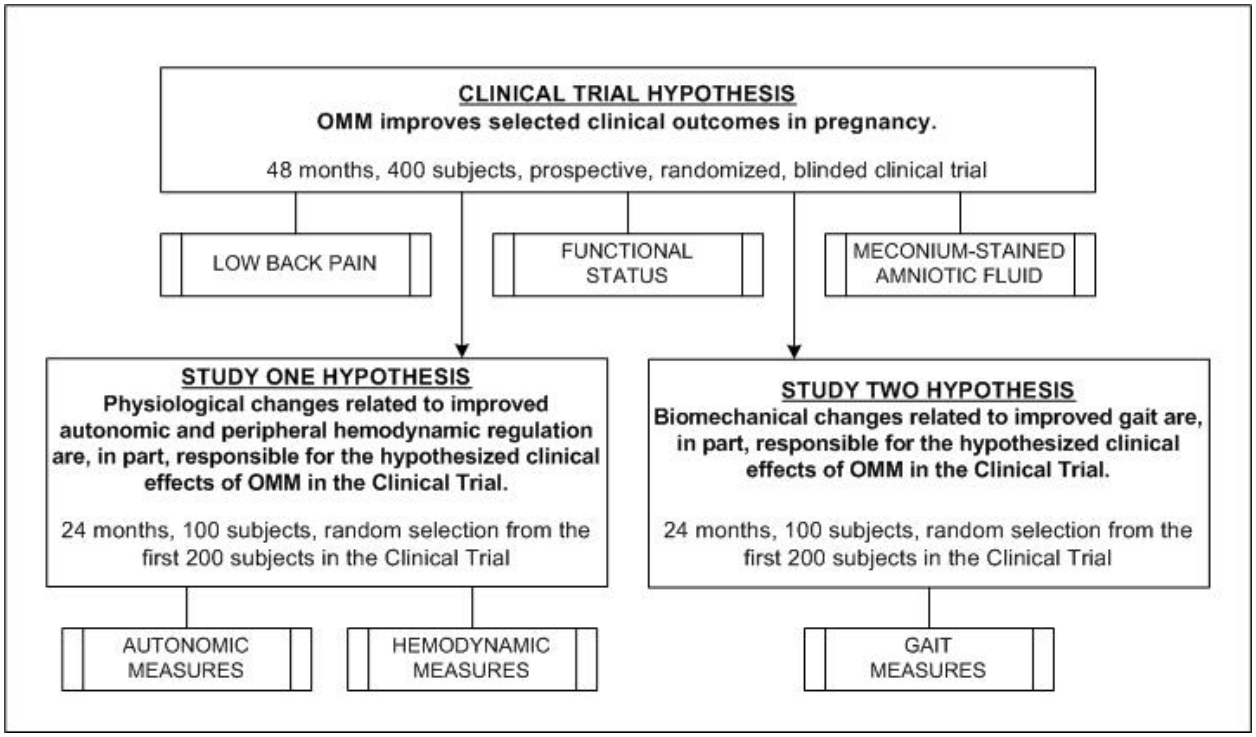
There are two studies reported in this dissertation. Both studies are sub-studies of the overall clinical trial investigating the safety and efficacy of OMM in treating low back pain during pregnancy. The overall clinical trial is funded by the National Institutes of Health National Center for Complementary and Alternative Medicine (NCCAM). This large research study was initiated in September 2006, as a K23 grant supported 5-year, 400-subject clinical trial. The two sub-studies were conducted with 60 subjects recruited from the clinical trial. This dissertation is focused on the acute effects of the two sub-studies: 1) responses to hemodynamic regulation during orthostasis and 2) the biomechanical effects of OMM as measured by gait analysis. All subjects in the sub-studies were concurrently participating in the clinical trial.

The clinical trial is ongoing, and is thus not reported in this dissertation. The methods for the clinical trial, however, are herein described, as are the methods used for each of the sub-studies, each guided by a separate hypothesis. . Therefore, this chapter of the dissertation contains sub-sections corresponding with the overall clinical trial and the two sub-studies. Within each subsection, I have described the relevant experimental design and methods. Each subsection includes the description of the research protocol, and the primary and secondary

outcome measures of interest, the process of subject recruitment and enrollment, power analysis, data management and analysis, and anticipated results for each hypothesis. The description of the OMM protocol and the specific treatment techniques and modalities used in the clinical trial is provided at the end of the description of the experimental design and methods. A complete description of the outcome measures is provided following the OMM protocol description. First, I have presented an overview of the research study timeline and entire research plan.

Grant Timeline: Subjects Enrolled and Completed

	Year 1	Year 2	Year 3	Year 4	Year 5
Clinical Study	100	100	100	100	Completion of Data
Study 1	50	50	0	0	Analysis and Manuscript
Study 2	50	50	0	0	Submission



EXPERIMENTAL DESIGN

Clinical Trial

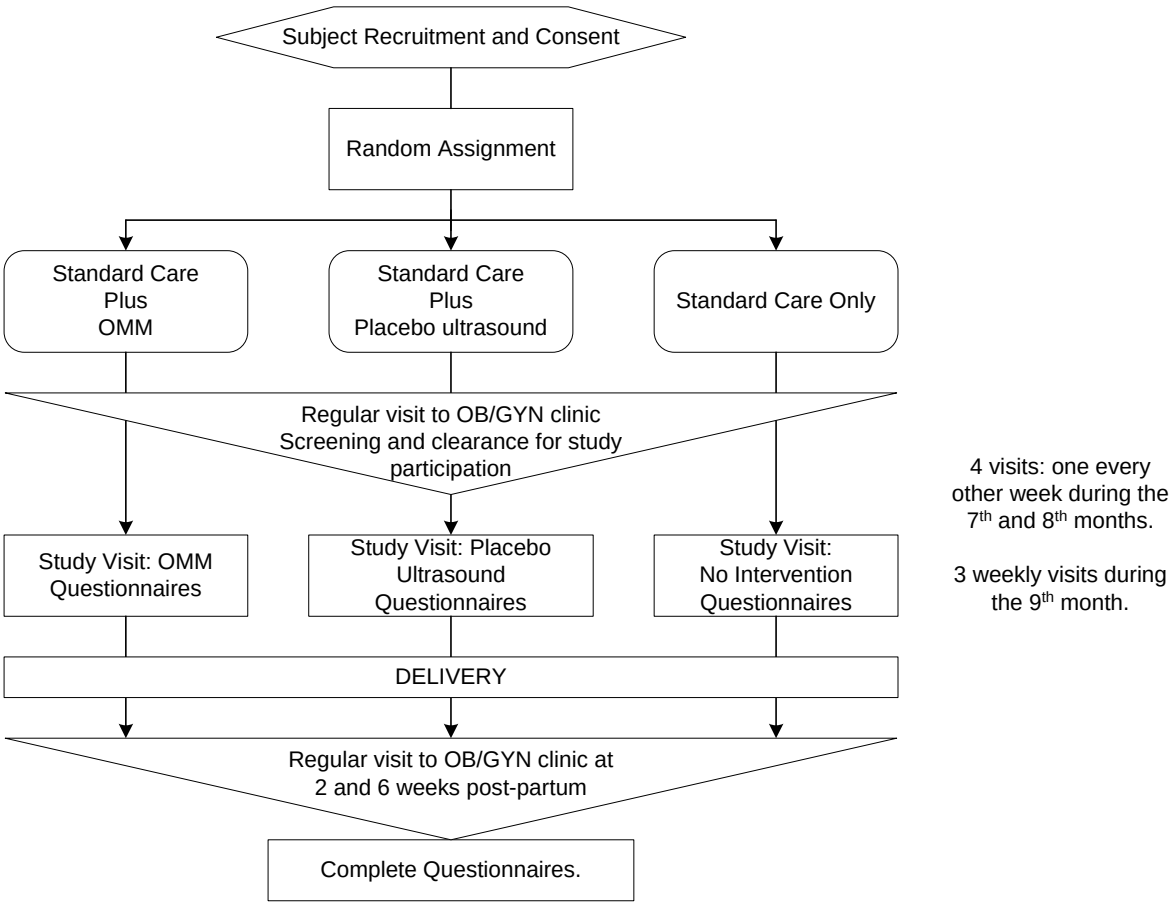
Clinical Trial Hypothesis: OMM improves selected clinical outcomes in pregnancy. These outcomes are low back pain, functional status, incidence of meconium-stained amniotic fluid, and complications of labor and delivery.

Study Protocol

The overall clinical trial is a randomized, placebo-controlled clinical trial conducted over 48 months in which a total of 400 women will participate. Patients of the OB/GYN clinic are approached about the study during their regularly scheduled visit to the obstetrician or midwife (OB/CNM) at 20-26 weeks of gestation. If agreeable to participating, the patient meets with the Clinical Research Coordinator to learn about the study, enroll, and give consent. After acceptance into the study, participants are randomly assigned to one of the three treatment groups and scheduled to be seen in the Research Clinic. This randomization is blocked to ensure equivalent numbers in each treatment group.

The flowchart below outlines the process for this study. All subjects in all study groups will be seen in Research Clinic on every study visit. We have taken many logistical precautions to safeguard the blinding of the OB/CNM and the subjects in the two active intervention groups. The subjects are asked to not disclose details of their treatment received unless specifically asked by their OB/CNM. This will maintain blinding of all persons involved in medical decision-making for the subject, yet allow for the OB/CNM to break blinding conditions as may rarely be necessary for appropriate care of the patient. If the OB/CNM deems it necessary to break

blinding, this will be discussed with the PI. As the PI is one of the physicians providing study treatments, she is not blinded, but is not involved in data collection.



At each prenatal appointment, the examining OB/CNM determines whether the study participant can safely proceed with this study's research protocol and send written approval for each research visit with the patient. If at any time the OB/CNM deems it inappropriate for the participant to continue in the research protocol, and/or their OB/CNM denies medical clearance for study participation on two occasions the subject will be released from the study.

Study treatment visits are scheduled to immediately follow the regular OB appointment, but may occur within 24 hours of the OB visit. This will be every other week during the 7th and 8th months of pregnancy (30, 32, 34 and 36 weeks) and weekly (for three weeks) during the 9th month (37, 38, and 39 weeks) for a total of 7 pre-partum visits if the patient reaches normal term gestation. At each visit, the participants will complete outcome questionnaires and receive the respective group intervention. In addition, there will be 2-week and 6-week post-partum visits for questionnaires only. Subjects will receive compensation for their time and travel at each study visit.

A physician who is board-eligible or board-certified by the American Osteopathic Board of Neuromusculoskeletal Medicine (AOBNMM) will perform the assessment and treatment of all subjects. The same physicians provide both the active intervention and the placebo treatment. While it is not be possible to blind the physician providing the treatment, the OB/CNM, OB/GYN staff, the OMM research coordinator and the study participants will be blinded. All participants will be directed specifically not to disclose details of their treatment or non-treatment group status to the OB/CNM and staff.

Clinical Study Outcome Measures

Outcomes measures include those listed in the table below. These questionnaires are described later in this chapter. Labor and delivery records will also be extracted for the variables listed in the following table. We will also collect information on targeted variables that may be peripherally associated with the primary outcomes of interest.

Group	Session 1 30 weeks	Session 2-4 Weeks 32, 34, and 36	Session 5-7 Weeks 37, 38, and 39	Postpartum 8 2 weeks postpartum	Postpartum 9 6 weeks postpartum
Group **A**: Osteopathic Manipulative Medicine	-Demographics -SCITA -RM-LBP&D -QVAS -SF-12v2 (2wk) -OMM	-RM-LBP&D -QVAS -SF-12v2 (2wk) -OMM	-RM-LBP&D -QVAS -SF-12v2 (1wk) -OMM	-RM-LBP&D -QVAS -SF-12v2 (2wk)	-SCITA -RM-LBP&D -QVAS -SF-12v2 (4wk)
Group **B**: Placebo ultrasound treatment	-Demographics -SCITA -RM-LBP&D -QVAS -SF-12v2 (2wk) -PUT	-RM-LBP&D -QVAS -SF-12v2 (2wk) -PUT	-RM-LBP&D -QVAS -SF-12v2 (1wk) -PUT	-RM-LBP&D -QVAS -SF-12v2 (2wk)	-SCITA -RM-LBP&D -QVAS -SF-12v2 (4wk)
Group **C**: Standard care	-Demographics -SCITA -RM-LBP&D -VAS -SF-12v2 (2wk)	-RM-LBP&D -QVAS -SF-12v2 (2wk)	-RM-LBP&D -QVAS -SF-12v2 (1wk)	-RM-LBP&D -QVAS -SF-12v2 (2wk)	-SCITA -RM-LBP&D -QVAS -SF-12v2 (4wk)
SCITA: Subject-Confidence-In-Treatment-Assessment RM-LBP&D: Roland-Morris Low Back Pain and Disability Questionnaire SF-12v2: Short Form General Health Survey			QVAS: Quadruple Visual Analog Scale OMM: Osteopathic Manipulative Medicine PUT: Placebo ultrasound treatment		

Table 2. Frequency of study visits and outcome measures

Clinical Study Subjects

Power Analysis

Because there are no known available published studies on the effects of OMM on low back pain in pregnant women, we have used several other methods to calculate our sample size for Study One. Of the measures in the clinical study, the largest sample size is required to measure the incidence of meconium staining. The data from the retrospective study (1)suggest that there was a 62% lower incidence of meconium-stained amniotic fluid in the OMM group as compared to the control group. Therefore, assuming a 62% reduction between groups, 80% power and a 5% significance level ($p<0.05$), we calculate that 110 subjects per treatment group

(330 subjects in total) would be sufficient to detect an effect of OMM on occurrence of meconium-stained amniotic fluid at delivery. Assuming a 20% drop-out rate we will recruit a total of 400 (minimum 396) subjects for the clinical trial.

Recruitment

Subjects are recruited from the Obstetrics and Gynecology (OB/GYN) clinic at the University of North Texas Health Science Center (UNTHSC) at Fort Worth during their second trimester (≤ 28 weeks gestation). During the pilot study, we averaged a 40% recruitment rate and had a 20% attrition rate. Assuming similar activity for this study, 400 patients will need to be recruited to allow for attrition and still have 330 complete the clinical study.

Inclusion and Exclusion Criteria

Inclusion criteria includes that the woman must be age 17 or older, 30 weeks or less of gestation at the start of the trial and have medical clearance from her OB/CNM at each study visit.

Women are ineligible for participation if any of the following conditions exist

1) Deemed high risk by the OB/CNM (including but not limited to: abruptio placenta, placenta previa, severe pre-eclampsia/eclampsia, vaginal bleeding, gestational diabetes);

2) Age 17 years or younger

Study subjects receiving any other manual therapies during the trial were released from the study.

If a subject stopped participating in the study, data was continuously collected with her permission. This is because the change in status may be an important consideration in our analysis. The reasons for discontinuation in the study were included for analysis purposes.

Clinical Study Data Management and Analysis

A 10-cm horizontal visual analogue scale is used to assess each subject's overall perception of low back pain before treatments associated with each visit. Changes are calculated from baseline data for each visit. Repeated measures ANOVA will be used for testing significant differences among the three groups (OMM Treatment, Placebo Ultrasound, Standard Care) across visits during the trial. *Post hoc* tests will be done for comparing group differences using adjusted type-I error t-test.

Functional status, quality of life and disability resulting from back pain are measured with the Roland-Morris Low Back Pain and Disability Questionnaire and the SF-12v2 Health Survey. Repeated measures ANOVA will be used to test for significant differences among the three groups (OMM Treatment, Placebo Ultrasound, Standard Prenatal Care) for each of these instruments as a whole and for their respective composite subscales. *Post hoc* tests will be done to further examine significant group differences.

For categorical variables, such as the presence or absence of a clinical finding, we will use multi-way contingency tables. Chi-square test will be used for testing proportions. Correlation tables will be produced. The incidence data of maternal and fetal complications in

pregnancy, labor and delivery will be analyzed using ANOVA or repeated measure ANOVA as appropriate. *Post hoc* tests will be conducted on all data where the ANOVA determines there are significant differences.

Clinical Study Anticipated Results

Based on results of previous studies and our preliminary findings, we expect that 1) subjects who receive OMM will have less progression of their back pain as measured by the Visual Analog Scale over the course of their third trimester than subjects who receive placebo ultrasound or standard care. We also anticipate 2) a difference in the functional status between the groups as measured by the Roland-Morris questionnaire. 3) Incidences of pregnancy complications such as meconium-staining and preterm delivery are also expected to be lower in the OMM group.

Clinical Study Limitations

Women may miss or change appointments, causing intervention time intervals to vary. In a natural setting, this is controlled as much as possible. Some women will participate in Study One and Study Two before and after the Clinical Study intervention. This will be addressed in the analysis of the data.

DISSERTATION STUDIES

There are many potential mechanisms by which OMM may provide benefit during the third trimester of pregnancy. This dissertation is an initial step in addressing two of these potential mechanisms: 1) enhancing hemodynamic and autonomic regulation and 2) alteration in gait biomechanics and function. In this dissertation, the acute effects of OMM on these mechanisms were assessed via 2 studies described below. Future studies will then investigate the longitudinal effects of regular OMM in pregnant patients.

Study One—Autonomic and Hemodynamic Study

Study One Hypothesis: OMM affects physiological measurements related to improved autonomic and peripheral hemodynamic regulation as assessed by the response to an orthostatic challenge.

Aim: To examine how OMM acutely affects autonomic balance during pregnancy,

Aim: To determine how OMM impacts lower extremity hemodynamics regulation during engagement of the skeletal muscle pump in the third trimester of pregnancy.

Autonomic Study Protocol

In a sub-population cohort (n=60) of the parent Clinical Study, a set of physiologic measures was obtained immediately before and after the respective Clinical Study Intervention visit: **(a)** baseline physiologic measures including basal autonomic control (heart rate variability) and leg volume (serial circumferential measures), and b) responses to a physiologic stimulus in

which autonomic control was measured during an orthostatic challenge (60^{o} head-up tilt--HUT) with and without skeletal muscle pump engagement (toe-raising).

Head-up tilt is a standard physiological stress used to assess one's ability to respond to a hemodynamic challenge via autonomically-mediated mechanisms. Second, engaging the skeletal muscle pump by performing intermittent toe raising was used to assess peripheral hemodynamic regulation during an orthostatic challenge. This served to assess the question whether OMM can impact structural restriction to venous return accompanying the third trimester of pregnancy.

Head-up tilt: Head-up tilt to 60^{o} will be performed on a hospital circle bed (Stryker). A foot plate will be used for support in the head-up position. Each position will be maintained for 5 minutes because numerous previous studies have shown that steady-state physiologic conditions are achieved within 2-3 minutes of a given change in body position.

Skeletal muscle pump: Engagement of the skeletal muscle pump will be performed during the orthostatic challenge. Subjects will raise up on their toes for 4 minutes in a cadence of 2 seconds up and 3 seconds down.

All measures were taken, and treatment visits occurred in the same physical location in the Research Clinic. The Study One protocol was repeated before and after the respective treatment intervention during week 30 of gestation.

For Study One, the woman was in the left lateral recumbent position and in a slight head-up position (10° head-up tilt) on a circular-frame bed that allowed for tilting to specific angles. The baseline measurements of heart rate (Lead II ECG), beat-to-beat arterial pressure (Finometer), and calf volume (serial circumferential measures and strain gauge plethysmograph) were taken. Details of each measurement are provided in the Outcome Measurements Section below. *Baseline:* Measures of heart rate, blood pressure variability, and calf volume were obtained. *Physiologic challenge:* After the baseline period, the patient was tilted to 60^{o} head-up tilt for 5 minutes followed by 4 minutes of intermittent calf muscle tension (toe raises) in a cadence of 2 seconds up and 3 seconds down. Following the toe raises, the subject rested at 60° tilt for 3 minutes.

Intervention:

The subject received the clinical trial intervention (OMM or placebo ultrasound) or a time-control (standard care) for Study One. Following the treatment (or equivalent time control in the standard care-only group), a second period of baseline data collection occurred followed by a repeat of the head-up tilt stimulus and toe raises. All measures were obtained continuously during the baseline and tilting periods and all physiologic data were recorded to a computerized data acquisition system (WINDAQ) for analysis.

Autonomic Outcomes Measures

Study One assessed (a) baseline physiologic measures including basal autonomic control (heart rate variability) and supine venous flow rate (plethysmography), and (b) responses to a physiologic stimulus in which autonomic control was measured during an orthostatic challenge

(60^{o} head-up tilt--HUT) with and without muscle pump engagement. *Heart rate:* Heart rate and R-R interval data was recorded continuously and used in the estimation of indices of heart rate variability. These measures are described in the measurement section below.

Power Analysis

The variance data from prior studies in which changes of heart rate variability were obtained during orthostatic challenges (head-up tilt or lower body negative pressure) were used to estimate statistical power and the target subject number for Study One(2-6). From this analysis, an n of 16 in each group in the 2x3 design should be sufficient to obtain a 50% effect size and achieve a power $\geq$ 0.8 (estimated range of power 0.82-0.90) with a significance level of $p<0.05$ for all variables. In anticipation of a 40% dropout rate, a target recruitment n will be a total of 60 patients to achieve 20 subjects in each group.

Recruitment

Subjects were recruited from the clinical trial enrollment (20 from each study treatment group). Separate informed consent processes occurred for participation in this subgroup of the Clinical Trial. Clearance was required from the OB physician before the woman participated in Study One.

Inclusion and Exclusion Criteria

Subjects were excluded if they reported a history of syncopal episodes.

Autonomic Study Data Management and Analysis

Statistical analyses:

Baseline data prior to the first physiologic interventions were compared across treatment groups with a one-way analysis of variance (ANOVA). Similarly, the pre-treatment responses to head-up tilt and to toe raise intervention were compared across treatment groups using the same one-way ANOVA approach. For all variables, these analyses were not significantly different ($p > 0.40$); therefore, individual responses for each treatment were compared before and after treatment to determine whether there was a treatment effect by use of a paired Student's T test. For data in which a test for normality failed, a Rank Sum test was used for these comparisons. An α level of 0.05 was set for significance

Autonomic Study Expected Results

It was anticipated that OMM would 1) improve autonomic balance directly, as evidenced by a change in HRV from before to after tilt, 2) improve peripheral hemodynamic regulation during engagement of the skeletal muscle pump, and 3) improved autonomic balance secondary to this improved hemodynamic regulation.

Study Two—Biomechanical Study

Study Two Hypothesis: Biomechanical changes related to improved gait are, in part, responsible for the hypothesized clinical effects of OMM in the Clinical Trial. This study evaluated functional and biomechanical changes in gait in the third trimester of pregnancy, and how OMM affected gait.

Biomechanical Study Protocol

The same subset of subjects from the Clinical Trial (N=60) who have agreed to participate in the Study One were also in Study Two.

A device called the GAITRite® walkway was used to measure stride length, stride width, foot angle of progression, gait symmetry, velocity, and all normal parameters of the stance phase of gait. As in Study One, these measures were taken before and after the Clinical Trial visits that occurred at week 30.

Initially, each patient was instructed on how to walk along a GAITRite® walkway at a normal, comfortable speed. The walkway was positioned so that at least two meters of space were present at each end of the walkway. All subjects began their gait evaluation by starting to walk two meters before the start of the walkway, and ended two meters beyond the end of the walkway. This allowed for acceleration and deceleration to occur off the walkway, and therefore not affect any parameters dependent on speed.

Once it was felt that the subject was able to walk in a consistent fashion, the subject walked the length of the walkway three times while data was being collected.

As the subjects were participating in measurements for both the autonomic study (Study One) and the biomechanical study (Study Two), the sequence of their visit was as follows: the subject presented for her regularly scheduled OB/CNM appointment and received clearance to participate in the study. The subject then came to the research clinic. The GAITRite® was the first measure performed, so the subject walked the length of the mat three times. She then lay on the circle bed and the autonomic measures, including the head-up tilt and muscle pump (toe raises) challenges, were taken. The subject then received her randomly assigned study treatment (OMM, Placebo Ultrasound, or time control). The autonomic measures were taken a second time, and then the subject concluded her research visit by walking the GAITRite® a second time.

Biomechanical Outcomes

Study Two assessed gait parameters including step length and width, stride length and width, cadence, velocity, base of support, single and double support, and toe in/toe out. These measures were taken before and after study treatments

Biomechanical Substudy Subjects

Power Analysis

The variance data for the selected variables to be assessed with the GaitRite® were obtained from a validation study(7) showing a high level of reproducibility. For determining a 20% change in each variable, a subject n of 16 per group will produce power ranging from 0.8-

0.94 with a significance level of $p<0.05$. Accounting for a dropout rate of 20%, a target recruitment n will be a total of 60 patients, 20 in each treatment group.

Recruitment

Subjects were recruited from the Clinical Trial. Separate informed consent processes occurred for participation in Study Two. Clearance was required from the OB/CNM before the woman participated in study activities.

Inclusion and Exclusion Criteria

Subjects were excluded from Study Two if they had a lower extremity injury that impacted their gait.

Biomechanical Study Data Management and Analysis

The GAITRite® enables data collection of many facets of the human gait cycle. Each of these parameters was averaged throughout each time the subject traversed the GAITRite® walkway and also averaged between the three attempts that they walked for each evaluation sequence. These gait parameters included the velocity of gait, symmetry of gait, stride length, stride width, the foot angle of progression, and also the period where these variables differed from side to side as in stride length, foot angle of progression or length of stance phase. These parameters were evaluated for both the left and right sides.

Each subject underwent four sessions of data collection (pre- and post- treatment week 30, and pre- and post-treatment week 36). Again as in the autonomic study, this dissertation will

focus on the acute effects of the study treatments at the 30 week visit only. When significant main effects were obtained, individual differences were determined from a *post-hoc* analysis using Tukey's multiple range test. Specifically we made comparisons to address and answer the following question: What is the effect vs. placebo in changing the above parameters of gait before and after a manipulative treatment both at 30 weeks gestation?

Biomechanical Study Expected Results

It is anticipated that the statistical analysis will demonstrate a significant difference in several parameters of gait both immediately before and after manipulation. It is possible that parameters of gait may be more normal after repeated use of the GAITRite® walkway due to a "practice effect". Therefore, it is possible that even the standard of care (no treat) group may see a slight improvement in parameters of gait before and after gait analysis that occurs three times on week 30. However, we hypothesize that the OMM treatment group will see a statistically significant improvement in many parameters of gait when compared to either placebo or standard care.

It is the intent of this line of research to better determine the progression of gait abnormalities that occur normally in pregnancy, to determine which of these parameters are most affected by osteopathic manipulative medicine, and at what point in the pregnancy is OMM most effective in normalizing gait.

DESCRIPTION OF INTERVENTIONS FOR CLINICAL TRIAL

Osteopathic Manipulative Medicine Modalities

The following material describes the OMM modalities used in the Clinical Trial for the group who received OMM plus standard care. As all participants in the Studies One and Two (autonomic and biomechanical studies) also received these interventions, this description is included for the purposes of the dissertation.

The physician used one or more of the below treatment modalities to treat the OMM Group participant:

- **Myofascial Release (MFR):** Used to treat fascial restriction. The physician's hands, guided by continual palpatory feedback, apply force directed at the restriction to achieve release of myofascial tissues. The physician can either directly engage a restrictive barrier, loading with a constant force until tissue release occurs, or guide the dysfunctional tissues along the path of least resistance until free movement is achieved.

- **Articulatory Treatment:** The joint and its associated region of somatic dysfunction are gently guided into the restrictive barrier within its range of motion, and the physician attempts to gently overcome the restriction. The physician may employ traction, compression, or gentle springing of the joint and have the patient inhale or exhale in an attempt to optimize alignment and range of motion of the joint.

- **Muscle Energy Treatment:** The joint and its associated region of somatic dysfunction are gently guided into the restrictive barrier, which limits the area's normal range of

motion. The patient is instructed to attempt to return to a neutral position, while the physician resists the patient's efforts. The patient is then instructed to desist from her efforts, and the physician then moves the dysfunctional region up to and against the new restrictive barrier.

- **Balanced ligamentous tension (BLT):** BLT addresses ligamentous strain. When the ligamentous articular mechanism of a joint is strained, it alters the permitted motion of that joint. By taking the joint into a position that balances the tension in the surrounding ligaments, the body is able to resolve the strain.

- **Soft Tissue:** A set of techniques that directly address the muscular and fascial structures of the body and their associated neural and vascular elements. Soft tissue techniques can involve traction or stretching, kneading or lateral stretching, and/or inhibition, which involves sustained deep pressure.

It is to be emphasized that the above Osteopathic Manipulative Medicine treatments (OMM) are relatively gentle. A major OMM modality that will be excluded from this protocol is High Velocity/Low Amplitude (or thrust), a direct technique that mobilizes joints with a short impulse of force. By eliminating this modality we may be eliminating a potentially useful treatment. However, due to the increasing ligamentous laxity that occurs in later pregnancy, the force used in a thrust technique is generally not necessary.

The OMM protocol addressed the regions of the body that would be most likely to be dysfunctional in an advancing pregnancy. As the fetus nears term, the growing weight and distention of the uterus commonly causes some specific dysfunctions in the mother. The increased lumbar lordosis, reduced compliance of the respiratory diaphragm, and congestion and pressure on the viscera and pelvic veins adversely affect venous drainage, lymphatic flow, autonomic tone to viscera, ventilatory function and musculoskeletal mechanics of the patient's body, as well as increasing pain and reducing physical functional capacity. Although the breadth of the protocol encompassed the majority of tissues from the base of the head to the pelvis, there were specific rationales for treating certain areas. These rationales involved application of the osteopathic philosophy and the concept of the interrelationship of structure and function. Use of OMM to improve the structural dysfunction is directed to decrease pain and improve overall functional status.

The goals and rationale for treatment according to region are:

- **Occipital-atlantal (OA) joint:** The occiput is the attachment site for many of the cervical muscles, which can become hypertonic due to the alteration of posture. The Vagus nerve, which exits the skull through the jugular foramen, courses through the cervical region to provide parasympathetic nerve supply to the upper gastrointestinal, pulmonary and cardiac systems(8).

- **The cervical vertebrae:** The phrenic nerve arises from the third, fourth, and fifth cervical nerves, and innervates the thoracoabdominal diaphragm. Somatic dysfunction of

these vertebrae can affect the functioning of the phrenic nerve and, therefore, of the thoracoabdominal diaphragm.

- **Clavicles and Sibson's fascia:** Terminal vessels of the lymphatic system drain into the subclavian veins in the infraclavicular space and pass through Sibson's fascia (thoracic inlet fascia) on their way back to the heart. A strain pattern induced in Sibson's fascia can decrease the caliber of lymphatic vessels and their ability to efficiently return lymph through the thoracic duct and/or lymphatic duct(9). Obstruction of lymphatic return results in edema and stasis of interstitial fluids.

- **Thoracoabdominal diaphragm and lower six ribs:** The thoracoabdominal (respiratory) diaphragm becomes more restricted in motion as the uterus expands superiorly. This can effect ventilation, rib and spine movement, venous and lymphatic fluid flow, and digestion as the esophagus passes through the diaphragm. The lower six ribs are the attachment of the thoracoabdominal diaphragm and their position and motion directly affects its function(10-12).

- **Thoracolumbar junction:** Attachment site of the crura of the diaphragm; the position and motion of the vertebrae directly affects the function of the thoracoabdominal diaphragm. Also sympathetic nervous supply to the uterus and pelvic organs is from spinal segments T12-L2. Thus treatment of this region is directed to improve autonomic tone of the uterus(8, 10, 11).

- **Pelvic diaphragm:** Treatment of the strain patterns in the myofascial planes of the pelvic diaphragm is directed to improve the mobility and supportive ability of the pelvic diaphragm, and to decrease neural impingement. Due to the ball-valve effect of the uterus, these tissues are prone to lymphatic congestion, and treatment to improve lymphatic flow may potentially decrease the incidence of constipation, hemorrhoids, and perineal lacerations(9).

- **lnnominates:** Decreased somatic dysfunction in this area is predicted to directly decrease low back pain and improve functional status. Realignment of the innominates may improve the ability of the pelvis to accommodate the fetus during the labor and delivery process(12). Somatic dysfunctions of the innominates can "also directly compromise the physical dimensions of the pelvic outlet, which can result in pelvic disproportion difficulties during delivery".(13)

- **Sacrum:** Treating the sacrum for somatic dysfunction is directed to improve its mobility and alignment so that the fetus has an uncompromised path of descent. Also, treatment of the sacrum will balance the parasympathetic nervous system tone to the uterus through the pelvic splanchnic nerves, thus preventing poor cervical dilation due to decreased parasympathetic tone during labor and delivery. Sacro-iliac dysfunction is thought to be the most common reason for severe low back pain in pregnancy(11, 14, 15).

- **Hips:** Somatic dysfunction of the hip flexors, internal and external rotators of the lower extremity, and femur can impact the alignment of the innominates and sacrum, and affect

gait. Treatment will be directed at improving the position and mobility of these structures and their associated myofascial components.

- **Cranium:** Subjects will also be treated with an Osteopathy in the Cranial Field technique, the compression of the fourth ventricle (CV4). This technique has been linked in the past with inducing labor in post-dates women(16), but is widely used during pregnancy and generally considered safe.

The treatment intervention session lasted approximately 20-30 minutes.

A standardized protocol for OMM is difficult to apply for every patient. In constructing the protocol to be used in this study, the goal was to create a protocol that would treat the most common dysfunctions seen in pregnancy in the majority of patients. As the protocol involved multiple treatment modalities applied to several different body regions, it will be difficult in determining precisely which specific treatment may decrease the incidence of a particular pregnancy complication. However, the scope of the Clinical Trial is only to determine the efficacy of OMM to decrease pain and increase functional status in pregnancy. If OMM proves to be efficacious, it must be left to future studies to further delineate the relationship between specific manual treatments and specific therapeutic benefits.

Placebo Ultrasound Interventions

The issue of placebo control treatments in osteopathic manipulation research is controversial. A placebo treatment is advocated in studies with manipulation because there may be many reasons a patient may exhibit benefit from treatment aside from the biomechanical,

fluid or neurological consequences of the manipulation itself. In addition to the structural changes induced by OMM, OMM may generate a positive clinical response because of the ancillary effects of: (1) the "laying on of hands"; (2) greater attention from and interaction with the treating physician; (3) an expectation of therapeutic effect. Thus, the use of a placebo or placebo control is generally warranted in trials of osteopathic manipulation to help control for the potential ancillary effects.

The goal in selecting a placebo is to: (1) provide an alternate treatment to OMM that provides a similar degree of physician-patient interaction to control for the potential effect of 'greater attention'; (2) provide an equal expectation of therapeutic effect; and (3) provide similar sensations of physical contact to simulate "laying on of hands". This all needs to occur without actually causing direct mechanical effects to the musculoskeletal, vascular or neurologic systems.

For this study, the placebo treatment was a subtherapeutic ultrasound systematically administered over the same major body regions as were addressed by the OMM. The same osteopathic physician who performed the OMM administered these subtherapeutic placebo ultrasound treatments. This protocol might have provided a genuine anticipation of therapeutic effect among participants, as it allowed for tactile stimulation over the same anatomical distribution as OMM provided in the treatment group, and also provided for similar time and attention as that given to participants in the OMM treatment group. The subjects in the placebo group received the subtherapeutic ultrasound treatments after each of their scheduled prenatal obstetrical visits. Thus, an ultrasound placebo treatment session lasted approximately 30 minutes,

the same as the OMM treatment. Ultrasound was applied for 2 minutes bilaterally at each of the areas of primary focus for the OMM including the neck, scapular region, thoraco-lumbar junction, lumbo-sacral junction, lumbar paraspinal region, sacro-iliac joint, and inguinal ligament at an intensity of 0.1W/cm^2 and 10% pulsed mode (i.e., at the lowest setting and with the greatest cycle interruption). These treatments were applied through the subjects' clothes in the same manner that OMM was provided without requiring the subjects to undress.

Standard Care Only

The experimental group receiving Standard Care only received standard obstetrical care from her obstetrician, but no experimental intervention. She saw the OMM physician at the research clinic to maintain the blinding conditions as closely as possible, completed her questionnaires and received her payment for the visit.

OUTCOME MEASUREMENTS

Clinical Trial

This section serves to review the focus of the ongoing clinical trial that will ultimately serve as a clinical correlate to the research performed for this dissertation.

Low back pain: Assessed using a Quadruple Visual Analog Scale Form (QVAS). The QVAS asks the subject to rate their pain "now, at it's average, worst and best." The QVASs will be administered each visit to evaluate low back pain. The visual analog scale is a simple linear scale for estimating relative intensity of pain. This measure has seen use in many studies, and is now well accepted as a reliable measure of pain(17).

Functional status: Assessed using two standardized self-reporting inventories, the Roland-Morris Low Back Pain and Disability Questionnaire and the SF-12v2 Health Survey. The Roland-Morris Low Back Pain and Disability Questionnaire is a brief self-reported questionnaire of functional problems related to low back pain(18). It is a well-established measure of functional status, and has been translated into many languages for use around the world. It has been shown to be sensitive to change in low back pain over time(19, 20). Ware's Short Form-12 or SF-12v2 Health Survey(21) is a multipurpose, brief general health survey with only 12 questions, which has been shown to be both reliable and valid, and has the advantages of being economical, easily administered, and easily assessed. It is used to estimate disease burden and detect changes in the patient's perception of their health status. Three forms of the SF-12v2 will be used to correlate with the planned treatment intervals

Meconium-stained amniotic fluid: Meconium staining is recorded at time of birth on the Hollister Maternal/Newborn Record System forms, which are used at the UNTHSC OB/GYN clinic and at Baylor All Saints Medical Center to record common conditions and occurrences of the pre-, peri-, and post-partum period. The Hollister System includes the Initial Pregnancy Profile, Prenatal Flow Record, Health History Summary, Obstetric Admitting Record, Labor Progress Chart, Labor and Delivery Summary, Recovery Flow Record and the Obstetrical Discharge Summary. Most of the data points in the forms will be used in the study.

A short questionnaire *(Subject Confidence in Treatment Assessment, or SCITA)* will be given before the interventional trial begins and a similar questionnaire after the trial ends. These questionnaires ask the subjects the degree to which they believe that the treatment they will

receive (have received) will be (has been) helpful in reducing discomfort, improving functional status and preventing problems associated with their pregnancy. The questionnaire will be in a Likert scale format and specific to the OMM / Placebo / Standard Care group into which the participant has been randomized. This questionnaire is critical to help determine whether any differential effect between outcomes of the three treatment groups is due to the effect of OMM or whether it is due to a differential potency of the placebo effect between the experimental groups. Demographic data including age, race, marital status, education level, occupation and insurance type will be collected for all subjects.

Study One: Autonomic Balance and Hemodynamic Control

Heart rate: Heart rate and R-R interval data were recorded continuously from a Lead II electrocardiogram. An alternative ECG lead was used if peak detection of the R wave of Lead II is problematic.

Arterial pressure: Measured non-invasively, by use of a Finapres photoplethysmographic monitor placed around the middle finger.

Heart rate & Blood pressure variability: Beat-to-beat values of R-R interval and systolic blood pressure was recorded on digitally into a data acquisition system (WINDAQ, Akron, OH). The data was then linearly interpolated and re-sampled at 2Hz 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 underwent a Hanning-window filtering and Fast Fourier transforms implemented to generate autospectra for each variable. These data analyses sequence conforms to the recommendations of the international consensus panel for the assessment of cardiovascular variability.(14) High frequency 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 (22) utilizing parasympathetic blockade and nerve stimulation. In the frequency region between 0.05 and 0.15 Hz, arterial pressure powers increase with laboratory stimuli that increase sympathetic cardiovascular influences (e.g., head-up tilting, mental stress) and decrease with conditions that decrease sympathetic cardiovascular influences (e.g., sleep and α-adrenergic blockade) Thus, low frequency power (0.05-0.15 Hz) of arterial pressure was used as an index of sympathetic activity. The ratio of low to high frequency power

of RR interval is widely recognized to be an index of the balance between the sympathetic and parasympathetic systems and was used for this purpose(23, 24).

Study Two: Gait

The GAITRite is a product of CIR Systems, Inc. For Study Two we measured stride length, stride width, foot angle of progression, gait symmetry, velocity, and all normal parameters of the stance phase of gait with a 4.26-m-long GAITRite® instrumented walkway and software (version 3.8B CIR Systems, Inc., Havertown, PA). The GAITRite® measures cadence, step length, velocity, and other gait parameters. All parameters were tracked, reported, and graphed. This helps to assess variability of steps, dynamic balance, and predict fall risk. As the subject ambulates across the walkway the system captures information. This is done without shoes.

Step length: Measured on the horizontal axis of the walkway from the heel point of the current footfall to the heel point of the previous footfall on the opposite foot. Stride length is measured on the line of progression between the heel points of two consecutive footfalls of the same foot.

Stride width is the average side-to-side distance between the center of the right footprint and the center of the left footprints.

Foot angle: Foot angle of progression is the average angle of each footprint in relation to longitudinal line formed down the center of the GAITRite walkway. The line representing the

angle of the footprint is defined by a line drawn through the most posterior point of the footprint and the midpoint of the widest part of the forefoot. The angle of progression is specific for both the right and left feet.

Gait symmetry: Refers to the degree of variance between the frequency of heel strike between the right and left foot. The average time between the moments of sequential heel strike for the left foot is compared to the average time between the moments of sequential heel strike for the right foot. The average difference between these times is a measure of gait symmetry.

Velocity: Velocity is the quotient of distance and ambulation time.

Risks to the Subjects

Human Subject Involvement and Characteristics

This clinical trial required the use of human subjects and was not exempt from Human Subjects Regulations. This clinical research project included pregnant women and therefore complied with the provisions of the regulations in Subpart D of the Code of Federal Regulations Title 45, Part 46 on "Protection of Human Subjects" (45 CFR 46). The risk to the pregnant women and their fetuses was considered minimal and our hypotheses were believed to be important and could not be tested in any other fashion. We are included pregnant women 18 years of age and older in our study. We have Institutional Review Board (IRB) approval at both the University of North Texas Health Science Center and John Peter Smith Medical Center.

Clinical Trial

A total of 400 subjects will be enrolled in the overall Clinical Trial and randomly assigned to one of the three following groups:

1) Group A will receive the active intervention with Osteopathic Manipulative Medicine treatments in addition to standard obstetrical care.

2) Group B will receive a placebo ultrasound treatment in addition to standard obstetrical care.

3) Group C will receive standard obstetrical care only.

Inclusion criteria for participating in this study are:

1) Must have medical clearance from their OB/CNM;

2) Must be enrolled prior to the 30^{th} week of pregnancy.

Exclusion criteria are:

1) Deemed high risk by the OB/CNM (including but not limited to: abruptio placenta, placenta previa, severe pre-eclampsia/eclampsia, vaginal bleeding, gestational diabetes);

2) Age of 17 years or younger. Females 17 years of age and younger are considered pediatric high risk pregnancies and, therefore, ineligible for inclusion.

3) For Studies One and Two, patients with a lower extremity injury (sprain or fracture) will be excluded due to potential edema from the injury and alteration of gait.

4) Patient self-reports syncopal episodes during pregnancy.

Study One—Autonomic Study

A subgroup of 100 Clinical Trial subjects was asked to participate in Study One and Study Two. Subjects in Study One and Study Two were randomly assigned to one of the three following groups:

1) Group A received the active intervention with Osteopathic Manipulative Medicine treatments in addition to standard obstetrical care.

2) Group B received a placebo ultrasound treatment in addition to standard obstetrical care.

3) Group C received standard obstetrical care only.

Source of Materials

This study obtained information from subject's existing medical chart to document pregnancy. Demographic information (age, race, marital status, educational level, occupation,

and insurance type) and medical history were also obtained from the existing medical chart. The chart was used as a source document for the pregnancy to document weight, blood pressure, and medications at each visit.

For the Clinical Trial, low back pain will be assessed using a Quadruple Visual Analog Scale Form (QVAS). These forms ask the subject to rate their pain "now", "at it's average", "worst" and "best." The QVASs will be administered each visit to evaluate low back pain. The visual analog scale is a simple linear scale for estimating relative intensity of pain. This measure has been used in many studies, and is now well accepted as a reliable measure of pain (25). Further, the QVAS has the advantage of being very brief and easy to use which facilitates its use in this study as a repeated measure to compare pain changes over the course of treatments and pregnancy.

The Roland-Morris Low Back Pain and Disability Questionnaire is a brief self-reported questionnaire of functional problems related to low back pain(18). It is a well-established measure of functional status, and has been translated into many languages for use around the world. It has been shown to be sensitive to change in low back pain over time(19, 20). Ware's Short Form-12, or SF-12v2 Health Survey is a multipurpose, brief general health survey with only 12 questions, which has been shown to be both reliable and valid, and has the advantages of being economical, easily administered, and easily assessed. It is used to estimate disease burden and detect changes in the patient's perception of their health status. The SF-12v2 is derived from the SF-36, which has 36 questions and has been documented in more than 1000 publications, and found to be useful in comparing general and specific populations, comparing the relative burden

of diseases, and differentiating the health benefits produced by a wide range of different treatments(21). Three forms of the SF-12v2 will be used to correlate with the planned treatment intervals; the forms will inquire about health during the period of the last week, last two weeks, or last four weeks, depending on the visit interval.

Meconium staining is recorded at time of birth on the Hollister Maternal/Newborn Record System forms, which are used at the UNTHSC OB/GYN clinic and at delivery hospitals to record common conditions and occurrences of the pre-, peri-, and post-partum period.

The Hollister System, which includes the Initial Pregnancy Profile, Prenatal Flow Record, Health History Summary, Obstetric Admitting Record, Labor Progress Chart, Labor and Delivery Summary, Recovery Flow Record and the Obstetrical Discharge Summary, will also be used to gather data and to determine the impact of OMM on other outcomes of pregnancy, labor and delivery such as incidence of high-risk status, incidence of pre-term labor, length of labor, use of forceps or suction device, and pain medication use. These objective measures will be collected from the patient's chart after delivery. Pre-, peri-, and post-natal clinical indicators, diagnoses and outcomes to be recorded and analyzed include: maternal blood pressures, proteinuria, peripheral edema, hyperreflexia, vaginal bleeding, glucosuria, birthing classes, drug and alcohol abuse history, uterine contractions (irritability), gestational diabetes, urinary tract infections, pre-eclampsia, eclampsia, pre-term labor, pre-term delivery, use of continuous Maternal Fetal monitor, use of intermittent Maternal Fetal monitor, augmentation of labor, caesarian-section conversion from spontaneous labor, use of forceps or vacuum assist for delivery, grade of perineal lacerations, episiotomies, induction of labor for post-term

pregnancies, dystocia, malpresentation (breech), placenta previa, placental abruption, cord prolapse, length of labor stages, significant late decelerations in fetal heart rate during labor, meconium staining, type of anesthesia and newborn APGAR scores.

A short questionnaire (Subject Confidence in Treatment Assessment, or SCITA) will be given before the interventional trial begins and a similar questionnaire after the trial ends. These questionnaires ask the subjects the degree to which they believe that the treatment they will receive (have received) will be (has been) helpful in reducing discomfort, improving functional status and preventing problems associated with their pregnancy. The questionnaire will be in a Likert scale format and specific to the OMM / Placebo / Standard Care group into which the participant has been randomized. This questionnaire is critical to help determine whether any differential effect between outcomes of the three treatment groups is due to the effect of OMM or whether it is due to a differential potency of the placebo effect between the experimental groups. Demographic data including age, race, marital status, education level, occupation and insurance type will be collected for all subjects.

Potential Risks

Clinical Trial

The potential risks of this study are primarily related to pregnancy and delivery and their inherent complications. These include but are not limited to: pregnancy induced hypertension, pre-eclampsia/eclampsia, placenta previa, placental abruption, malpresentations, umbilical cord prolapse, meconium aspiration, premature rupture of membranes, premature labor, pre-term delivery, failure to progress leading to caesarian section, post-partum hemorrhage, and death.

However, in the totality of literature reviewed on the topic of manipulation for the obstetric patient, there were no incidences of adverse outcome attributable to OMM. The treatments proposed employ intermittent forces of low magnitude (light to moderate pressure). The most common side effect or complication from receiving OMM is a mild to moderate discomfort during the treatment and a mild soreness after treatment.

There are no expected additional risks for the placebo ultrasound treatment and standard of care groups. Subtherapeutic levels of ultrasound were used, meaning that although the ultrasound machine is turned on, there were no actual ultrasound waves being emitted from the wand head.

Study One—Autonomic Study

Subjects who received patch electrodes for either an EKG or EMG may experience minor, localized skin irritations from adhesive in the leads. There are no known risks to the subject from the measurements of non-invasive photoplethysmographic blood pressure. The risks of whole-body head-up tilting include the potential of syncope and vagomimetic arrhythmias. This risk is generally small and was further minimized by excluding patients with a history of syncope either before or during this pregnancy. If pre-syncopal symptoms occurred, the tilt-table was immediately returned to the horizontal position. Moreover, the risks of these events are very small at tilt angles of 60° held for only 6 minutes, and were further minimized by the protocol design which includes purposeful skeletal muscle pumping of the lower legs. To prevent any complications due to compression of the vena cava, all subjects laid on their left sides, not on their backs.

Subjects were asked not to receive OMM or other manual therapies during current pregnancy. If the subject decided to receive OMM, they were removed from the study.

Study Two—Biomechanical Study

The greatest risks associated with Study Two and the GAITRite® Walkway were tripping or slipping. These risks were minimized by ensuring that the walkway was properly set up according to operating manual instructions and by keeping the area around the walkway free from clutter and securing cords and cables properly. Subjects were also be encouraged to walk barefoot rather than open toed, open backed, or high heeled shoes. The walkway is coated with a non-slip surface to ensure that risks are minimized.

Adequacy of Protection against Risks

Recruitment and Informed Consent

Subjects were recruited from the OB/GYN Clinic at the University of North Texas Health Science Center at Fort Worth, TX using several recruitment methods. These methods included OB/CNM referral, posted flyers at the front desk and in the waiting room of the OB/CNM Clinic. Potential subjects were given the phone number of the research coordinator for more information. The research coordinator conducted the initial screening either in person or by telephone. After the initial screening, subjects reviewed and signed the informed consent with the research coordinator. All Clinical Trial, Study One, and Study Two visits took place in the research clinic at UNTHSC.

Subgroups of Clinical Trial subjects were randomly selected for participation in Study One and Two. Subjects participating in Study One or Two reviewed and signed the informed consent with the research coordinator.

Informed consent was obtained by a trained clinical research coordinator (CRC) or other designated trained research team member. The CRC informed subjects of the nature of the research study, inclusion/exclusion criteria, potential risks and benefit of the study, and the subject's right to withdraw at anytime during the study without penalty or detriment to medical care. The original informed consent was kept separately in a locked file cabinet and not in the research chart where there may be a risk of breach in confidentiality.

After completing the informed consent process, subjects were randomly assigned to one of the three treatment conditions and scheduled to be seen in the Research Clinic. Subjects were asked not to disclose details of their treatment received unless specifically asked by their obstetrician. This helped maintain blinding, yet allowed for the obstetricians to break blinding conditions as may rarely be necessary for appropriate care of the patient. If the OB/GYN physician deemed it necessary to break blinding it was discussed with the PI.

Study participants were compensated for their time and travel expenses.

Protection Against Risks

Potential subjects were informed of the potential risks and benefits of the proposed research and clearly informed that their decisions to participate (or refusal to participate) would

in no way affect their care at the UNTHSC OB/CNM clinic. Participants completed their prenatal visit before receiving study treatments. The OB/CNM signed a release at each visit to authorize continued participation in the clinical trial. The development of a significant pregnancy complication was reason for immediate exclusion from further involvement in the study protocol.

All OMM and placebo ultrasound treatments were performed by trained and licensed physicians. If adverse events occurred, they were reported to the Institutional Review Board. If any subject was injured during participation, she was immediately referred to the appropriate healthcare resource.

All records and medical information was kept as confidential as possible under current local, state, and national law. Only key personnel in the study, the UNTHSC Institutional Review Board, the John Peter Smith Medical Center Institutional Review Board, and regulatory agencies were allowed access to the data. Subject records were kept in a locked file cabinet in a centralized location, and all data was reported in aggregate with no personal identifiers. The database does not contain personal identifiers. All subjects were given a code number for the database.

Potential Benefits of Research to the Subjects and Others

Based on anecdotal reports published by physicians who use OMM in obstetrics, pregnant women who receive OMM tend to have fewer complications and problems than are usually associated with pregnancy. The potential benefits of participating in this study included:

1. potential for decreased likelihood of complications of pregnancy and childbirth; 2. potential reduction in low back pain, before and after delivery; and 3. potential for increased feeling of well-being and quality of life. Others may benefit if OMM is found to be efficacious and provides insight into an additional treatment for women who are pregnant.

Risk Benefit Analysis

The potential benefits of participation for individual subjects include the possibility of better health outcomes, particularly in relation to complications of pregnancy, labor, and delivery, as well as low back pain and functional status. The potential benefits for the biomedical community include increased understanding of OMM and pregnancy, increased understanding of mechanisms of OMM, and improved evidence base and safety profile for a complimentary and alternative treatment for pregnancy.

Importance of the Knowledge to be Gained

Many women suffer from pain and decreased overall quality of life associated with pregnancy. Few medications or procedures are approved to minimize this negative impact on these women. OMM is a safe, non-pharmacologic intervention that may provide relief to this population. Additionally, this clinical trial may provide an indication as to whether OMM can decrease complications associated with pregnancy. Any intervention which can positively impact the incidence of pregnancy complications is of great importance to healthcare. If efficacious in decreasing pregnancy complications, OMM could be advocated as a low cost, low tech adjunct for decreasing pregnancy complications in places where high technology and high cost interventions are unavailable.

Data and Safety Monitoring Plan

The Principal Investigator was primarily responsible to ensure that Adverse and Serious Adverse Events were appropriately reported to the IRB and the funding organization. The Principal Investigator directed the Research Coordinator and any key personnel providing study related treatments to be alert for any subject who may have been having problems. All subjects continued with routine prenatal and post-partum obstetrical care to remain in the study. Participants were withdrawn from the study if they develop significant complications of their pregnancy.

This project, encompassing the Clinical Trial, Autonomic and Biomechanical studies (Studies 1 and 2) is being monitored by a Data and Safety Monitoring Board (DSMB) to ensure the highest standard of thoroughness and competency regarding the safety of our subjects and the integrity of our data.

The DSMB for this study consists of a committee of five members that will have at least two regularly scheduled meetings annually and other meetings as necessary according to the demands of the trial. The DSMB examines statistical reports with scientific diligence to ensure integrity of the data collection and assess the data for any trends that may relate to the safety of the trial. The DSMB holds both closed and open sessions as appropriate to review all adverse events and reports to the PI without compromising the blinding of the study. All of the members are from outside of the key personnel, and one is from another institution. With the understanding that one person may fulfill more than one role, the five roles are as follows:

1) Ethicist- an individual with the experience and knowledge in the role of advisor on the ethical principles surrounding issues that may arise in the conduct of clinical trials

2) Obstetrician- a board-certified expert in the field of obstetrics and women's health and familiar with the principles of osteopathic medicine

3) OMM specialist- an expert in the field of Osteopathic Manipulation with practice experience and knowledge in the outcome measures

4) Statistician/epidemiologist- an individual with the background and experience in the analysis and interpretation of data from clinical trial

5)) Basic scientist- an individual with knowledge and experience of human physiology clinical trials and the physiological outcome measures used in the study.

REFERENCES

1. King HH, Tettambel MA, Lockwood MD, Johnson KH, Arsenault DA, Quist R. Osteopathic manipulative treatment in prenatal care: A retrospective case control design study. J Am Osteopath Assoc. 2003 Dec;103(12):577-82.

2. Smith ML, Raven PB. Cardiovascular responses to lower body negative pressure in endurance and static exercise-trained men. Medicine & Science in Sports & Exercise. 1986 Oct;18(5):545-50.

3. Carter R,3rd, Watenpaugh DE, Wasmund WL, Wasmund SL, Smith ML. Muscle pump and central command during recovery from exercise in humans. J Appl Physiol. 1999 Oct;87(4):1463-9.

4. Ogoh SS. Carotid baroreflex responsiveness to head-up tilt-induced central hypovolaemia: Effect of aerobic fitness. J Physiol (Lond); J Physiol (Lond). 2003;551(2):601-8.

5. Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. Autonomic Neuroscience-Basic & Clinical. 2004 Jun 30;113(1-2):55-62.

6. Butler GC, Yamamoto Y, Xing HC, Northey DR, Hughson RL. Probing heart rate and blood pressure control mechanisms during graded levels of lower body negative pressure (LBNP). Microgravity Quarterly. 1992 Apr;2(2):133-40.

7. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. Gait Posture. 2005 Dec;22(4):317-21.

8. Kuchera ML, Kuchera WA. Osteopathic Considerations in Systemic Dysfunction. Revised 2nd Ed. ed. Columbus, OH: Greyden Press; 1994. p. 55,85; 187;193.

9. Johnson K. An integrated approach for treating the OB patient: Treating the five diaphragms of the body, part I. AAO Journal. 1991(Winter):6-9.

10. Hitchcock ME. Osteopathic care in pregnancy. Osteopathic annals. 1976;4(12):405.

11. Graham KE, Shaw HH, Mills M, Cotton L. Pregnancy, 3rd trimester and pre-delivery. In: Anatomic and Physiologic Basis of Osteopathic Manipulative Medicine In Visceral Disease. 1st ed. Tulsa, Oklahoma: Oklahoma State University College of Osteopathic Medicine; 2001. p. 74-75.

12. Stiles EG. Osteopathic manipulation in a hospital environment. J Am Osteopath Assoc. 1976 Dec;76(4):243-58.

13. Licciardone JC, Nelson KE, Glonek T, Sleszynski SL, des Anges C. Osteopathic manipulative treatment of somatic dysfunction among patients in the family practice clinic setting: A retrospective analysis. J Am Osteopath Assoc. 2005 Dec;105(12):537-44.

14. Berg G, Hammar M, Moller-Nielsen J, Linden U, Thorblad J. Low back pain during pregnancy. Obstetrics & Gynecology. 1988 Jan;71(1):71-5.

15. Daly JM, Frame PS, Rapoza PA. Sacroiliac subluxation: A common, treatable cause of low-back pain in pregnancy. Fam Pract Res J. 1991 Jun;11(2):149-59.

16. Gitlin RS, D.O., Wolf DL,D.O. Uterine contractions following osteopathic cranial manipulation--a pilot study. JAOA. 1992;92:1183.

17. Turk DC, Melzack R. Handbook of pain assessment. New York: Guilford Press; 1992.

18. Roland M, Morris R. A study of the natural history of back pain. part I: Development of a reliable and sensitive measure of disability in low-back pain. Spine. 1983 Mar;8(2):141-4.

19. Stratford PW, Binkley J, Solomon P, Gill C, Finch E. Assessing change over time in patients with low back pain. Phys Ther. 1994 Jun;74(6):528-33.

20. Beurskens AJ, de Vet HC, Koke AJ. Responsiveness of functional status in low back pain: A comparison of different instruments. Pain. 1996 Apr;65(1):71-6.

21. Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 health survey. Lincoln, RI: QualityMetric Incorporated; 2000.

22. 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 Jun;25(6):1276-86.

23. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, 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 Aug;59(2):178-93.

24. Malliani A, Lombardi F, Pagani M. Power spectrum analysis of heart rate variability: A tool to explore neural regulatory mechanisms. Br Heart J ; Br Heart J. 1994 Jan [cited 4/6/2009];71(1):1-2.

25. Turk DC, Melzack R. Psychophysical approaches to pain measurement and assessment. In: Handbook of pain assessment. New York : Guilford Press, c1992.; 1992. p. 11-192.

CHAPTER 4

DEVELOPMENT OF A CLINICAL AND RESEARCH PROTOCOL FOR OSTEOPATHIC MANIPULATIVE MEDICINE IN THIRD TRIMESTER PREGNANCY

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ABSTRACT

Background: Pregnancy is a time of physical and physiological changes to a woman's body. Many of these changes can predispose pregnant women to low back pain and its associated disability, as well as to complications of pregnancy, labor and delivery. Based on the premise that Osteopathic Manipulative Medicine (OMM) can help mitigate this process of change and concomitant pain, this doctoral research study was conducted as a prospective randomized placebo-controlled trial to evaluate the efficacy of OMM during pregnancy.

Methods: This study sought to enroll 400 women at or before 30 weeks of gestation. Subjects were randomized into one of three treatment groups: OMM protocol, placebo ultrasound, or standard care only. Study treatments were given after the subjects' routine prenatal visits during the third trimester. Primary outcomes were: pain, measured with a visual analogue scale, functionality using a questionnaire for back-specific disability, and occurrence of selected outcomes of pregnancy, labor and delivery, including meconium-staining of the amniotic fluid, preterm labor, conversion to caesarean section, incidence of high-risk status, and labor time.

Conclusion: This paper describes the manipulative medicine protocol and ultrasound placebo interventions used in the trial, and reviews the literature that provided the background for its design.

Trial registration: http://www.clinicaltrials.gov, NCT00426244

INTRODUCTION

Since the days of A.T. Still, osteopathic physicians have treated patients with any sort of clinical diagnosis or complaint, firm in the belief that by removing impediments to optimal function, they were helping the patient's own inherent mechanisms to promote healing and normalization of the body's processes. Pregnancy is perhaps the clinical condition that most powerfully illustrates this belief. During pregnancy dramatic physiological and biomechanical changes can cause significant pain, disability and stress to the mother, and may pose risks to the newborn. Although anecdotal reports support osteopathic management as a method of reducing complications of pregnancy, labor and delivery, there is a paucity of well-designed research to evaluate the safety and efficacy of Osteopathic Manipulative Medicine (OMM) in pregnancy. Therefore this study was designed to investigate the effects of OMM on selected outcomes of pregnancy, labor and delivery.

BACKGROUND AND SIGNIFICANCE

Despite decades of theory development and practice of osteopathic manipulative medicine (OMM), there are few rigorously controlled mechanistic studies of how OMM impacts the human body. Osteopathic physicians are trained to use examination of the musculoskeletal system in diagnosis and treatment of many conditions. OMM treatments are used to help the body adjust to environmental stressors to maintain or restore optimum health. Environmental stressors include trauma, infection, nutrition, and social experiences. OMM is a body-based

modality in which the patient is evaluated and treated as a whole to improve physiologic functioning and remove impediments to recovery from illness or debilitating conditions.

For this research protocol, OMM is defined as a collection of manual medicine techniques that are theoretically linked through assessment, diagnosis and treatment to an array of musculoskeletal disorders, systemic illnesses and other dysfunctional conditions of the human body. In this research we have applied specific OMM techniques to reduce or eliminate impediments to proper structure and function to assist the body's self-healing mechanisms.

BACKGROUND

Low Back Pain During Pregnancy

For this clinical study, low back pain is defined as self-reported chronic and/or acute low back and posterior pelvic pain. Back pain occurs frequently during pregnancy, with incidence rates varying between 48-90%. The pain can be mild or severe enough to interfere with daily activities. For example, up to 30% of 950 pregnant women reported in a survey that they had to stop performing at least one daily activity because of low back pain, thus negatively impacting their quality of life and that of their children.(1) As a gravid uterus grows, its increasing size and weight tilts the pelvis forward, which increases the lordosis in the lumbar region of the spine.(2) This alteration in posture strains the ligaments, muscles, and joints of the surrounding areas, which can cause pain. In addition, hormonal influences, especially of relaxin,(3) contribute to structural instability of the pelvis by allowing the sacroiliac joints(4) and pubic symphysis to widen.(5) Because of the bony instability and strain, the muscles frequently become hypertonic to add some support, and hypertonic muscles contribute to the feeling of pain and stiffness. Other

musculoskeletal factors that have been shown to relate to the development of low back pain in pregnancy are depth of lumbar lordosis,(6) sacroiliac subluxation,(4) sacral shearing,(7) and muscle fatigue.(8) For many years, these conditions have been treated by osteopathic physicians using OMM. Due to the potential risk to mother and child, many of the pharmaceutical treatments commonly used for low back pain, such as muscle relaxants and pain medication, are not recommended for use during pregnancy. Pregnant women frequently are left to endure the pain until the end of their pregnancy(9).

Manipulation has been shown to affect some of these musculoskeletal dysfunctions common in pregnancy. Daly *et al.*, (4) in a small pilot study (n=11), demonstrated that pregnant women with low back pain and sacroiliac subluxation responded well to manipulation of their sacroiliac joints, and 91% had significant relief of their low back pain. These results were supported by a similar small study (n=20) by McIntyre in 1996 with 75% of those patients reporting elimination of their pain.(10) Brady *et al.* reported a statistically significant decrease of their pregnant patients' pain after OMM (n=97).(11) Chiropractic manipulation, which tends to primarily use High Velocity-Low Amplitude (HVLA) or thrust techniques, has also been shown to decrease or relieve back pain during pregnancy.(12), (13). Manipulation is widely considered to be safe; in both the osteopathic and chiropractic literature, no negative outcomes have been reported as a result of manipulation during pregnancy.

In a recent study, Licciardone *et al.* found that patients who received OMM reported less pain and greater satisfaction with their back care. The treatment group also reported better physical functioning and mental health at one month into the trial.(14) Other studies have shown

that subjects who receive OMM use less medication for their back pain,(15) and improve sooner(16) than subjects who do not receive manipulation. There is an argument in the literature that manipulation has not been unequivocally proven to be of statistically significant benefit, and must be studied more to reach a decisive conclusion.(17) However, manipulation has been shown repeatedly to be of some benefit, and is widely considered safe.(18)

Functional status

Low back pain can be a source of significant disability during pregnancy. In 2004, Wang *et al.* reported that of 950 women that responded to a survey, 57% complained that low back pain interfered with their daily activities, 46.7% avoided some activity because of pain, 30.5% avoided exercise, and 10.6% had missed work because of low back pain.(1) This amount of disability can impact quality of life, and make it difficult for women to care for themselves, their other children, or to work outside of the home.

In a pilot study conducted at UNTHSC, an OMM protocol very similar to that presented in this dissertation was used to study the effect of OMM on low back pain and functional status in pregnant women. Results from that study indicate that OMM lessens or halts the deterioration in back-specific functioning that often characterizes the third trimester of pregnancy and thereby provides an important clinical benefit(19).

Meconium-stained Amniotic Fluid and Preterm Labor

Meconium-stained amniotic fluid (MSAF) and preterm labor occur in approximately 12.5-14% and 11.6%, respectively (20, 21)of all births. Both of these are considered

complicating factors of labor and delivery, and both have been linked to increased maternal stress. MSAF usually occurs in term or near-term pregnancies, and is linked with peripartum intrauterine stress and hypoxia. {{84 Klingner,M.C. 1999}}In about 5-10% of infants born through MSAF, Meconium Aspiration Syndrome occurs, with the development of respiratory distress, pneumonitis, and an associated death rate of about 12%.(22) Stress has also been implicated as a major risk factor in preterm labor and delivery.(21) MSAF and preterm delivery carry with them significant risks to the newborn, such as meconium aspiration syndrome as already mentioned, respiratory distress syndrome, congenital heart disease, infection, and other complications that can impact their survival rate and health.

King *et al.* (23) found a significant decrease in the incidence of MSAF and preterm labor in women who received OMM during pregnancy. Although the exact mechanism of this interaction is not understood, it can be described with scientific theories using the principles of osteopathic medicine, in the following way. As stated, pregnancy is a time of significant physiological and biomechanical change. The body, in its need to maintain an efficient state of homeostasis, must adapt to those changes. Anything that impedes the body's adaptation will decrease its efficiency, resulting in increased stress. Osteopathic philosophy states that structure and function are reciprocally interrelated, thus as structure is altered, so is function, and by improving the structure, the function improves as well. Therefore, decreasing the structural/postural stress may improve the body's ability to adjust to the physiological demands of pregnancy.

Pain itself is a stressor, and can increase the sympathetic tone within the autonomic nervous system. Two pilot studies have supported this relationship between pain and increased sympathetic tone and the moderating effects of OMM on autonomic balance. In the first study, inhibitory OMM was applied to the thoracic paraspinal region of healthy subjects with the aim of impacting the sympathetic chain ganglia which lies just anterior to the rib heads. Using a measure of heart rate variability, results indicated that the inhibitory mode of paravertebral manipulation was effective in shifting the autonomic balance to a greater parasympathetic predominance. This is consistent with a reduction in net sympathetic neural tone(2). The second study showed a similar effect on heart rate variability, but the OMM in this study was directed at the upper cervical spine, where it would be theorized to have more effect on the vagus nerve(24).

Therefore, OMM may impact maternal stress in two ways: one, by decreasing low back pain, and indirectly impacting sympathetic tone; and two, by addressing the anatomical structures related to the sympathetic or parasympathetic nervous system and more directly by decreasing the sympathetic tone.

Maternal-fetal Outcomes of Labor and Delivery

OMM offers more to the expectant mother than reduction of her back pain. Anecdotal and empirical reports of the benefit of prenatal OMM have been around as long as osteopathic medicine. Many DOs have surveyed their practices, and compared outcomes of pregnancy among patients treated and not treated with OMM with national averages. For example, Lillian Whiting, D.O. reported an average labor time of 9 hours, 54 minutes in 99 cases that received OMM, an average of 21 hours, 6 minutes for 24 cases without OMM, compared to a national

average at the time (1911) of 15 hours, 29 minutes. Similar results have been found by other osteopathic physicians, while other reported findings include decreased labor pain, less use of pain medication during delivery, less use of forceps, and less nausea and vomiting during pregnancy. In addition, the finding of decreased labor times has been corroborated in the chiropractic literature (6, 10, 21, 25-31).

More recently, two retrospective studies were completed by King et al.(23, 32) The first of these reports reviewed records of 155 women who received OMM during pregnancy at four different sites, and compared the incidence of certain outcomes with the national averages. They found a lower incidence of meconium-stained amniotic fluid (7.1% versus the national average of 14.6%), preterm delivery (3.2% versus a national average of 10.0%), and use of forceps (6.4% versus a national average of 19.5%).(31) King expanded this study in 2003, increasing the number of reviewed charts to 321, with a control (no OMM) group at each of the four sites. Results were similar, with a statistically significant reduction in the incidence of meconium-stained amniotic fluid and preterm delivery, while a marginally significant reduction (P=.07) in the use of forceps was reported.(23)

These findings are important because of the potential to mitigate the serious consequences that can accompany meconium-staining or preterm delivery. It is also important for physicians to consider that there can be a major economic impact of maternal-fetal risks in that almost half of all neonatal hospital charges are for premature infants.(21) The cost of an uncomplicated delivery averaged about $6,400, while a complicated delivery ranged from $20,000 to $400,000(33). It is not uncommon for these babies to have long-term complications,

which add to the cost of their care. Therefore, if OMM offers a low-risk intervention that could reduce the number of infants that are born prematurely or through meconium stained amniotic fluid, it would be important to consider incorporating it into standard prenatal care. The long-range implication could mean a significant decrease in health care costs and improved maternal and fetal health.

In summary, if a low-risk intervention, such as osteopathic manipulation, can improve pain, functional status, and outcomes of labor and delivery in pregnant women, it would be reasonable and preferred to incorporate it into prenatal care. The goals of the current study are to evaluate the safety and efficacy of OMM in third trimester pregnancy. This paper describes the protocol used in the study and reviews the literature providing the foundation for the protocol.

EXPERIMENTAL DESIGN

Study Hypothesis: OMM improves selected clinical outcomes in pregnancy. These outcomes are low back pain, functional status, incidence of meconium-stained amniotic fluid, and complications of labor and delivery.

Study Protocol

This study is a prospective, randomized, controlled, and blinded (phase 2?) clinical trial over 48 months with a sample of 400 gravid women. Patients of the OB/GYN clinic at the University of North Texas Health Science Center were approached about the study during their regularly scheduled visit to the obstetrician or midwife (OB/CNM) at 20-26 weeks of gestation. If they agreed to participate the Clinical Research Coordinator provided them with information

about the study, and obtained informed consent prior to enrolling them. After study enrollment the women were randomly assigned to one of the three treatment groups. This randomization process is blocked to ensure equivalent numbers in each treatment group. The flowchart below outlines the process for this study.

All subjects in all study groups are seen by a OMM physician on every study visit. Logistical precautions to safeguard the blinding of the obstetrical care provider, either a physician specializing in Obstetrics and Gynecology (OB/GYN) or a Certifed Nurse Midwife (OB/CNM) and the subjects in the two active intervention groups. The subjects are asked to not disclose details of their treatment received unless specifically asked by their OB/CNM. This is protective of blinding, but also permits the OB/CNM to break blinding conditions if absolutely required for appropriate care of the patient. Unblinding did not occur without prior discussion and agreement of the principal investigator.

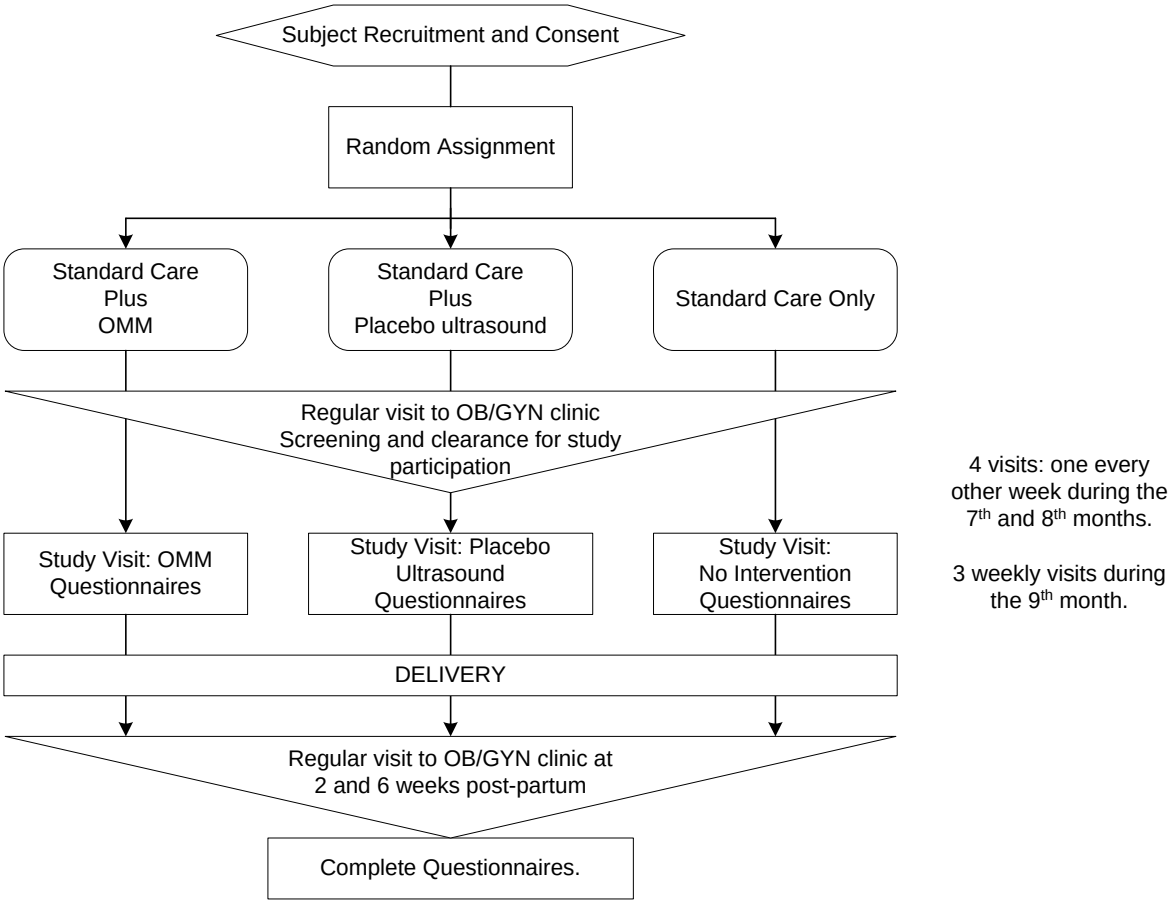

Figure 1

At each prenatal appointment, the examining OB/CNM determined whether the study participant could safely proceed with the research protocol and sent written approval for each research visit with the patient. If at any time the OB/CNM deems it inappropriate for the participant to continue in the research protocol, and/or their OB/CNM denies medical clearance for study participation on two occasions the subject is released from the study.

Study treatment visits are scheduled to immediately follow the regular OB appointment, but may occur within 24 hours of the OB visit. This occurs every other week during the 7th and 8th months of pregnancy (30, 32, 34 and 36 weeks) and weekly (for three weeks) during the 9th

month (37, 38, and 39 weeks) for a total of 7 pre-partum visits if the patient reaches normal term gestation. At each visit, the participants complete outcome questionnaires and receive the respective group intervention. In addition, there are 2-week and 6-week post-partum visits for questionnaires only. Subjects receive compensation for their time and travel at each study visit.

A physician who is board-eligible or board-certified by the American Osteopathic Board of Neuromusculoskeletal Medicine (AOBNMM) will perform the assessment and treatment of all subjects. The same physicians provide both the active intervention and the placebo treatment. While it is not possible to blind the physician providing the treatment, the OB/CNM, OB/GYN staff, the OMM research coordinator and the study participants are blinded. All participants are directed specifically not to disclose details of their treatment or non-treatment group status to the OB/CNM and staff.

Outcome Measures

The primary hypothesis of this study was that OMM would improve low back pain and functional status in third trimester pregnancy, and would reduce the incidence of certain complications of pregnancy, labor and delivery.

Outcome measures:

Pain measured with the Quadruple Visual Analog Scale(34),

Functionality measured with the Roland-Morris Disability Questionnaire(35),

Labor and delivery outcomes including information from the hospital medical chart and delivery record on high-risk status, weeks of gestation, labor time, and amniotic fluid color.

Measurement instruments:

Pain: the Quadruple Visual Analog Scale (QVAS) is a 4 question form that asks the subject to rate her back pain "now, at its average, best and worst" since her last visit.

Functional Status:The Roland-Morris Low Back Pain and Disability Questionnaire is a brief self-reported questionnaire of functional problems related to low back pain(35). It is a well-established measure of functional status, and has been translated into many languages for use around the world. It has been shown to be sensitive to change in low back pain over time(15, 36).

Clinical Study Subjects

Power Analysis

Because there are no known available published studies on the effects of OMM on low back pain in pregnant women, we have used several other methods to calculate our sample size for this study. Of the measures used, the largest sample size is required to measure the incidence of meconium staining. The data from the retrospective study(37)suggest that there was a 62% less incidence of meconium-stained amniotic fluid in the OMM group as compared to the control group. Therefore, assuming a 62% reduction between groups, 80% power and a 5% significance level ($p<0.05$), we calculate that 110 subjects per treatment group (330 subjects in total) would be sufficient to detect an effect of OMM on occurrence of meconium-stained amniotic fluid at delivery. Assuming a 20% drop-out rate we will recruit a total of 400 (minimum 396) subjects for this study.

Recruitment

Subjects are recruited from the Obstetrics and Gynecology (OB/GYN) clinic at the University of North Texas Health Science Center (UNTHSC) at Fort Worth during their second trimester (≤ 28 weeks gestation). During the pilot study, we averaged a 40% recruitment rate and had a 20% attrition rate. Assuming similar activity for this study, 400 patients will need to be recruited to allow for attrition and still have 330 complete the clinical study.

The study protocol maintains approval by the Institutional Review Board (IRB) of the University of North Texas Health Science Center. Additionally, a Data Safety and Monitoring Board (DSMB) has been established, and closely monitors the study for subject safety. The study was registered with ClinicalTrials.gov in January 2007 (ClinicalTrials.gov identifier, NCT00426244).

Inclusion and Exclusion Criteria

Inclusion criteria includes that the woman must be age 17 or older, 30 weeks or less of gestation at the start of the trial and have medical clearance from her OB/CNM at each study visit..

Women are ineligible for participation if any of the following conditions exist

1) Deemed high risk by the OB/CNM (including but not limited to: abruptio placenta, placenta previa, severe pre-eclampsia/eclampsia, vaginal bleeding, gestational diabetes);

2) Age 17 years or younger

Study subjects receiving any other manual therapies during the trial were released from the study.

If a subject stopped participating in the study, data was continuously collected with her permission. This is because the change in status may be an important consideration in our analysis. The reasons for discontinuation in the study were included for analysis purposes.

Clinical Study Expected Results

Based on results of previous studies and our preliminary findings, we expect that 1) subjects who receive OMM will have less progression of their back pain as measured by the Visual Analog Scale over the course of their third trimester that subjects who receive placebo ultrasound or standard care. We also anticipate 2) a difference in the functional status between the groups as measured by the Roland-Morris questionnaire and 3) Incidences of pregnancy complications such as meconium-staining and preterm delivery are also expected to be lower in the OMM group.

DESCRIPTION OF INTERVENTIONS FOR CLINICAL STUDY--OMM Protocol

Osteopathic Manipulative Medicine Techniques

The following material describes the OMM modalities used in this study for the group receiving OMM plus standard care. The physician may have used one or more of the below treatment modalities to treat the OMM Group study subject.

- *Myofascial Release (MFR):* Used to treat fascial restriction. The physician's hands, guided by continual palpatory feedback, apply force directed at the restriction to achieve

release of myofascial tissues. The physician can either directly engage a restrictive barrier, loading with a constant force until tissue release occurs, or guide the dysfunctional tissues along the path of least resistance until free movement is achieved.

- *Articulatory Treatment***:** The joint and its associated region of somatic dysfunction are gently guided into the restrictive barrier within its range of motion, and the physician attempts to gently overcome the restriction. The physician may employ traction, compression, or gentle springing of the joint and have the patient inhale or exhale in an attempt to optimize alignment and range of motion of the joint.

- *Muscle Energy Treatment:* The joint and its associated region of somatic dysfunction are gently guided into the restrictive barrier, which limits the area's normal range of motion. The patient is instructed to attempt to return to a neutral position, while the physician resists the patient's efforts. The patient is then instructed to desist from her efforts, and the physician then moves the dysfunctional region up to and against the new restrictive barrier.

- *Balanced ligamentous tension (BLT):* BLT addresses ligamentous strain. When the ligamentous articular mechanism of a joint is strained, it alters the permitted motion of that joint. By taking the joint into a position that balances the tension in the surrounding ligaments, the body is able to resolve the strain.

- *Soft Tissue:* A set of techniques that directly address the muscular and fascial structures of the body and their associated neural and vascular elements. Soft tissue techniques can involve traction or stretching, kneading or lateral stretching, and/or inhibition, which involves sustained deep pressure.

The above Osteopathic Manipulative Medicine treatments (OMM) are relatively gentle. A major OMM modality that is excluded from this protocol is High Velocity/Low Amplitude (or thrust), a direct technique that mobilizes joints with a short impulse of force. By eliminating this modality we may be eliminating a potentially useful treatment. However, due to the increasing ligamentous laxity that occurs in later pregnancy, the force used in a thrust technique is generally not necessary.

The OMM protocol addresses the regions of the body that are most likely to be dysfunctional in an advancing pregnancy. As the fetus nears term, the growing weight and distention of the uterus commonly causes some specific dysfunctions in the mother. The increased lumbar lordosis, reduced compliance of the respiratory diaphragm, and congestion and pressure on the viscera and pelvic veins adversely affect venous drainage, lymphatic flow, autonomic tone to viscera, ventilatory function and musculoskeletal mechanics of the patient's body, as well as increasing pain and reducing physical functional capacity. Although the breadth of the protocol encompasses the majority of tissues from the base of the head to the pelvis, there are specific rationales for treating certain areas. These rationales involve application of the osteopathic philosophy and the concept of the interrelationship of structure and function. Use of OMM to

improve the structural dysfunction is directed to decrease pain and improve overall functional status.

The goals and rationale for treatment according to region are:

- *Occipital-atlantal (OA) joint:* The occiput is the attachment site for many of the cervical muscles, which can become hypertonic due to the alteration of posture. The Vagus nerve, which exits the skull through the jugular foramen, courses through the cervical region to provide parasympathetic nerve supply to the upper gastrointestinal, pulmonary and cardiac systems(38).

- *The cervical vertebrae:* The phrenic nerve arises from the third, fourth, and fifth cervical nerves, and innervates the thoracoabdominal diaphragm. Somatic dysfunction of these vertebrae can affect the functioning of the phrenic nerve and, therefore, of the thoracoabdominal diaphragm.

- *Clavicles and Sibson's fascia:* Terminal vessels of the lymphatic system drain into the subclavian veins in the infraclavicular space and pass through Sibson's fascia (thoracic inlet fascia) on their way back to the heart. A strain pattern induced in Sibson's fascia can decrease the caliber of lymphatic vessels and their ability to efficiently return lymph through the thoracic duct and/or lymphatic duct(39). Obstruction of lymphatic return results in edema and stasis of interstitial fluids.

- *Thoracoabdominal diaphragm and lower six ribs:* The thoracoabdominal (respiratory) diaphragm becomes more restricted in motion as the uterus expands superiorly. This can effect ventilation, rib and spine movement, venous and lymphatic fluid flow, and digestion as the esophagus passes through the diaphragm. The lower six ribs are the attachment of the thoracoabdominal diaphragm and their position and motion directly affects its function(40-42).

- *Thoracolumbar junction:* Attachment site of the crura of the diaphragm; the position and motion of the vertebrae directly affects the function of the thoracoabdominal diaphragm. Also sympathetic nervous supply to the uterus and pelvic organs is from spinal segments T12-L2. Thus treatment of this region is directed to improve autonomic tone of the uterus(38, 40, 41).

- *Pelvic diaphragm:* Treatment of the strain patterns in the myofascial planes of the pelvic diaphragm is directed to improve the mobility and supportive ability of the pelvic diaphragm, and to decrease neural impingement. Due to the ball-valve effect of the uterus, these tissues are prone to lymphatic congestion, and treatment to improve lymphatic flow may potentially decrease the incidence of constipation, hemorrhoids, and perineal lacerations(39).

- *lnnominates:* Decreased somatic dysfunction in this area is predicted to directly decrease low back pain and improve functional status. Realignment of the innominates may improve the ability of the pelvis to accommodate the fetus during the labor and delivery

process(42). Somatic dysfunctions of the innominates can "also directly compromise the physical dimensions of the pelvic outlet, which can result in pelvic disproportion difficulties during delivery"(43).

- *Sacrum:* Treating the sacrum for somatic dysfunction is directed to improve its mobility and alignment so that the fetus has an uncompromised path of descent. Also, treatment of the sacrum will balance the parasympathetic nervous system tone to the uterus through the pelvic splanchnic nerves, thus preventing poor cervical dilation due to decreased parasympathetic tone during labor and delivery. Sacro-iliac dysfunction is thought to be the most common reason for severe low back pain in pregnancy.(4, 43, 44)

- *Hips:* Somatic dysfunction of the hip flexors, internal and external rotators of the lower extremity, and femur can impact the alignment of the innominates and sacrum, and affect gait. Treatment will be directed at improving the position and mobility of these structures and their associated myofascial components.

- *Cranium:* Subjects will also be treated with an Osteopathy in the Cranial Field technique, the compression of the fourth ventricle (CV4). This technique has in the past been linked with inducing labor in post-dates women(45), but is widely used during pregnancy and generally considered safe.

The treatment intervention session lasted approximately 20-30 minutes.

A standardized protocol for OMM is difficult to apply for every patient. In constructing the protocol to be used in this study, the goal was to create a protocol that would treat the most common dysfunctions seen in pregnancy in the majority of patients. As the protocol involves multiple treatment modalities applied to several different body regions, it is difficult to determine precisely which specific treatment may decrease the incidence of a particular pregnancy complication. However, the scope of the clinical study is only to determine the efficacy of OMM to decrease pain and increase functional status in pregnancy. If OMM proves to be efficacious, it must be left to future studies to further delineate the relationship between specific manual treatments and specific therapeutic benefits.

Placebo Ultrasound Interventions

The issue of placebo control interventions in osteopathic manipulation research is controversial. A placebo treatment is advocated in studies with manipulation because there may be many reasons a patient may exhibit benefit from treatment aside from the biomechanical, fluid or neurological consequences of the manipulation itself. In addition to the structural changes induced by OMM, OMM may generate a positive clinical response because of the ancillary effects of: (1) the "laying on of hands"; (2) greater attention from and interaction with the treating physician; (3) an expectation of therapeutic effect. Thus, the use of a placebo or placebo control is generally warranted in trials of osteopathic manipulation to help control for the potential ancillary effects.

The goal in designing a placebo is to: (1) provide an alternate treatment to OMM that provides a similar degree of physician-patient interaction to control for the potential effect of

'greater attention'; (2) provide an equal expectation of therapeutic effect; and (3) provide similar sensations of physical contact to simulate "laying on of hands". This all needs to occur without actually causing direct mechanical effects to the musculoskeletal, vascular or neurologic systems.

For this study, the placebo treatment was a subtherapeutic ultrasound systematically administered over the same major body regions as addressed by the OMM. The same osteopathic physician who performs the OMM will administer these subtherapeutic placebo ultrasound treatments. This protocol may provide a genuine anticipation of therapeutic effect among participants, as it allows for tactile stimulation over the same anatomical distribution as OMM provided in the treatment group, and also provides for similar time and attention as that given to participants in the OMM treatment group. The subjects in the placebo group will receive the subtherapeutic ultrasound treatments after each of their scheduled prenatal obstetrical visits. Thus, an ultrasound placebo treatment session will last approximately 30 minutes, the same as the OMM treatment. Ultrasound will be applied for 2 minutes bilaterally at each of the areas of primary focus for the OMM including the neck, scapular region, thoraco-lumbar junction, lumbo-sacral junction, lumbar paraspinal region, sacro-iliac joint, and inguinal ligament at an intensity of $0.1 W/cm^2$ and 10% pulsed mode (i.e., at the lowest setting and with the greatest cycle interruption). These treatments will be applied through the subjects' clothes in the same manner that OMM is provided without requiring the subjects to undress.

Standard Care Only

The experimental group receiving Standard Care only will receive standard obstetrical care from her obstetrician, but no experimental intervention. She will see the OMM physician at the research clinic to maintain the blinding conditions as closely as possible, complete her questionnaires and receive her payment for the visit.

CONCLUSION

The OMM protocol used in this study on third-trimester pregnancy is pertinent to both clinical and research purposes. It consists of well-defined, standardized techniques that are universally taught at colleges of osteopathic medicine in the United States, and is therefore easily replicated and generalizable. A 20-minute protocol applied in conjunction with standard prenatal care is also feasible to implement in a clinical practice. We expect the results of this study will identify whether or not OMM impacts the investigated outcomes of pregnancy, labor and delivery and will help guide the future treatment of pregnant women.

REFERENCES

1. Cheng YW, Nicholson JM, Nakagawa S, Bruckner TA, Washington AE, Caughey AB. Perinatal outcomes in low-risk term pregnancies: Do they differ by week of gestation? Obstet Gynecol ; Obstet Gynecol ; Am J Obstet Gynecol. 2008 Oct;199(4):370.e1,370.e7.

2. Kinzler D. Sustained inhibitory rib-raising and microneurographic measurement of sympathetic nerve activity under cold-pressor stress. Thesis University of North Texas Health Science Center Unpublished. 2007.

3. Kristiansson P, Svardsudd K, von Schoultz B. Serum relaxin, symphyseal pain, and back pain during pregnancy. American Journal of Obstetrics & Gynecology. 1996 Nov;175(5):1342-7.

4. Cheng YW, Nicholson JM, Nakagawa S, Bruckner TA, Washington AE, Caughey AB. Perinatal outcomes in low-risk term pregnancies: Do they differ by week of gestation? Am J Obstet Gynecol. 2008 Oct;199(4):370.e1,370.e7.

5. R.E Brady, J. Rottman, R.E. Kappler, E.K. Veith. Osteopathic manipulation to treat musculoskeletal pain associated with pregnancy. JAOA. 1997;97(8):479.

6. Whiting LM. Can the length of labor be shortened by osteopathic treatment. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1911;11:917.

7. Treadwell RC, Magnus WW. Sacral shear: Review and a new treatment method for obstetrical patients. . 1996(Spring):16-18.

8. Anderson C. Exercise and pregnancy. ICA REVIEW. 2004:52-61.

9. Heckman JD, Sassard R. Musculoskeletal considerations in pregnancy.[see comment]. Journal of Bone & Joint Surgery - American Volume. 1994 Nov;76(11):1720-30.

10. Troyanovich S. Pregnancy and the chiropractic advantage. Today's Chiropractic. 1992;21(6):46-48.

11. Franklin ME, Conner-Kerr T. An analysis of posture and back pain in the first and third trimesters of pregnancy. Journal of Orthopaedic & Sports Physical Therapy. 1998 Sep;28(3):133-8.

12. Anderson C. Exercise and pregnancy. ICA REVIEW. 2004:52-61.

13. Iverson GD, Coleridge ST, Fulda KG, Licciardone JC. What factors influence a family physician's decision to refer a patient to a specialist?. Rural & Remote Health. 2005 Jul-Sep;5(3):413.

14. Ogoh SS. Carotid baroreflex responsiveness to head-up tilt-induced central hypovolaemia: Effect of aerobic fitness. J Physiol (Lond); J Physiol (Lond). 2003;551(2):601-8.

15. Stratford PW, Binkley J, Solomon P, Gill C, Finch E. Assessing change over time in patients with low back pain. Phys Ther. 1994 Jun;74(6):528-33.

16. Smutny CJ, Wells MR, Bosak A. Osteopathic considerations in parkinson's disease. J Am Osteopath Assoc. 1998;98(7):389.

17. Licciardone J, Gamber R, Cardarelli K. Patient satisfaction and clinical outcomes associated with osteopathic manipulative treatment. J Am Osteopath Assoc. 2002 Jan;102(1):13-20.

18. Morris ME, Bilney B, Matyas TA, Dalton GW. Short-term relationships between footstep variables in young adults. Gait Posture. 2007 Feb;25(2):229-35.

19. Stoll ST, Buchanan S, Hensel KL, King HH, Fulda KG, Licciardone JC. Osteopathic manipulative treatment of back pain and related symptoms during pregnancy: A randomized controlled trial. In press .

20. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. Gait Posture. 2005 Dec;22(4):317-21.

21. TAYLOR GW. The osteopathic management of nausea and vomiting of pregnancy. J Osteopath (Kirksville). 1948 Apr;55(4):14-6.

22. Licciardone JC, Gamber RG, Russo DP. Quality of life in referred patients presenting to a specialty clinic for osteopathic manipulative treatment. J Am Osteopath Assoc. 2002 Mar;102(3):151-5.

23. Licciardone JC, Fulda KG, Smith-Barbaro P. Rating interest in clinical research among osteopathic medical students. J Am Osteopath Assoc. 2002 Aug;102(8):410-2.

24. Giles PD. Effects of cervical manipulation on cardiac autonomic control. 2006.

25. Whiting L. The osteopathic management of pregnancy, and the reduction of obstetrical mortality. J Am Osteopath Assoc ; JAOA. 1934;33(8):531-533.

26. Still E. Osteopathic obstetrics. Journal of Osteopathy. 1897;4(4):203-204.

27. Dooley W. Osteopathy's contribution to prenatal care. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1946;46(1):6-7.

28. Guthrie RA. Lumbar inhibitory pressure for lumbar myalgia during contractions of the gravid uterus at term. J Am Osteopath Assoc. 1980 Dec;80(4):264-6.

29. Guthrie RA, Martin RH. Effect of pressure applied to the upper thoracic (placebo) versus lumbar areas (osteopathic manipulative treatment) for inhibition of lumbar myalgia during labor. J Am Osteopath Assoc. 1982 Dec;82(4):247-51.

30. Hart LM. Obstetrical practice. J Am Osteopath Assoc ; J Am Osteopath Assoc. 1918:609.

31. King HH. Osteopathic manipulative treatment in prenatal care: Evidence supporting improved outcomes and health policy implications. AAO Journal. 2000(10):25-33.

32. Fulda KG, Licciardone JC, Rene A, Blakley S. A study of hepatitis A seropositivity in dallas county, texas, 1998 through 1999. Tex Med. 2002 Dec;98(12):50-5.

33. Laman J, King M. Promoting healthy babies. Feb. 1994.

34. Turk DC, Melzack R. Handbook of pain assessment. New York: Guilford Press; 1992.

35. Roland M, Morris R. A study of the natural history of back pain. part I: Development of a reliable and sensitive measure of disability in low-back pain. Spine. 1983 Mar;8(2):141-4.

36. Beurskens AJ, de Vet HC, Koke AJ. Responsiveness of functional status in low back pain: A comparison of different instruments. Pain. 1996 Apr;65(1):71-6.

37. King HH, Tettambel MA, Lockwood MD, Johnson KH, Arsenault DA, Quist R. Osteopathic manipulative treatment in prenatal care: A retrospective case control design study. J Am Osteopath Assoc. 2003 Dec;103(12):577-82.

38. Kuchera ML, Kuchera WA. Osteopathic Considerations in Systemic Dysfunction. Revised 2nd Ed. ed. Columbus, OH: Greyden Press; 1994. p. 55,85; 187;193.

39. Johnson K. An integrated approach for treating the OB patient: Treating the five diaphragms of the body, part I. AAO Journal. 1991(Winter):6-9.

40. Hitchcock ME. Osteopathic care in pregnancy. Osteopathic annals. 1976;4(12):405.

41. Graham KE, Shaw HH, Mills M, Cotton L. Pregnancy, 3rd trimester and pre-delivery. In: Anatomic and Physiologic Basis of Osteopathic Manipulative Medicine In Visceral Disease. 1st ed. Tulsa, Oklahoma: Oklahoma State University College of Osteopathic Medicine; 2001. p. 74-75.

42. Stiles EG. Osteopathic manipulation in a hospital environment. J Am Osteopath Assoc. 1976 Dec;76(4):243-58.

43. Licciardone JC, Nelson KE, Glonek T, Sleszynski SL, des Anges C. Osteopathic manipulative treatment of somatic dysfunction among patients in the family practice clinic setting: A retrospective analysis. J Am Osteopath Assoc. 2005 Dec;105(12):537-44.

44. 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 Jun;25(6):1276-86.

45. Gitlin RS, D.O., Wolf DL,D.O. Uterine contractions following osteopathic cranial manipulation--a pilot study. JAOA. 1992;92:1183.

CHAPTER 5

ACUTE IMPROVEMENT IN HEMODYNAMIC CONTROL AFTER OSTEOPATHIC MANIPULATIVE MEDICINE IN THE THIRD TRIMESTER OF PREGNANCY

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ABSTRACT

Background: Osteopathic Manipulative Medicine (OMM) is a body-based modality in which the patient is evaluated and treated as a whole to improve physiologic functioning (including autonomic control) and remove impediments to recovery from illness. During pregnancy, many physiological changes occur, including decreased mean arterial pressure and systemic vascular resistance, increased circulating volume, heart rate, and cardiac output. In addition, evidence for altered neural control of blood pressure during pregnancy may adversely affect the response to stress in these women. OMM is theorized to improve peripheral circulation by treating the fascial planes through which the blood vessels travel, and to improve autonomic balance by improving the tissues around the nervous system, thus optimizing its function. Therefore, we hypothesized that OMM acutely improves both the autonomic and hemodynamic control in women during the third trimester of pregnancy.

Methods: Fifty-eight subjects were recruited from the obstetric clinics of the University of North Texas Health Science Center at 30 weeks gestation. Subjects were randomized into one of three treatment groups: OMM, placebo ultrasound, or standard care only (N=20, 19 and 19 in each group respectively).

Results: Measurements during the study included hemodynamic measurements, heart rate, and heart rate variability measurements as an index of autonomic function. Measurements were recorded in response to head-up tilt with and without engagement of the skeletal muscle pump. The response to tilt was not affected by OMM or placebo ultrasound, however, the systolic blood pressure response to toe raising was increased after OMM and was accompanied by a lower heart rate and enhanced vagal control of heart rate.

Conclusions: These data suggest that OMM improved hemodynamic control during engaging of the skeletal muscle pump that 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(1). These changes present a physiologic stress to the mother. In addition, maternal stress can have significant implications for the fetus. Despite a well-defined understanding of alterations of physiology associated with pregnancy and how the autonomic nervous system controls short-term cardiovascular function, there is a general lack of knowledge regarding the autonomic control of hemodynamic function during pregnancy. Moreover, there have been no studies on the effect of Osteopathic Manipulative Medicine (OMM) on hemodynamic control in pregnancy.

Increased resting sympathetic output has been linked to pregnancy- induced hypertension,(2) and preeclampsia(3). In addition, corticotrophin-releasing hormone, which is elevated in situations of increased maternal stress, has been linked to preterm labor(4, 5). 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, and this is known to adversely affect long-term health. Heart rate variability (HRV) has been shown to be a marker of autonomic tone. HRV measures fluctuations in autonomic input to the heart by the vagus nerve from the

parasympathetic system and the effects of epinephrine and norepinephrine by the sympathetic system.(6)

As noted above, it is unknown whether these changes in autonomic function manifest as altered hemodynamic control. Limited literature suggests that hemodynamic control does change throughout the course of pregnancy. 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 in which the sympathetic-mediated vasoconstrictor responses are blocked. (7) The response to standing has been studied more extensively (8-12). Although not a prevalent problem, orthostatic hypotension during pregnancy may be a concern in part because of these reduced compensatory responses as well as a structural limitation of venous return imparted by the size and position of the uterus.

One of the theoretical mechanisms of Osteopathic Manipulative Medicine (OMM) is that it affects autonomic balance through improving the tissues around the nervous system, thus reducing any pressure on the nerves themselves, and optimizing the function of the system. If indeed, OMM 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. A recent study from this laboratory demonstrated that OMM can reduce directly-measured sympathetic neural activity in healthy individuals.(13) In this study, we examined the acute effects of OMM on autonomic balance by comparing the HRV before and after OMM treatments.

A second theoretical benefit of OMM is the improvement of pelvic mobility and structural restrictions. These restrictions within the pelvic girdle can be significant due to the presence of the large uterus and accompanying body postural changes that occur 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 compressed lymphatic and venous vessels and impede fluid return to central circulation. In the presence of somatic dysfunction in the pelvis, this impedance may be exacerbated. In this study, we tested the hypothesis that OMM improves the hemodynamic control during both an orthostatic challenge (head-up tilt) and during engagement of the skeletal muscle pump.

METHODS

Subjects: Fifty-eight volunteers (age 18-34) who were seen in the obstetrics clinic between the 28th and 30th week of pregnancy were recruited for this study. After screening for inclusion/exclusion criteria, these 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. The primary exclusion criteria included 1) self-reported history of syncopal episodes, 2) patients deemed to be high risk by the obstetrician (including but not limited to: abruptio placenta, placenta previa, severe pre-eclampsia/eclampsia, vaginal bleeding, gestational diabetes), 3) patients 17 years or younger (females 17 years of age and younger are considered pediatric high risk pregnancies and, therefore, ineligible for inclusion), and 4) patients with a lower extremity injury (sprain or fracture).

Upon arrival to the laboratory on the experimental day, the subject was instrumented for the measurements of heart rate (Lead II ECG) and beat-to-beat arterial pressure (Finometer). The subject then laid down in the left lateral recumbent position and in a slight head-up position (10° head-up tilt) on a circular-frame bed (Stryker) that allows for tilting to specific angles. After a period of 20 minutes of quiet rest, baseline data were collected. This included baseline heart rate, blood pressure, leg volume, estimates of stroke volume and assessment of heart rate variability as determined from a 5 minute period of continuous heart rate measurement during quiet uncontrolled breathing. All measures were recorded on a computerized data acquisition system (WINDAQ) for analysis.

The same measures were then obtained continuously during an orthostatic challenge (60^{o} head-up tilt—HUT) with and without skeletal muscle pump engagement (toe-raising). After the baseline period, the patient was tilted to 60^{o} head-up tilt for 5 minutes followed by 4 minutes of intermittent calf muscle tension (toe raises) in a cadence of 2 seconds up and 3 seconds down. The toe raise was performed such that the heel rose to approximately one inch off the base of the bed. Following the toe raises, the subject recovered for an additional 5 minutes. The 5 minute period of tilting was adequate to obtain a clear steady-state period and obtain sufficient data to estimate heart rate variability measures. Likewise, the four minute period of toe raising allow 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: OMM, placebo ultrasound, or standard care only. The OMM group participants received a 20-30 minute standardized set of hands-on treatments to her head, neck, abdominal diaphragm, back, pelvis, sacrum, and pelvic diaphragm. Placebo ultrasound group participants received a 20 minute subtherapeutic ultrasound systematically administered over the same major body regions as addressed by the OMM treatment. These treatments were applied through the subjects' clothes in the same manner that OMM was provided without requiring the subjects to undress. Subjects in the standard care only group received no treatment, but instead had 20 minutes of quiet time between measurements.

Measurements: Arterial pressure was measured non-invasively, by use of a Finometer photoplethysmographic monitor placed around the middle finger. Heart rate variability was estimated as follows: beat-to-beat values of R-R interval were recorded digitally into a data acquisition system (WINDAQ, Akron, OH). The data were then linearly interpolated and re-sampled at 2Hz 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.(6) High frequency (HF) power of RR interval (0.2-0.4 Hz), similar to normal respiratory rhythm, will be 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 RR interval is widely recognized to be an index of the balance between the sympathetic and parasympathetic systems and will be used for this purpose.(15, 16)

Analyses:

Power Analysis. The variance data from prior studies in which changes of heart rate variability were obtained during orthostatic challenges (head-up tilt or lower body negative pressure) were used to estimate statistical power and the target subject number(17-21). From this analysis, an N of 18 in each group was determined to be sufficient to obtain a 50% effect size and achieve a power $\geq$ 0.8 (estimated range of power 0.82-0.90) with a significance level of $p<0.05$ for all variables. In anticipation of a 40% dropout rate, a target recruitment N will be a total of 60 patients to achieve 20 in each treatment group.

Statistical analyses: Baseline data prior to the first physiologic interventions were compared across treatment groups with a one-way analysis of variance (ANOVA). Similarly, the pre-treatment responses to the head-up tilt and toe raise interventions were compared across treatment groups using the same one-way ANOVA approach. For all variables, these analyses were not significantly different ($p > 0.40$); therefore, individual responses for each treatment were compared before and after treatment to determine whether there was a treatment effect by use of a paired Student's T test. For data in which a test for normality failed, a Rank Sum test was used for these comparisons. An α level of 0.05 was set for significance.

RESULTS

Baseline conditions

The baseline data are summarized in Table 1. As noted by these data, there were no significant differences in baseline blood pressure, heart rate or any of the measures of autonomic control derived from assessment of heart rate variability ($p > 0.58$). Therefore, there was no requirement to correct for baseline differences or shifts within the analyses of the responses to interventions described below.

None of the treatments significantly affected baseline measures of blood pressure, heart rate or any of the indices of heart rate variability (all comparisons $p > 0.29$) .

Baseline responses to head-up tilt

The baseline responses to head-up tilt are summarized in Figures 1-3. The blood pressure responses to head-up tilt shown in Figure 1 suggest that mean arterial pressure was maintained or slightly increased in all groups ($0.05 > p > 0.13$), while the systolic arterial pressure was not significantly affected in any of the groups ($p > 0.20$). Heart rate responses to head-up tilt were consistently increased in all groups and there were no differences between the groups as shown in Figure 2. Finally, Figure 3 summarizes the heart rate variability responses to head-up tilt for each group. The HF power of the power spectrum was significantly reduced in all groups during the head-up tilt ($p < 0.01$), whereas, LF power did not significantly change, however the resulting HF/LF power was consistently decreased (($p < 0.01$).

Baseline responses to toe raising

The baseline responses to toe raising are summarized in Figures 4-6. The blood pressure responses to toe raising are summarized in Figure 4. Both mean arterial pressure and systolic arterial pressure were increased relative to passive tilt in all groups ($p<0.01$). Heart rate tended to decrease slightly in all three groups, however, there were no significant differences between the groups ($p =0.72$) as shown in Figure 5. The data in Figure 6 summarize the changes in heart rate variability indices during toe raising for each group. The HF power of the power spectrum did not change significantly, however, there was a tendency for a slight increase ($0.05>p>0.11$). Likewise the LF power did not change significantly, however the HF/LF power consistently increased in all groups ($p < 0.01$) and there were no differences in the response between the groups ($p = 0.59$).

Treatment effects on the response to head-up tilt

The respective treatment effects on the responses to head-up tilt are summarized in Table 2. The changes in blood pressure, heart rate and heart rate variability measures before and after each respective treatment were not different for either the individual effects or between the groups (all comparisons $p>0.35$) .

Treatment effects on the response to toe raising

The effect of each treatment on the responses to toe raising are summarized in Figures 7-9. There was no significant effect of either the standard care or ultrasound placebo treatment conditions on the response of any variables to the toe raising maneuver (all comparisons $p>0.46$). In contrast, OMM treatment had significant effects to enhance the increase in systolic

blood pressure during head-up tilt as shown in Figure 7. The heart rate response to toe raising demonstrated a greater decrease after the OMM treatment as shown in Figure 8. Finally, accompanying these responses was a tendency for enhanced vagal control (HF power) and vagal predominance (HF/LF ratio) during toe raising after the OMM treatment as shown in Figure 9.

DISCUSSION

This study is the first to address the effects of osteopathic manipulative medicine (OMM) on the autonomic and hemodynamic control in healthy women in their third trimester of pregnancy. Autonomic control has been shown to be altered at many stages of pregnancy and this in turn may impact both how these women manage stressful states and how their structural changes may impact hemodynamic regulation during an orthostatic challenge. In this study, the primary finding was that OMM can improve the hemodynamic response associated with engagement of the skeletal muscle pump via toe raising; this is associated with a reduced heart rate and enhanced parasympathetic state as assessed by heart rate variability indices. There was no effect of OMM on basal measures of heart rate variability or on the response to head-up tilt alone, thus it appears that the OMM benefit observed during toe raising was due to improvement in the support of venous return during the toe raising maneuver.

Pregnancy and autonomic and hemodynamic changes

Pregnancy is accompanied by significant changes in the hemodynamic state of a woman, the autonomic state and autonomic control mechanisms, and the ability to respond to physiological and psychological stressors. Complications of maladaptive cardiovascular control are a serious problem when it occurs in pregnant women. Preeclampsia, pregnancy-induced hypertension, peripartum cardiomyopathy and other pathologic states can put both the mother and fetus at serious risk, and have been related to abnormal autonomic balance(22-24). The normal changes in hemodynamic and autonomic function are significant alone, however, in the presence of a developing co-morbidity, these

natural effects of pregnancy may create a further risk for the patient. Hemodynamic changes accompanying pregnancy include an impairment of neural control of blood pressure as evidenced by the pressor responses to Valsalva's maneuver and exercise (7, 25-28) . The response to standing or head-up tilt is somewhat variable depending on the study. Syncopal symptoms tend to be increased particularly in the second and early third trimester of pregnancy (8, 29). This appears to be due in part to a reduction in cardiac output (8, 10). Perhaps more importantly is a reduction in the reflex autonomic responses leading to compensatory tachycardia and vasoconstriction (8, 12). The heart rate responses also tend to be reduced during an orthostatic challenge (12, 29, 30), however, some studies suggest that the heart rate response is unchanged (7, 10, 11, 31). So the responses appear to be variable in these healthy women. In addition, there is limited data to suggest that in mid- to late pregnancy the catecholamine response to orthostasis is reduced (12, 32). Perhaps more importantly, the changes in heart rate variability indices of autonomic control suggest that pregnancy is accompanied by a blunting of the vagal control as evidenced by reduced time-domain measures as well as the high frequency power of the power spectrum of heart rate (26, 33, 34). Collectively, these data suggest that both autonomic and hemodynamic control is blunted in pregnancy. As noted before, this state may represent a condition in which a pregnant woman is unable to respond as effectively to physiological stressors which may in turn place them an undue risk.

OMM effects on the response to Tilt

There were no significant differences in the response to tilt with any of the treatment conditions. The lack of the OMM effect suggests that there was not a direct effect of OMM on the basal autonomic state or its control. Previous studies have suggested that certain OMM techniques can enhance vagal control of heart rate and show increased HF power and HF/LF ratio consistent with a shift to a greater vagal predominance in the autonomic balance(15). In this study this lack of direct effect on autonomic function was also observed as the baseline indices of heart rate variability were unchanged after OMM. 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 treatment.

OMM effects on the response to Toe Raising

The most significant finding in this study was am improvement in the blood pressure response to toe 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 pre-treatment conditions; however, only the OMM produced an alteration in this response. The OMM treatment lead to an enhanced blood pressure increase during the toe raising maneuver which was accompanied by a reduction in heart rate and shift to a more parasympathetic predominant autonomic balance as evidenced by the HF/LF ratio of the heart rate spectrum. 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. Therefore, it follows that the primary improvement was mediated by an improvement in the venous return during the toe raising maneuver and that the enhancement in heart rate and autonomic balance was secondary to the enhanced blood pressure.

An application of osteopathic reasoning would support that OMM would enhance venous return. During pregnancy, the weight and size of the uterus compresses on venous and lymphatic vessels, creating a ball-valve effect which increases the pooling of blood in the lower extremities. OMM 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 flow in blood vessels, and therefore contribute to restricted venous drainage and tissue congestion, and therefore greater pooling. Releasing this strain can increase venous return to central circulation (38).

Clinical Significance and Conclusion

The autonomic and hemodynamic effects of OMM described in this paper could have significant clinical implications for pregnant women. 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. The shift in autonomic tone toward a more parasympathetically-dominant state could also impact the incidence of complications such as peri-partum cardiomyopathy, pregnancy- induced hypertension,(2) and preeclampsia(3)., all of which have been linked to sympathetically-dominant states. (22-24).

Few medications or procedures are approved to effectively treat these conditions in pregnancy due to potential risk to the fetus. OMM is a safe, non-pharmacologic intervention that may provide benefit to this population. Additionally, this clinical trial may provide an indication as to whether OMM can decrease complications associated with pregnancy. Any intervention which can positively impact the incidence of pregnancy complications is of great importance to healthcare. If efficacious in decreasing pregnancy complications, OMM 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.

REFERENCES

1. Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. Obstet Gynecol Surv. 1994 Dec;49(12 Suppl):S1-14.

2. Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: A systematic review and meta-analysis of randomized controlled trials. BMC Musculoskeletal Disorders. 2005;6:43.

3. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia -- a state of sympathetic overactivity. N Engl J Med. 1996 Nov 14;335(20):1480-5.

4. Hobel C, Culhane J. Role of psychosocial and nutritional stress on poor pregnancy outcome. J Nutr. 2003 May;133(5 Suppl 2):1709S-17S.

5. McLean M, Smith R. Corticotrophin-releasing hormone and human parturition. Reproduction. 2001 Apr;121(4):493-501.

6. Berg G, Hammar M, Moller-Nielsen J, Linden U, Thorblad J. Low back pain during pregnancy. Obstetrics & Gynecology. 1988 Jan;71(1):71-5.

7. 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.

8. Pyorala T. Cardiovascular response to the upright position during pregnancy. Acta Obstet Gynecol Scand ; Acta Obstet Gynecol Scand. 1966;45:Suppl 5:1-116.

9. Easterling TR, Schmucker BC, Benedetti TJ. The hemodynamic effects of orthostatic stress during pregnancy. Obstet Gynecol ; Obstet Gynecol. 1988 Oct;72(4):550-2.

10. Clark SL, Cotton DB, Pivarnik JM, Lee W, Hankins GD, Benedetti TJ, et al. Position change and central hemodynamic profile during normal third-trimester pregnancy and post partum. Obstet Gynecol ; Am J Obstet Gynecol. 1991 Mar;164(3):883-7.

11. Droste S, Sorensen T, Price T, Sayers M, Benedetti T, Easterling T, et al. Maternal and fetal hemodynamic effects of autologous blood donation during pregnancy. Obstet Gynecol ; Am J Obstet Gynecol. 1992 Jul;167(1):89-93.

12. 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 ; Br J Obstet Gynaecol. 1985 Jul;92(7):722-31.

13. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. Gait Posture. 2003 Feb;17(1):68-74.

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 Jun;25(6):1276-86.

15. Giles PD. Effects of cervical manipulation on cardiac autonomic control. 2006.

16. Still E. Osteopathic obstetrics. Journal of Osteopathy. 1897;4(4):203-204.

17. Smith ML, Raven PB. Cardiovascular responses to lower body negative pressure in endurance and static exercise-trained men. Medicine & Science in Sports & Exercise. 1986 Oct;18(5):545-50.

18. Carter R,3rd, Watenpaugh DE, Wasmund WL, Wasmund SL, Smith ML. Muscle pump and central command during recovery from exercise in humans. J Appl Physiol. 1999 Oct;87(4):1463-9.

19. Ogoh SS. Carotid baroreflex responsiveness to head-up tilt-induced central hypovolaemia: Effect of aerobic fitness. J Physiol (Lond); J Physiol (Lond). 2003;551(2):601-8.

20. Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. Autonomic Neuroscience-Basic & Clinical. 2004 Jun 30;113(1-2):55-62.

21. Butler GC, Yamamoto Y, Xing HC, Northey DR, Hughson RL. Probing heart rate and blood pressure control mechanisms during graded levels of lower body negative pressure (LBNP). Microgravity Quarterly. 1992 Apr;2(2):133-40.

22. Perinatal overview [homepage on the Internet]. . Available from: http://marchofdimes.com/peristats/.

23. Klingner MC, Kruse J. Meconium aspiration syndrome: Pathophysiology and prevention. Journal of the American Board of Family Practice. 1999 Nov-Dec;12(6):450-66.

24. King HH, Tettambel MA, Lockwood MD, Johnson KH, Arsenault DA, Quist R. Osteopathic manipulative treatment in prenatal care: A retrospective case control design study. J Am Osteopath Assoc. 2003 Dec;103(12):577-82.

25. Eckberg DL. Parasympathetic cardiovascular control in human disease: A critical review of methods and results. Am J Physiol ; Am J Physiol. 1980 Nov;239(5):H581-93.

26. Ekholm EM, Piha SJ, Antila KJ, Erkkola RU. Cardiovascular autonomic reflexes in mid-pregnancy. Br J Obstet Gynaecol ; Br J Obstet Gynaecol. 1993 Feb;100(2):177-82.

27. 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 ; Eur Heart J. 1993 Nov;14(11):1519-23.

28. Matthews KA, Rodin J. Pregnancy alters blood pressure responses to psychological and physical challenge. Psychophysiology; Psychophysiology. 1992 Mar;29(2):232-40.

29. 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 ; Acta Soc Med Ups. 1960;65:314-25.

30. Widlund G. The cardio-pulmonary function during pregnancy. Acta Obstet Gynecol Scand. 1945;25:1-125.

31. Ekholm EM, Piha SJ, Antila KJ, Erkkola RU. Autonomic cardiovascular responses in pregnancy. A longitudinal study. Clin Auton Res. 1994;4:161-5.

32. Barron WM, Mujais SK, Zinaman M, Bravo EL, Lindheimer MD. Plasma catecholamine responses to physiologic stimuli in normal human pregnancy. Obstet Gynecol ; Am J Obstet Gynecol. 1986 Jan;154(1):80-4.

33. Ekholm EM, Antila KJ, Piha SJ, Jalonen J, Metsala T, Erkkola RU. Changes in autonomic cardiovascular control in mid-pregnancy. Clin Physiol. 1992;12:527-36.

34. Van Hoogenhuyze D, Weinstein N, Martin GJ, Weiss JS, Schaad JW, Sahyouni XN, 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 ; Am J Cardiol. 1991 Dec 15;68(17):1668-76.

35. Laughlin MH. Skeletal muscle blood flow capacity: Role of muscle pump in exercise hyperemia. Am J Physiol. 1987 Nov;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 HF. Muscle pumping in the dependent leg. Circ Res ; Circ Res. 1966 July 1;19(1):180-90.

38. Kuchera ML, Kuchera WA. Osteopathic Considerations in Systemic Dysfunction. Revised 2nd Ed. ed. Columbus, OH: Greyden Press; 1994. p. 55,85; 187;193.

Table 1: Baseline Physiologic Data for All Treatment Conditions

	Standard Care	**Placebo**	**OMM**	**P value**
MBP (mmHg)	81± 4	76±4	77±3	0.82
SBP (mmHg)	125±5	120±6	118±4	0.75
HR (bpm)	84±6	81±4	90±5	0.58
Heart Rate Variability Indices				
HF power (bpm^2)	2.8±1.3	3.6±1.5	3.2±1.1	0.73
LF power (bpm^2)	4.6±1.9	4.8±1.5	3.6±1.7	0.61
HF/LF ratio (units)	0.61±0.43	0.76±0.51	0.88±0.46	0.77

P values are based on a one-way ANOVA comparing the three treatment conditions.

Table 2: Treatment Effects on the Response to Head-Up Tilt

	Standard Care	**Placebo**	**OMM**	**P value**
MBP (Δ mmHg)	3± 3	-2±3	5±3	>0.82
SBP (Δ mmHg)	4±5	3±3	4±2	>0.51
HR (Δ bpm)	3±3	1±4	3±2	>0.68
Heart Rate Variability Indices				
HF power (Δ bpm^2)	-0.2±0.8	-0.4±1.1	-1.0±1.0	>0.39
LF power (Δ bpm^2)	1.6±1.2	0.7±1.0	0.9±0.7	>0.41
HF/LF ratio (Δ units)	-0.41±0.53	-0.82±0.39	-0.61±0.41	>0.47

All data represent changes from baseline to steady-state tilt during the fifth minute of tilt. P values illustrated are the lowest *p* value for any given treatment modality for each variable. There were no significant treatment effects demonstrated for any variable.

FIGURE LEGENDS

Figure 1. These data represent the average responses (changes) of mean arterial and systolic arterial pressure changes in response to the 60^{o} head-up tilt intervention during the pre-treatment trial for each treatment group. The p values illustrated are for the individual groups as a *change* from baseline. All data are means $\pm$ SEM.

Figure 2. These data represent the average responses (changes) of heart rate in response to the 60^{o} head-up tilt intervention during the pre-treatment trial for each treatment group. There was a significant increase in heart rate in all trials and there were no significant differences between the responses between groups ($p = 0.43$ per a one-way ANOVA). All data are means $\pm$ SEM.

Figure 3. These data represent the average responses (changes) of the heart rate variability measures in the frequency domain. High frequency (HF) spectral power (0.15-0.40 Hz), low frequency (LF) spectral power (0.085-0.115 Hz) and the HF/LF ratio were assessed. The change from baseline to the period of head-up tilt was compared. Asterisks indicate a significant change from baseline ($p < 0.05$). All data are means $\pm$ SEM.

Figure 4. These data represent the average responses (changes) of mean arterial and systolic arterial pressure changes in response to toe raising during the 60^{o} head-up tilt intervention. These data are for the determination of the response to toe raising prior to any treatment and thus were obtained during the pre-treatment trial for each treatment group. Asterisks indicate a significant change from baseline ($p < 0.05$). All data are means $\pm$ SEM.

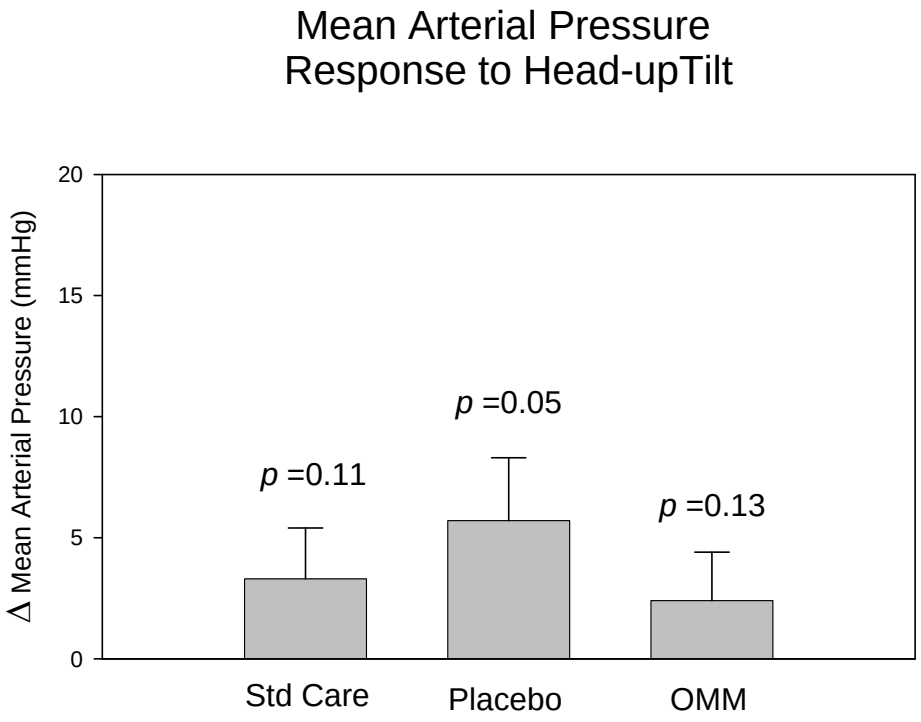
Figure 5. These data represent the average responses (changes) of heart rate in response to toe raising during the 60^{o} head-up tilt intervention. These data are for the determination of the response to toe raising prior to any treatment and thus were obtained during the pre-treatment trial for each treatment group. Asterisks indicate a significant change from baseline (p <0.05). All data are means $\pm$ SEM.

Figure 6. These data represent the average responses (changes) of the heart rate variability measures in the frequency domain for the response to toe raising prior to any treatment and thus were obtained during the pre-treatment trial for each treatment group.. High frequency (HF) spectral power (0.15-0.40 Hz), low frequency (LF) spectral power (0.085-0.115 Hz) and the HF/LF ratio were assessed. Asterisks indicate a significant change from baseline (p <0.05). All data are means $\pm$ SEM.

Figure 7. These data represent the *treatment effects* on the average responses (changes) of mean arterial and systolic arterial pressure changes in response to toe raising during the 60^{o} head-up tilt intervention. These data are for the determination of the response to toe raising before and after each respective treatment. Asterisks indicate a significant change from baseline (p <0.05). All data are means $\pm$ SEM.

Figure 8. These data represent the *treatment effects* on the average responses (changes) of heart rate in response to toe raising during the 60^{o} head-up tilt intervention. These data are for the determination of the response to toe raising before and after each respective treatment. Asterisks indicate a significant change from baseline (p <0.05). All data are means $\pm$ SEM.

Figure 9. These data represent the *treatment effects* on the average responses (changes) of the heart rate variability measures in the frequency domain for the response to toe raising before and after each respective treatment. High frequency (HF) spectral power (0.15-0.40 Hz), low frequency (LF) spectral power (0.085-0.115 Hz) and the HF/LF ratio were assessed. Asterisks indicate a significant change from baseline (p <0.05). All data are means $\pm$ SEM.


Mean Arterial Pressure
Response to Head-upTilt
Δ Mean Arterial Pressure (mmHg)
20
15
10
5
0
p =0.11
p =0.05
p =0.13
Std Care
Placebo
OMM

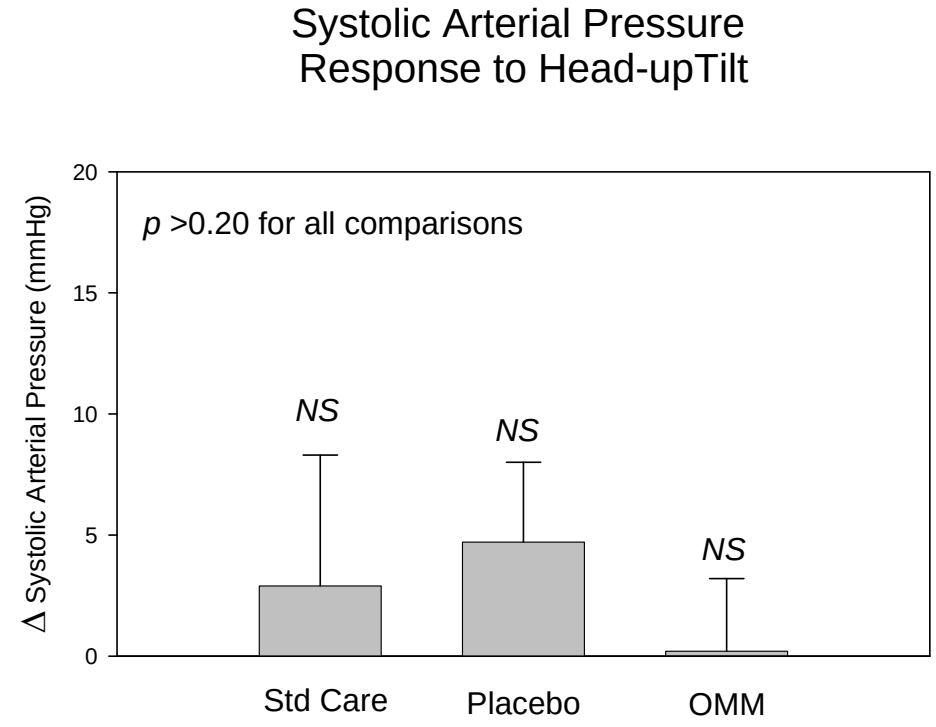

Systolic Arterial Pressure
Response to Head-upTilt
Δ Systolic Arterial Pressure (mmHg)
20
15
10
5
0
p >0.20 for all comparisons
NS
NS
NS
Std Care
Placebo
OMM

Figure 1

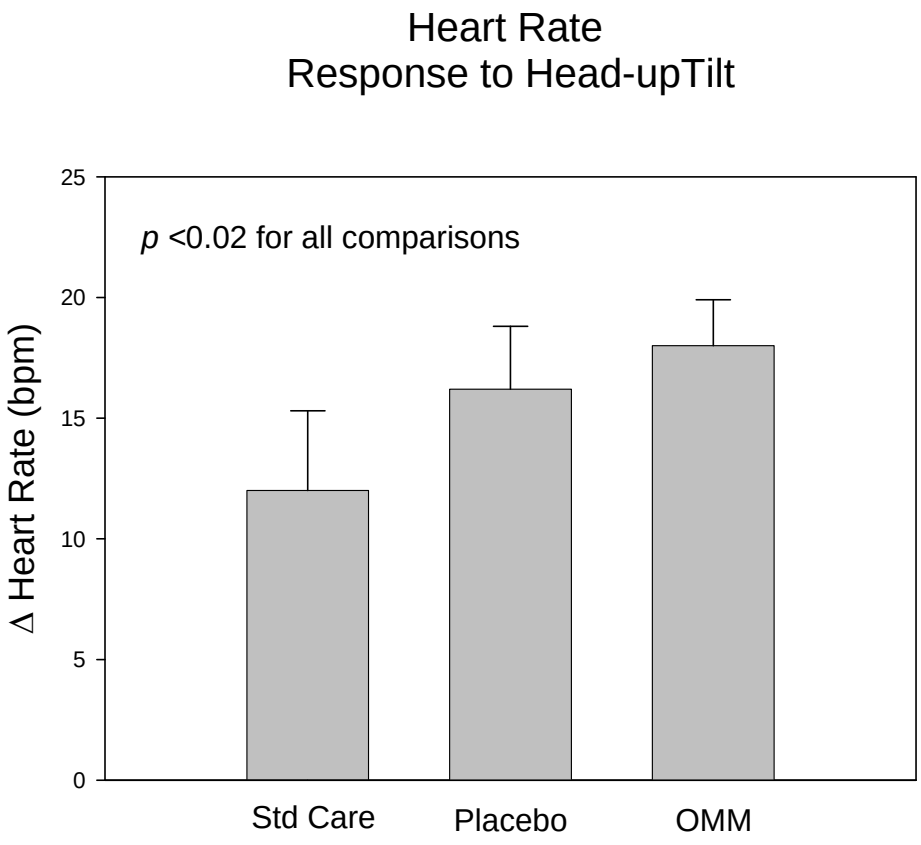

Heart Rate
Response to Head-upTilt
p <0.02 for all comparisons
Δ Heart Rate (bpm)
25
20
15
10
5
0
Std Care
Placebo
OMM

Figure 2

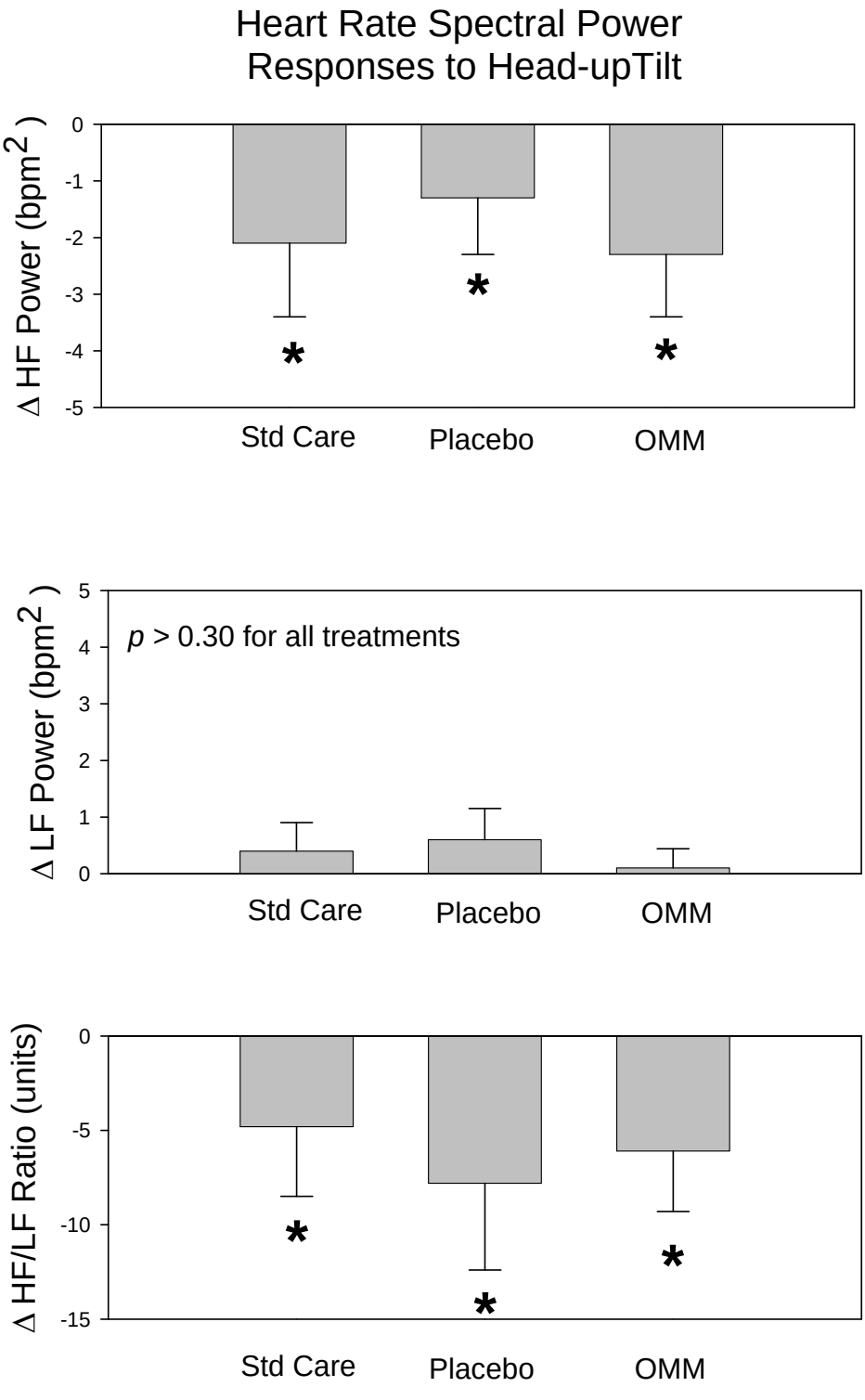
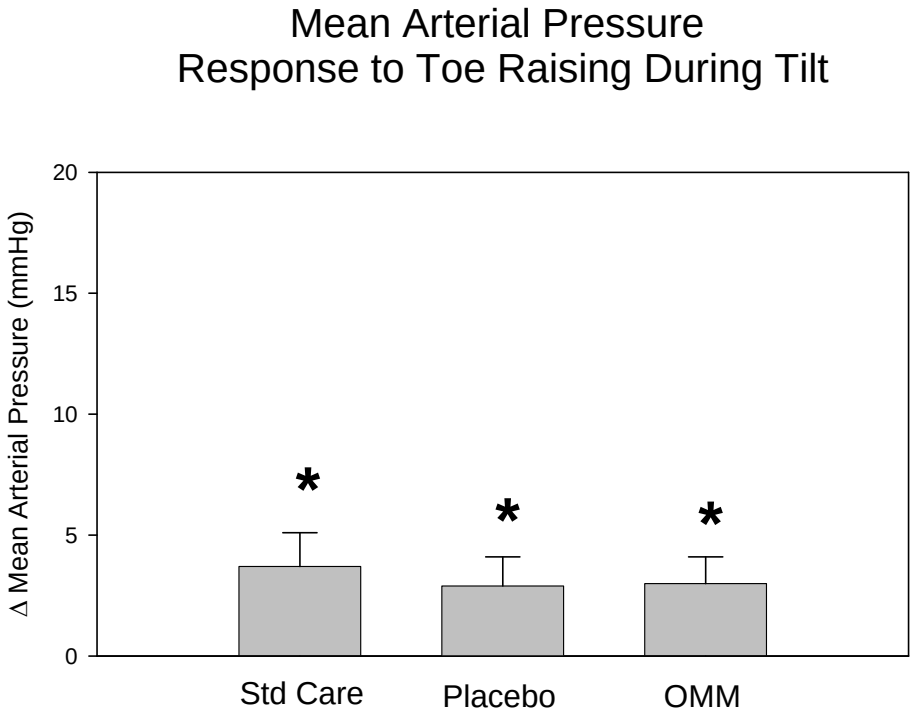

Heart Rate Spectral Power
Responses to Head-upTilt
Δ HF Power (bpm2)
0
-1
-2
-3
-4
-5
*
*
*
Std Care
Placebo
OMM
Δ LF Power (bpm2)
5
4
3
2
1
0
p > 0.30 for all treatments
Std Care
Placebo
OMM
Δ HF/LF Ratio (units)
0
-5
-10
-15
*
*
*
Std Care
Placebo
OMM

Figure 3


Mean Arterial Pressure
Response to Toe Raising During Tilt
Δ Mean Arterial Pressure (mmHg)
20
15
10
5
0
*
*
*
Std Care
Placebo
OMM

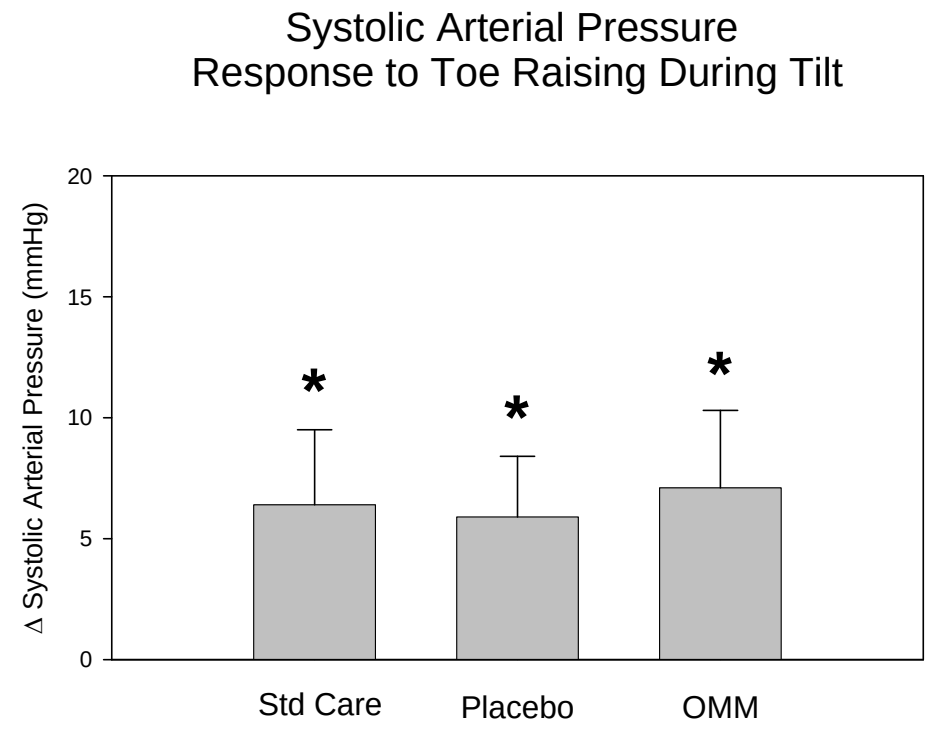

Systolic Arterial Pressure
Response to Toe Raising During Tilt
Δ Systolic Arterial Pressure (mmHg)
20
15
10
5
0
*
*
*
Std Care
Placebo
OMM

Figure 4

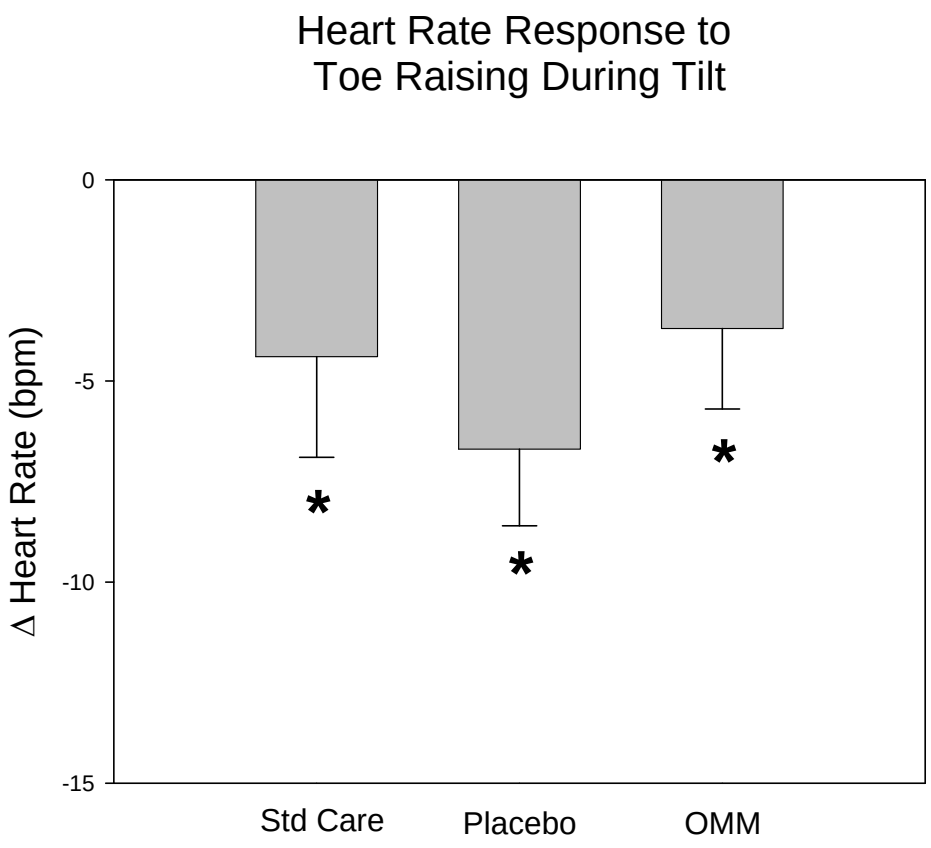

Heart Rate Response to
Toe Raising During Tilt
0
-5
-10
-15
Δ Heart Rate (bpm)
*
*
*
Std Care
Placebo
OMM

Figure 5

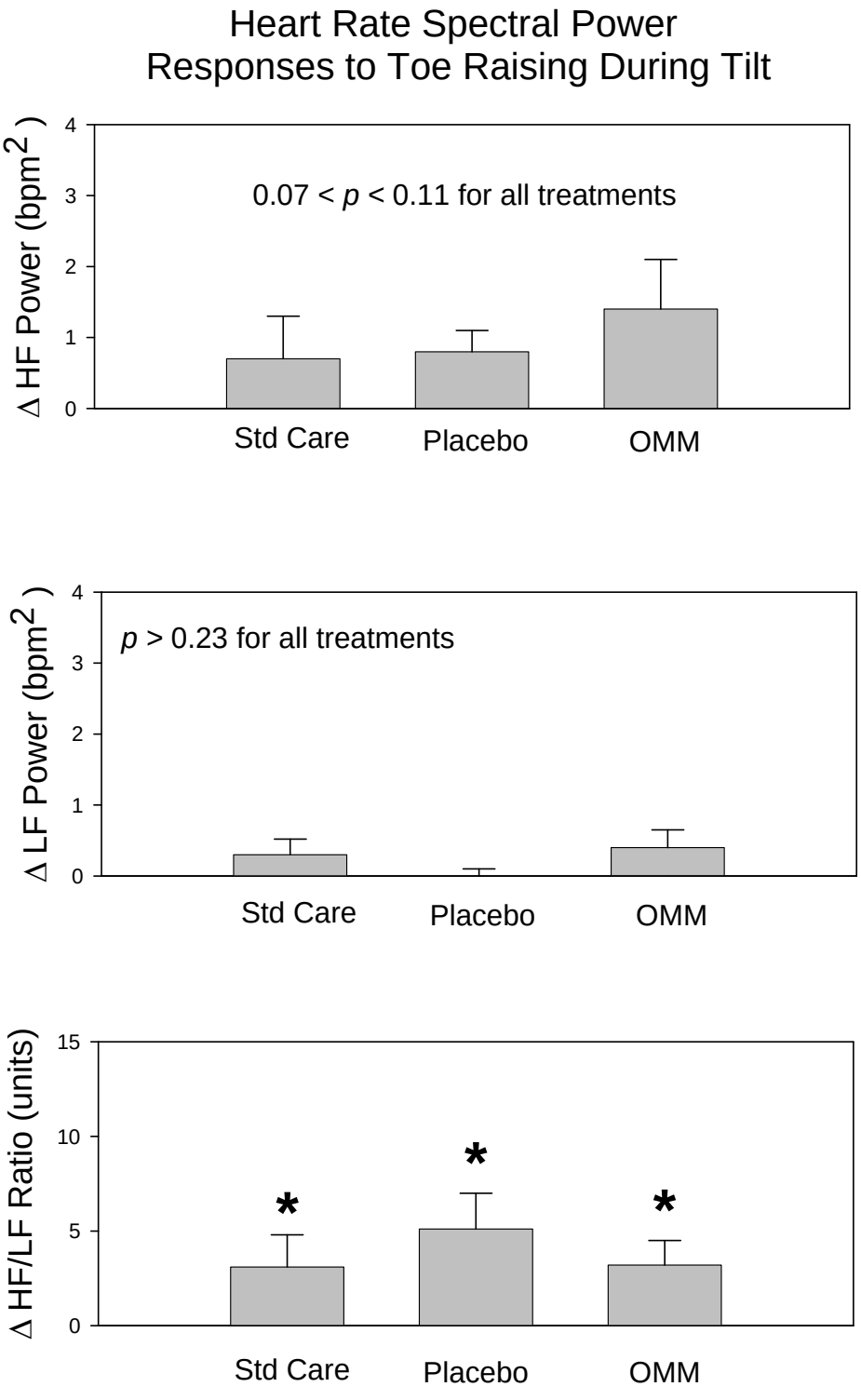
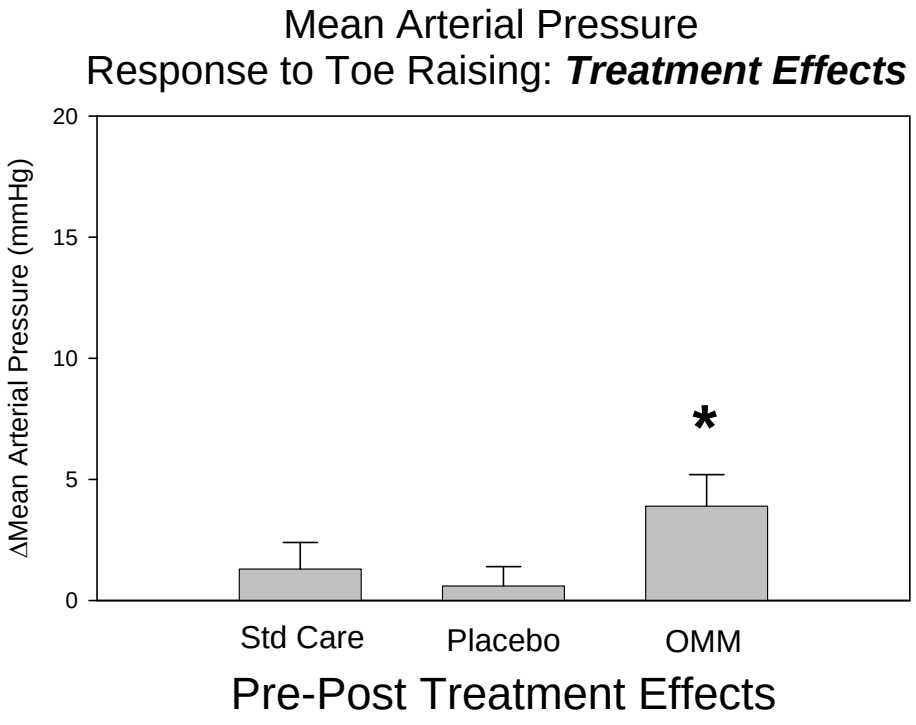

Heart Rate Spectral Power
Responses to Toe Raising During Tilt
Δ HF Power (bpm2)
0.07 < p < 0.11 for all treatments
Std Care
Placebo
OMM
Δ LF Power (bpm2)
p > 0.23 for all treatments
Std Care
Placebo
OMM
Δ HF/LF Ratio (units)
*
*
*
Std Care
Placebo
OMM

Figure 6


Mean Arterial Pressure
Response to Toe Raising: Treatment Effects
ΔMean Arterial Pressure (mmHg)
20
15
10
5
0
*
Std Care
Placebo
OMM
Pre-Post Treatment Effects

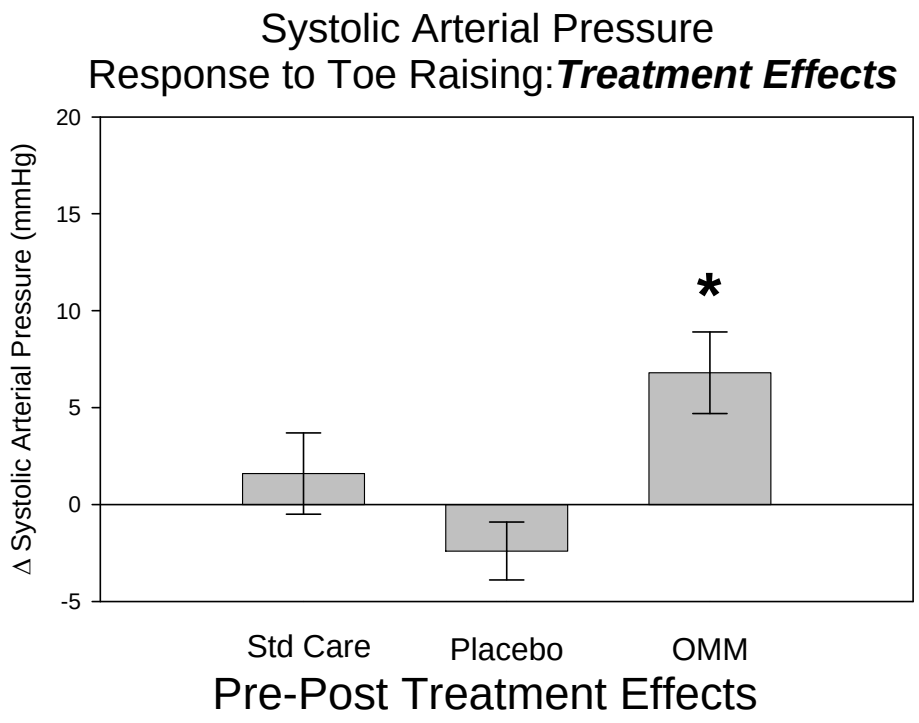

Systolic Arterial Pressure
Response to Toe Raising:Treatment Effects
Δ Systolic Arterial Pressure (mmHg)
20
15
10
5
0
-5
*
Std Care
Placebo
OMM
Pre-Post Treatment Effects

Figure 7

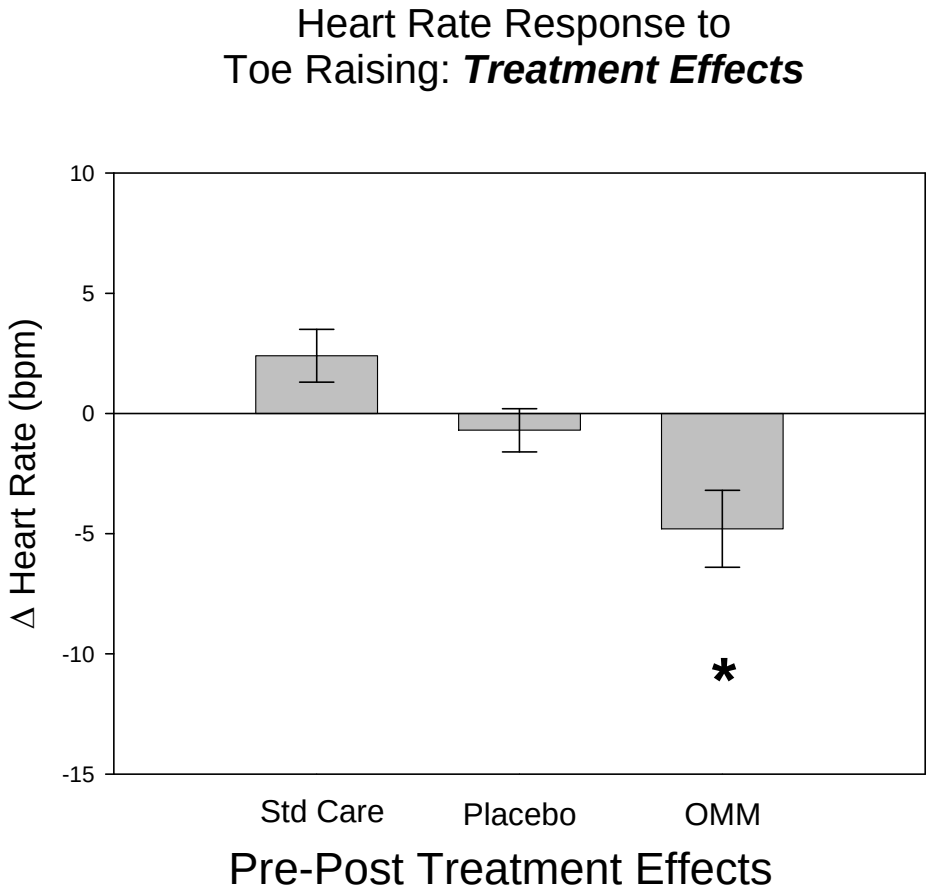

Heart Rate Response to
Toe Raising: ***Treatment Effects***
10
5
0
-5
-10
-15
Δ Heart Rate (bpm)
*
Std Care
Placebo
OMM
Pre-Post Treatment Effects

Figure 8

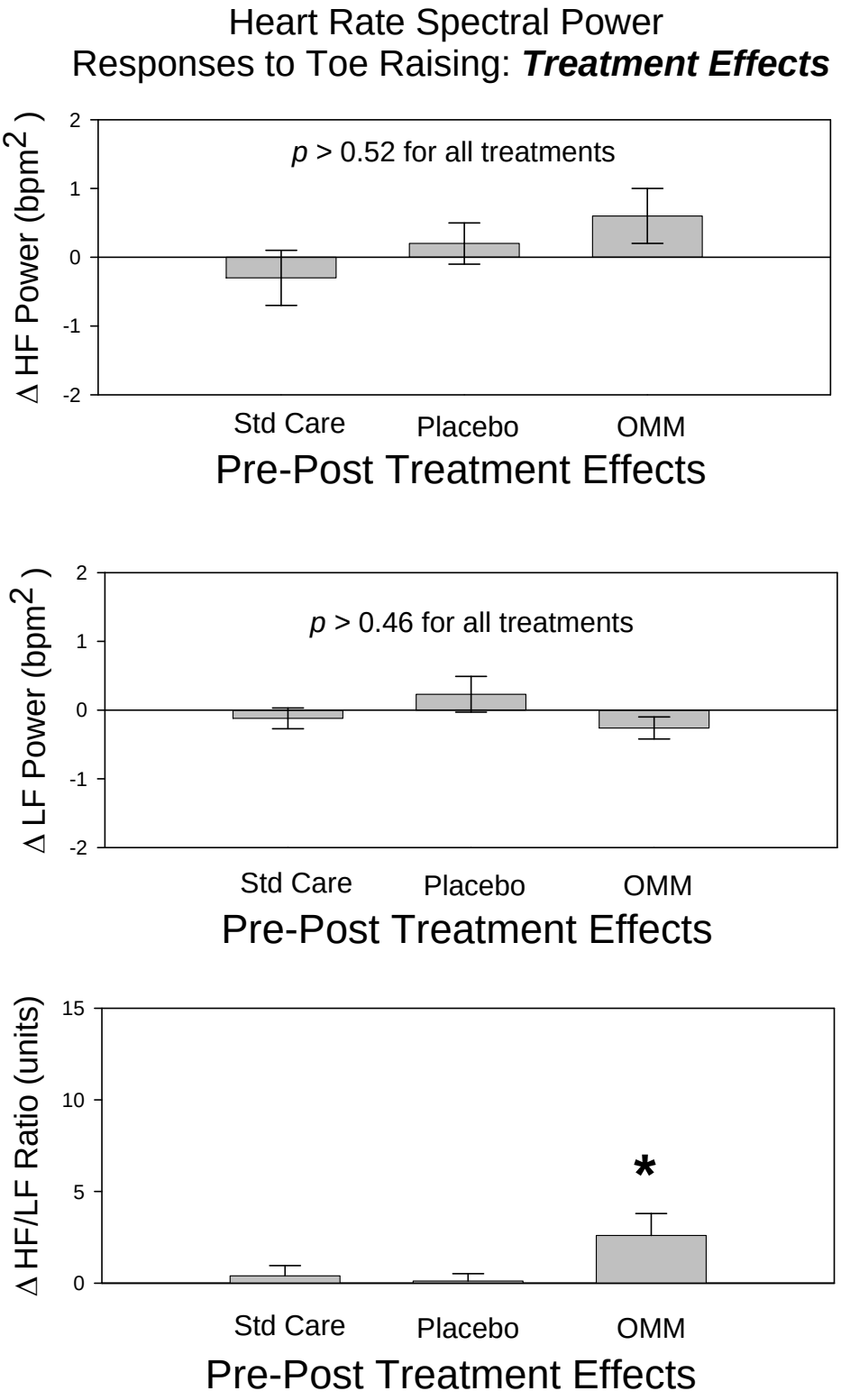

Heart Rate Spectral Power
Responses to Toe Raising: ***Treatment Effects***
Δ HF Power (bpm2)
2
1
0
-1
-2
p > 0.52 for all treatments
Std Care
Placebo
OMM
Pre-Post Treatment Effects
Δ LF Power (bpm2)
2
1
0
-1
-2
p > 0.46 for all treatments
Std Care
Placebo
OMM
Pre-Post Treatment Effects
Δ HF/LF Ratio (units)
15
10
5
0
*
Std Care
Placebo
OMM
Pre-Post Treatment Effects

Figure 9

CHAPTER 6

ACUTE CHANGES IN GAIT AFTER OMM TREATMENT IN PREGNANCY

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ABSTRACT

Background: Osteopathic Manipulative Medicine (OMM) is a body-based modality in which the patient is evaluated and treated as a whole to improve physiologic functioning and remove impediments to recovery from illness. During pregnancy, many musculoskeletal changes occur, including increased lumbar lordosis, anterior shift in the center of gravity, anterior rotation of the pelvic ilia, and external rotation of the lower extremities. These observed postural changes may translate into changes in gait that may be affected by OMM. Therefore, we tested the hypothesis that OMM acutely improves selected parameters of gait in third trimester of pregnancy.

Methods: Sixty subjects were recruited from the obstetric clinics of the University of North Texas Health Science Center at 30 weeks gestation. Subjects were randomized into one of three treatment groups: OMM, placebo ultrasound, or standard care (N=20 in each group). Subjects walked three times on an instrumented walkway before and after their study treatment. We used one-way ANOVAS to compare velocity, cadence, step length, stride length, step width, stride width, single and double support time, base of support, and angle of progression before and after treatment between each group.

Results: There were no statistically significant differences between groups at baseline. In addition, there were no statistically significant differences between pre-and post-treatment values for all spatiotemporal gait parameters. However, stride width and base of support showed a trend toward significance.

Conclusions: These data fail to elucidate the effect of OMM on gait parameters during the third trimester of pregnancy. There were several confounding factors as well as low power in this study, therefore caution is warranted when interpreting the results. Further studies using improved methodology may improve statistical significance and unmask an acute effect.

INTRODUCTION

Despite decades of theory development and practice of osteopathic manipulative medicine (OMM), there are few rigorously controlled mechanistic studies of how OMM impacts the human body.

Osteopathic physicians are trained to use examination of the musculoskeletal system in diagnosis and treatment of many conditions. OMM treatments are used to help the body adjust to environmental stressors to maintain or restore optimum health and function. OMM is a body-based modality in which the patient is evaluated and treated as a whole to improve physiologic functioning and remove impediments to recovery from illness.

During pregnancy, many musculoskeletal changes occur. As a gravid uterus grows, its increasing size and weight tilts the pelvis forward, which increases the lordosis in the lumbar region of the spine.(1) This alteration in posture strains the ligaments, muscles, and joints of the surrounding areas, which can cause pain. In addition, hormonal influences, especially of relaxin (2) contribute to structural instability of the pelvis by allowing the sacroiliac joints(3) and pubic symphysis to widen(4). Because of the bony instability and strain, the muscles frequently become hypertonic to add some support, and hypertonic muscles contribute to the feeling of pain and stiffness. As pregnancy progresses, the postural changes described begin to affect the gait. As the uterus enlarges and rotates the pelvis anteriorly, the strain is transferred into the hip joints and contributes to an external rotation of the lower extremities. This can widen the stance of gait, increasing the work of standing and walking, and possibly contributing to increased strain and discomfort. The exact changes of gait that develop with pregnancy have not been well

documented. Application of the osteopathic model, though, would suggest that relieving some of the biomechanical strains of advancing pregnancy would improve gait. The effects of OMM have been studied in patients with gait disorders relating to Parkinson's disease, with good outcomes(5, 6). Improvements of several parameters of gait were noted after as little as one OMM treatment,(7) and persisted after a series of treatments ceased(8). Just as specific gait changes in pregnancy have not been well documented, the impact on any of those changes by OMM has also not been documented.

For this study, OMM is defined as a collection of manual techniques that are theoretically linked through assessment, diagnosis and treatment to an array of musculoskeletal disorders, systemic illnesses and other dysfunctional conditions of the human body. OMM aims to reduce or eliminate impediments to proper structure and function to assist the body's self-healing mechanisms. More specifically, Osteopathic physicians use OMM to identify restrictions of motion, tenderness, tissue changes, and asymmetry (somatic dysfunction), and to aid in repairing injured, damaged, or compromised tissue.

METHODS

This study of the acute biomechanical effects of OMM in pregnancy is a substudy of a larger, NIH-funded project investigating the clinical effects of OMM. Funded in September 2006, this K23 grant supports a 5-year, 400-subject clinical trial along with the 2-year substudy. A subset of subjects from the clinical study (N=60) will also participate in this gait study.

Subjects were recruited from the obstetric clinics of the University of North Texas Health Science Center (UNTHSC). Subjects had to be between 18 and 34 years of age, less than 30 weeks pregnant, and not considered high risk by her medical provider. Clearance was required from the OB/CNM before the woman could participate in substudy activities. This study was approved by the institutional review board of UNTHSC, and all subjects participated in informed consent process and signed an IRB-approved consent form.

For measurement of gait parameters, a 4.26-m-long GAITRite® instrumented walkway and software (version 3.8B CIR Systems, Inc., Havertown, PA) were used to calculate step and stride length, step and stride width, foot angle of progression, single and double support, velocity, cadence and base of support. All measures were taken before and after the subject's study treatment at her 30 week appointment.

Initially, each patient was instructed on how to walk along the GAITRite ® walkway at a normal, comfortable speed. The walkway was positioned so that at least two meters of space were present at each end of the walkway. All subjects began their gait evaluation by starting to walk two meters before the start of the walkway, and end two meters beyond the end of the walkway. This allowed for acceleration and deceleration to occur off the walkway, and therefore not affect any parameters dependent on speed. Once it was felt that the subject was able to walk in a consistent fashion, the subject walked the length of the walkway three times while data was being collected.

Subjects were then randomized into one of three treatment groups: OMM, placebo ultrasound (US), or standard care (SC). OMM group participants received a 20-30 minute

standardized set of hands-on treatments to her head, neck, abdominal diaphragm, back, pelvis, sacrum, and pelvic diaphragm. Placebo US group participants received a 20-minute subtherapeutic ultrasound systematically administered over the same major body regions as addressed by the OMM treatment. These treatments were applied through the subjects' clothes in the same manner that OMM was provided without requiring the subjects to undress. Subjects in the SC group received no treatment, but instead had 20 minutes of quiet time between measurements.

Biomechanical Substudy Data Management and Analysis

The GAITRite® carpet enables data collection of many facets of the human gait cycle and has been shown to be a valid and reliable tool to measure spatiotemporal gait parameters (9-11). After the subjects performed their walks before and after treatment, each footfall of each walk is evaluated to ensure complete contact with the GAITRite® walkway. Then parameters for evaluation are selected. These gait parameters include the velocity of gait, base of support, cadence, stride length, step length, stride width, step width, double and single support time, and toe in/toe out angle. Each of these parameters is averaged for 3 walks on the carpet for each evaluation sequence. The averages were imported into SigmaStat (Systat Software, Inc. version 3.5), where paired *t*-tests were performed on each variable to compare pre- and post-treatment effects.

RESULTS

Demographics

All subjects were healthy pregnant women between the ages of 18 and 35. Descriptive statistics for subject demographics are presented in Table 1. 53% of subjects had completed high school, 26% completed some college, and 19% had a college degree. 53% were white, 34% black, 2% Asian, and 10% other. Subjects were slightly overweight with a mean BMI of 31.78 kg/m^2.

Spatiotemporal gait characteristics

Twenty subjects were randomized to each treatment group. The spatiotemporal variables for all three treatment groups at baseline are shown in Table 2.

	OMM	US	SC
Velocity (cm/sec)	96.63±3.78	98.80±3.45	100.07±3.92
Cadence (steps/min)	104.31±2.57	103.17±2.09	105.00±2.32
Step length (cm)	55.72±1.35	57.34±1.13	57.02±1.53
Stride length (cm)	111.58±2.71	114.86±2.26	113.79±3.16
Step width (cm)	57.42±1.29	59.03±1.05	58.77±1.45
Stride width (cm)	13.07±0.65	13.30±0.66	13.42±0.61
Base of support (cm)	11.84±0.64	12.17±0.59	12.00±0.449
Single support (%)	0.43±0.001	0.43±0.01	0.42±0.01
Double support (%)	0.31±0.01	0.31±0.02	0.31±0.01
Toe in/out (°)	4.38±1.14	3.87±1.36	4.96±1.24

Table 2. Baseline data n=20 for each group.

Randomization check

To determine if baseline differences in spatiotemporal gait variables existed between treatment groups one-way ANOVAs were computed. The comparison was based on treatment group, and the significance was set at $p < 0.05$. There were no significant differences between treatment groups for all variables at baseline. Baseline BMI comparison between groups showed

no significant differences between groups, with the mean BMI for the OMT, US and SC groups 31.13, 32.50 and 31.70 respectively ($p>0.05$).

Results by Gait Variable

Velocity (cm/sec)

There were no significant differences in pre- and post-treatment velocity values for all treatment groups ($p > 0.05$). However, analysis of pre and post-placebo ultrasound data for individual participants showed a trend toward significance ($p=0.232$) with increased velocity post-treatment.

Cadence (step/min)

Cadence is defined as a recurrent rhythmical series during walking. Cadence is related to the symmetry of gait, i.e. a person who limps would walk with an asymmetrical cadence. There were no significant differences in pre- and post-treatment cadence values for all treatment groups ($p > 0.05$). However, analysis of pre and post-placebo ultrasound data for individual participants showed a trend toward significance ($p=0.186$).

Step Length (cm)

Step length is defined as the distance from a point of contact with the ground of one foot to the following occurrence of the same point of contact with the other foot. There were no significant differences in pre- and post-treatment step length values all treatment groups ($p > 0.05$).

Stride Length (cm)

Step length is defined as the distance between two successive placements of the same foot, consisting of two step lengths. There were no significant differences in pre- and post-treatment stride length values all treatment groups ($p > 0.05$).

Step Width (cm)

Step Width is defined as the distance between the center of the right foot and the center of the left foot for one step (2 foot falls). There were no significant differences in pre- and post-treatment step width values for all treatment groups ($p > 0.05$).

Stride Width (cm)

Stride width is defined as the distance between the center of the right foot and the center of the left foot for one stride (3 foot falls). There were no significant differences in pre- and post-treatment stride width values for all treatment groups ($p > 0.05$).

Base of Support (cm)

Base of support is defined as the area between both feet. There were no significant differences in pre- and post-treatment base of support values for all treatment groups ($p > 0.05$). However, examination of pre and post-treatment for individual participants showed a trend towards a significant decrease in base of support for all three treatment groups (OMM, $p=0.336$; US; $p=0.322$; SC, $p=0.233$).

Single Support Time (%)

Single support time is defined as the amount of time the participant spends on one foot during the gait cycle. There were no significant differences in pre- and post-treatment for single support time ($p > 0.05$) for all groups. The comparison between pre and post-placebo ultrasound for individual participants showed a trend toward significance ($p=0.22$).

Double Support Time (%)

Double support time is defined as the amount of time the participant spends on two feet during the gait cycle. There were no significant differences in pre- and post-treatment double support values ($p > 0.05$) for all treatment groups.

Toe In/Out Angle (°)

Toe in and toe out angle is defined as the angle between the centerline of the front of the foot relative to the midline of the body. There were no significant differences in pre- and post-treatment toe in/out values for all treatment groups ($p > 0.05$).

DISCUSSION

This study is the first to date that examines spatiotemporal variables of gait in third-trimester pregnancy before and after a placebo-controlled, randomized OMM treatment protocol. The goal of this study was to examine the acute effects of OMM on gait parameters. As described, as advancing pregnancy changes the center of gravity, pelvic rotation and musculo-ligamentous tensions across the low back, pelvis and hips, it seems reasonable that gait changes would follow. However, without a true baseline comparison before the onset of the current pregnancy, it is unknown which, if any, gait parameters changed over the course of the first 30 weeks of gestation. A pilot study of 7 subjects in New Jersey indicated a relationship between ilial rotations and stride length (7). Although subjects were evaluated and treated for ilial rotations, we did not observe that difference.

Our results of the study may have been confounded by several factors. The first confounder may have been the time between the study treatment and the gait analysis. All subjects in this gait study were also participating in a physiological study that required the subject to lie on her left side for up to an hour both before and after study treatments. The sequence of the visits was as follows: gait measures, physiology measures, study treatment, physiology measures, gait measures, so there was a considerable amount of time between gait evaluations. Future studies may consider changing that sequence or using a different group of subjects so that the measures can be obtained temporally closer to the study treatment.

A second potential confounder is also related to the participation in the physiology study. The entire study session could last between 2 and 3 hours. By the time the subjects got to the second gait evaluation, they may have been in a hurry to leave, and so walked faster. Again, future studies may consider using a metronome to control for cadence.

The space used for the GAITRite® carpet may have confounded our results. Due to the length of the GAITRite® carpet, there was limited space in which it could be placed without blocking office workspace. The location in which we placed it (a rarely used hallway) lacked natural optical flow. For example, part of the walkway had walls on each side. In addition, the mat passes through a narrow doorway with a height significantly lower than the surrounding ceiling and there are several open doorways along the path of the walkway. The inclusion of obstacles during gait testing has been shown to confound step characteristics during gait experiments (12). Further, some participants were asked to walk toward a target located on the opposite wall. Concentrating on a target during walking has been shown to increase variability of certain spatiotemporal gait parameters (13) and may have reduced the participants' ability to walk naturally. Taken together, these walking conditions hindered our ability to reproduce an everyday walking environment. Moreover, the multiple obstacles and narrow walkway could have distracted the participants and thus may not have allowed for a true measurement of comfortable gait.

A potential anomaly that arises from these data is the difference in velocity, cadence, and single support time in the placebo ultrasound group. As stated, there are no ultrasound waves being emitted from the wand and therefore no true treatment effect from the ultrasound. This treatment condition is meant to control for time and attention interaction as the same physician

provides the ultrasound treatment as provides the OMM. Having no plausible explanation of why the placebo ultrasound treatment would make a difference, we are left to infer that there were not enough participants enrolled at the time of these analyses to reveal a true difference between treatment groups.

The power in the study was very low. We set our power at 0.80 for treatment effect, and the highest power obtained was 0.13, with the majority of our outcome measures powering at 0.05. Enrollment is continuing in both the clinical trial and in the substudy. When completed, both studies will have the targeted power, however due to severe time constraints we were unable recruit the necessary number of participants needed to reach a power of 0.80 for this substudy.

In conclusion, this preliminary investigation has provided a model for future studies investigating the changes in gait during third trimester pregnancy as well as the effect that OMM may have on gait.

Table 1: Demographics

Type of Treatment	**N**	**%**
OMT	20	33.3
Placebo Ultrasound	20	33.3
Standard Care	20	33.3
Age	**N**	**%**
18-20	19	33.3
21-25	25	43.9
26-30	11	19.2
31- 35	2	3.6
Ethnicity	**N**	**%**
Hispanic	16	28.6
Non-Hispanic	40	71.4
Race	**N**	**%**
Black/African-American	16	34
Asian	1	2.1
White/Caucasian	25	53.2
Other	5	10.6
Marital Status	**N**	**%**
Never Married	34	59.6
Married	20	35.1
Separated	1	1.8
Divorced	2	3.5
Education Level	**N**	**%**
Grade School	1	1.8
High School	30	52.6
Some College	15	26.3
Associate Degree	6	10.5
Bachelor's Degree	5	8.8
Occupation	**N**	**%**
Professional	3	5.7
Service	7	13.2
Sales	9	17
Homemaker	13	24.5
Unemployed	21	39.6
Insurance	**N**	**%**
HMO/PPO/POS	12	21.4
Medicare	1	1.8
Medicaid	43	76.8
BMI	**N**	**%**
< 18.5	0	0
18.5-25	8	18.6
26-30	12	27.9
31-35	13	30.23
35-40	8	18.6
>40	2	4.65

REFERENCES

1. Kinzler D. Sustained inhibitory rib-raising and microneurographic measurement of sympathetic nerve activity under cold-pressor stress. Thesis University of North Texas Health Science Center Unpublished. 2007.

2. Kristiansson P, Svardsudd K, von Schoultz B. Serum relaxin, symphyseal pain, and back pain during pregnancy. American Journal of Obstetrics & Gynecology. 1996 Nov;175(5):1342-7.

3. Cheng YW, Nicholson JM, Nakagawa S, Bruckner TA, Washington AE, Caughey AB. Perinatal outcomes in low-risk term pregnancies: Do they differ by week of gestation? Am J Obstet Gynecol. 2008 Oct;199(4):370.e1,370.e7.

4. R.E Brady, J. Rottman, R.E. Kappler, E.K. Veith. Osteopathic manipulation to treat musculoskeletal pain associated with pregnancy. JAOA. 1997;97(8):479.

5. Smutny CJ, Wells MR, Bosak A. Osteopathic considerations in parkinson's disease. J Am Osteopath Assoc. 1998;98(7):389.

6. Wells MR, Giantinoto S, D'Agate D, Areman RD, Fazzini EA, Dowling D, et al. Standard osteopathic manipulative treatment acutely improves gait performance in patients with parkinson's disease. J Am Osteopath Assoc. 1999 Feb;99(2):92-8.

7. Phillips J. Treatment of innominate rotations: Impact on spatial and temporal parameters of gait H. THE JOURNAL OF MANUAL. 2004:169-70.

8. Wells MR, McCarty CL, Smutny CJ, Scandalis TA, Dittrich F, Fazzini EA. Osteopathic manipulation in the management of parkinson's disease: Preliminary findings [meeting abstracts]. J Am Osteopath Assoc. 2000;100(8):522.

9. Morris ME, Bilney B, Matyas TA, Dalton GW. Short-term relationships between footstep variables in young adults. Gait Posture. 2007 Feb;25(2):229-35.

10. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. Gait Posture. 2005 Dec;22(4):317-21.

11. Bilney B, Morris M, Webster K. Concurrent related validity of the GAITRite walkway system for quantification of the spatial and temporal parameters of gait. Gait Posture. 2003 Feb;17(1):68-74.

12. Sparrow WA, Tirosh O. Gait termination: A review of experimental methods and the effects of ageing and gait pathologies. Gait Posture. 2005 Dec;22(4):362-71.

13. Wearing SC, Urry SR, Smeathers JE. The effect of visual targeting on ground reaction force and temporospatial parameters of gait. Clin Biomech. 2000 Oct;15(8):583-91.

FIGURE LEGEND

Figure 1: Base of Support Before and After OMM
Indicates a trend towards a narrower base of support after treatment (p=0.336)

Figure 2: Base of Support Before and After Placebo Ultrasound
Indicates a trend towards a narrower base of support after treatment (p=0.322)

Figure 3: Base of Support Before and After Standard Care Only
Indicates a trend towards a narrower base of support after time control (p=0.233)

Figure 4: Stride Width Before and After OMM
Indicates a trend towards a narrower stride width after treatment (p=0.323)

Figure 5: Stride Width Before and After Placebo Ultrasound
Indicates a trend towards a narrower stride width after treatment (p=0.325)

Figure 6: Stride Width Before and After Standard Care Only
Indicates a trend towards a narrower stride width after time control (p=0.311)

Figure 7: Velocity Before and After OMM
No significant change in velocity after treatment (p=0.615)

Figure 8: Velocity Before and After Placebo Ultrasound
Indicates a trend towards a increased velocity after treatment (p=0.232)

Figure 9: Velocity Before and After Standard Care Only
No significant change in velocity after treatment (p=0.686)

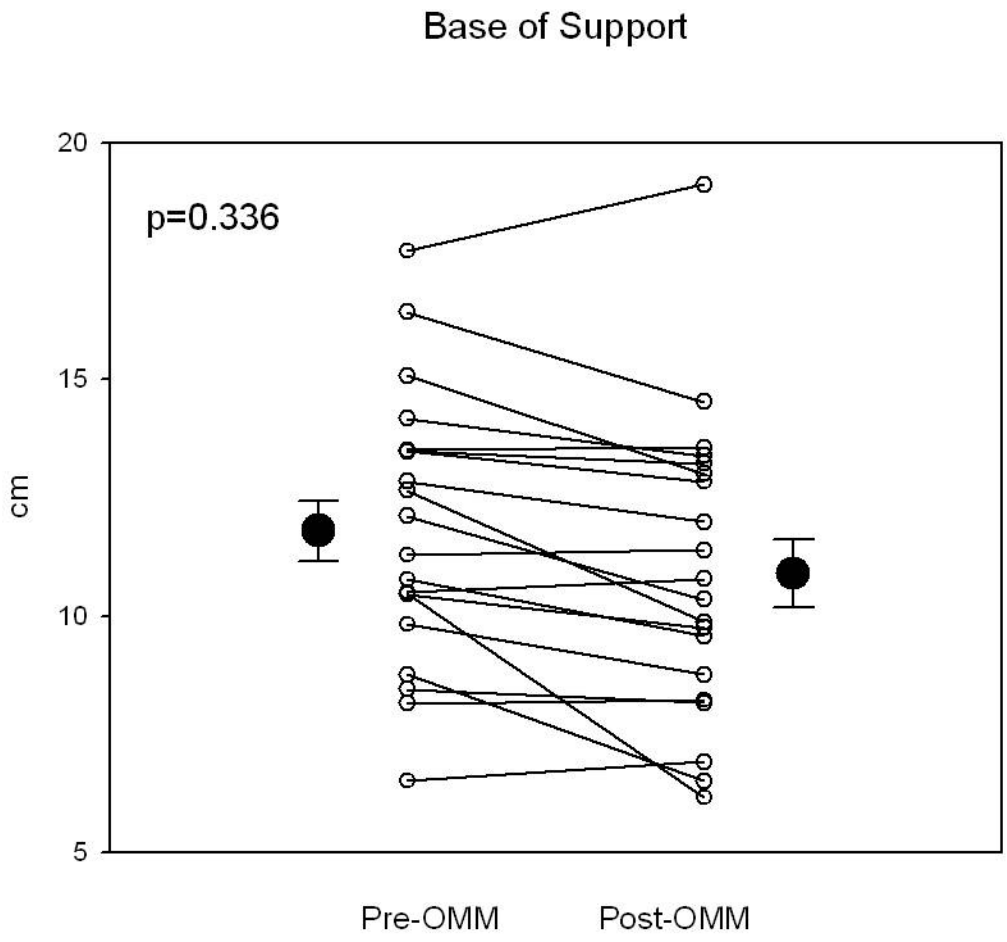

Figure 1: Base of Support Before and After OMM

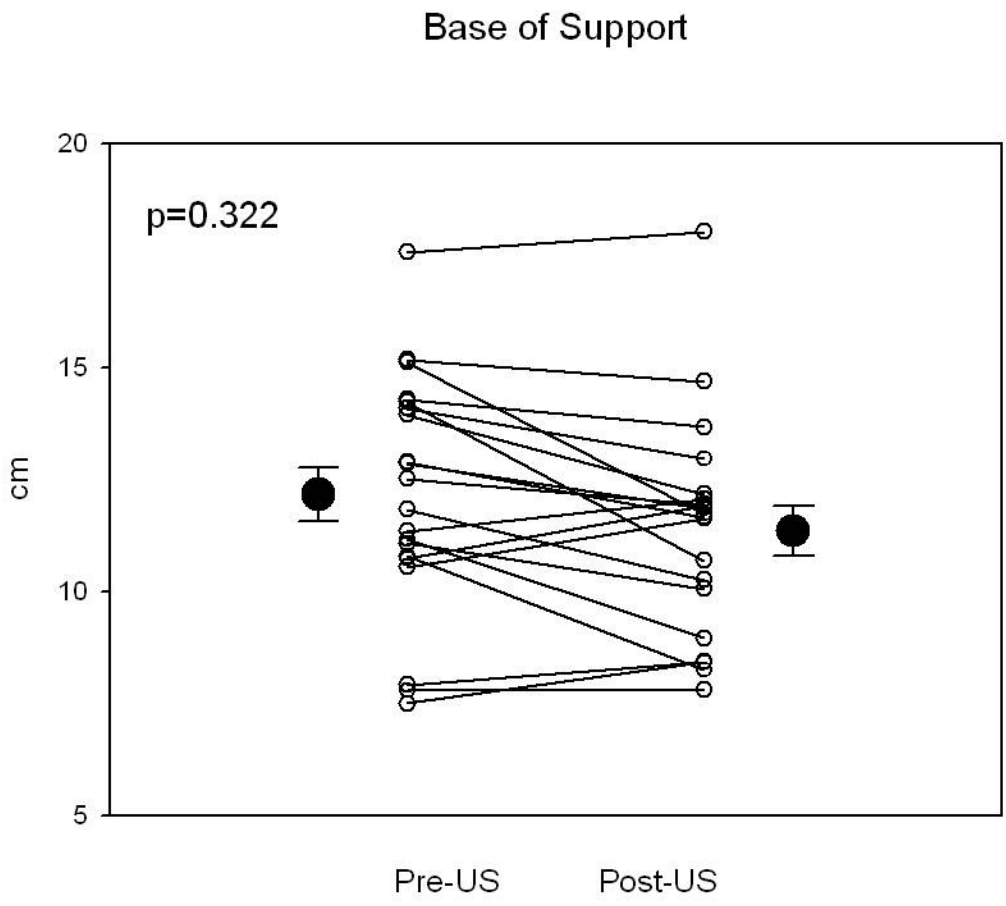

Figure 2: Base of Support Before and After Placebo Ultrasound

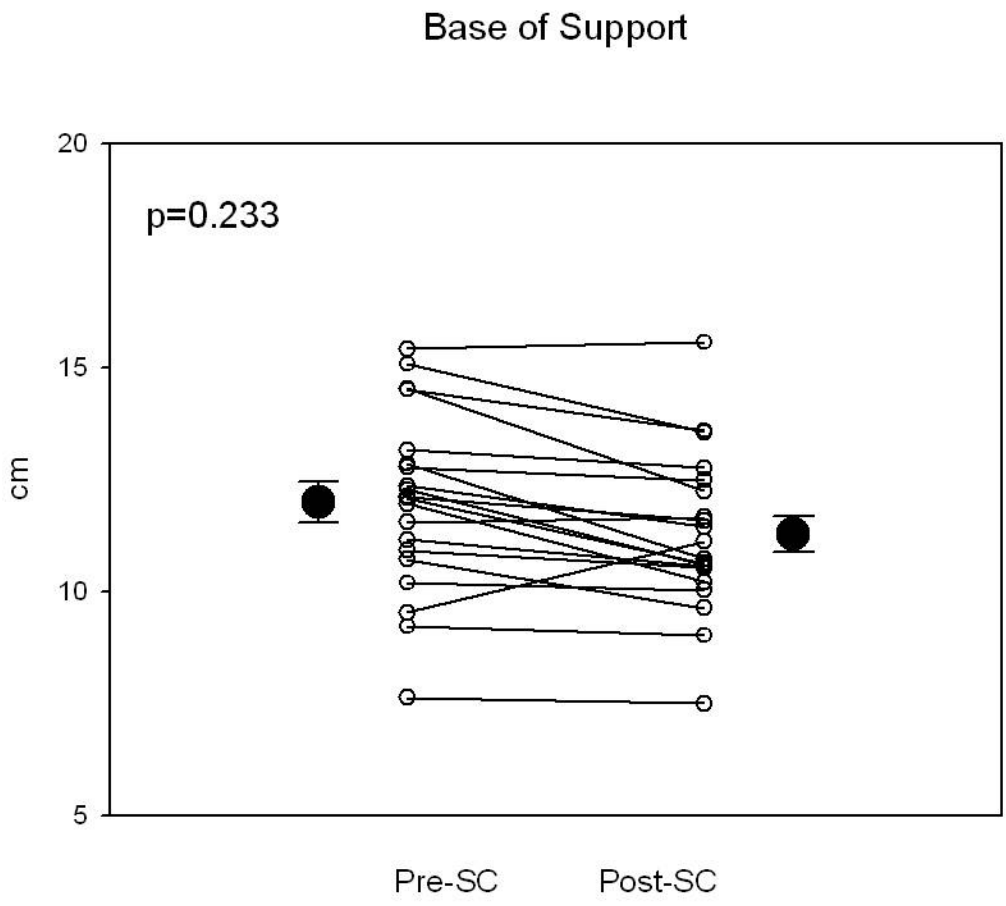

Figure 3: Base of Support Before and After Standard Care Only

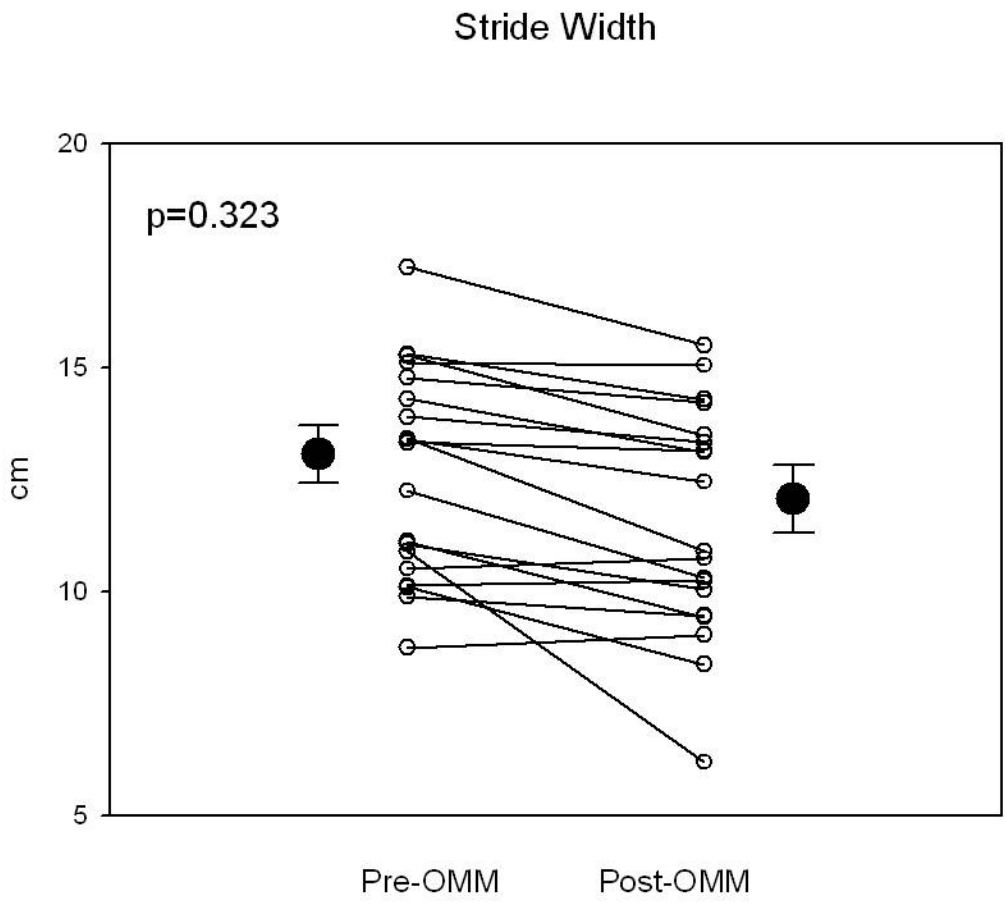

Figure 4: Stride Width Before and After OMM

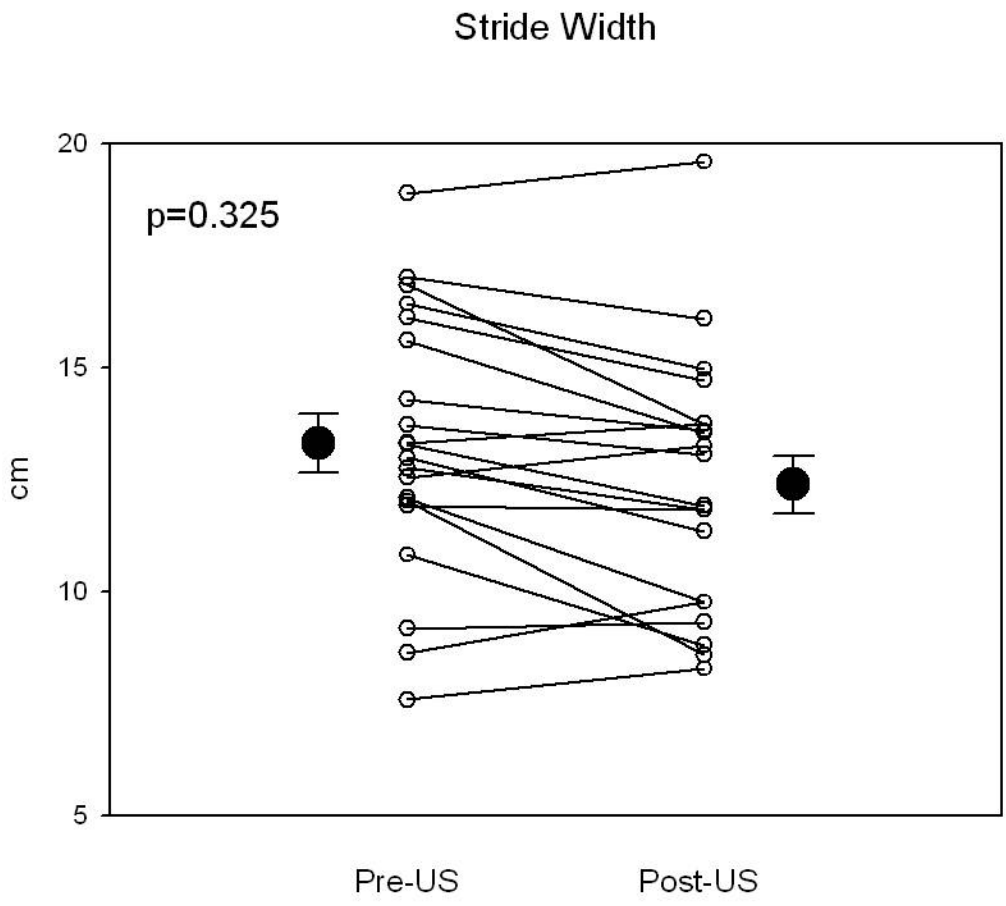

Figure 5: Stride Width Before and After Placebo Ultrasound

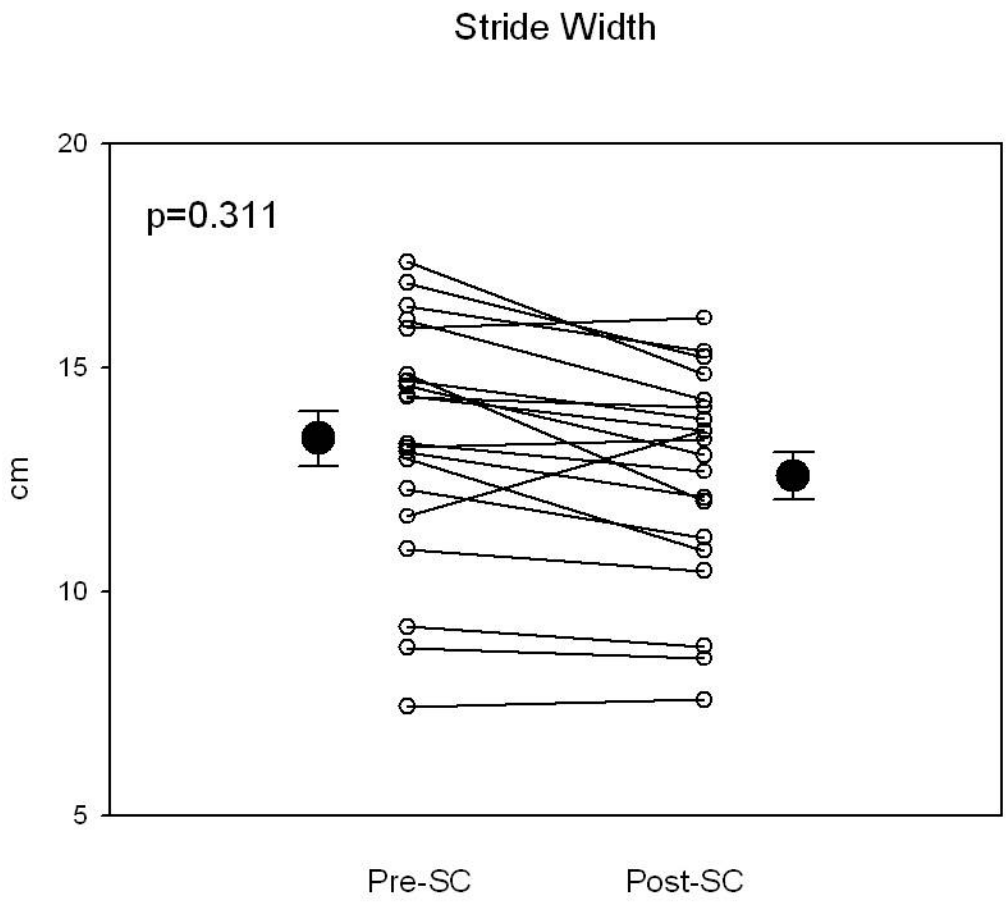

Figure 6: Stride Width Before and After Standard Care Only

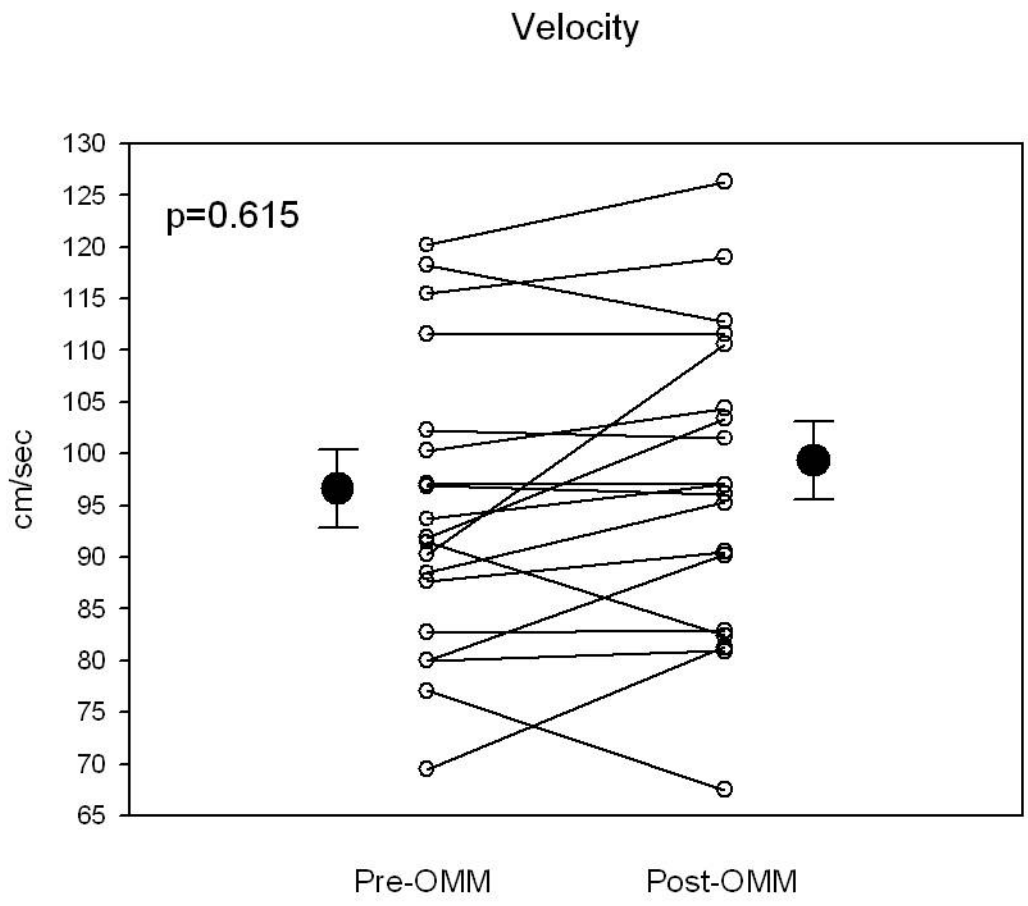

Figure 7: Velocity Before and After OMM

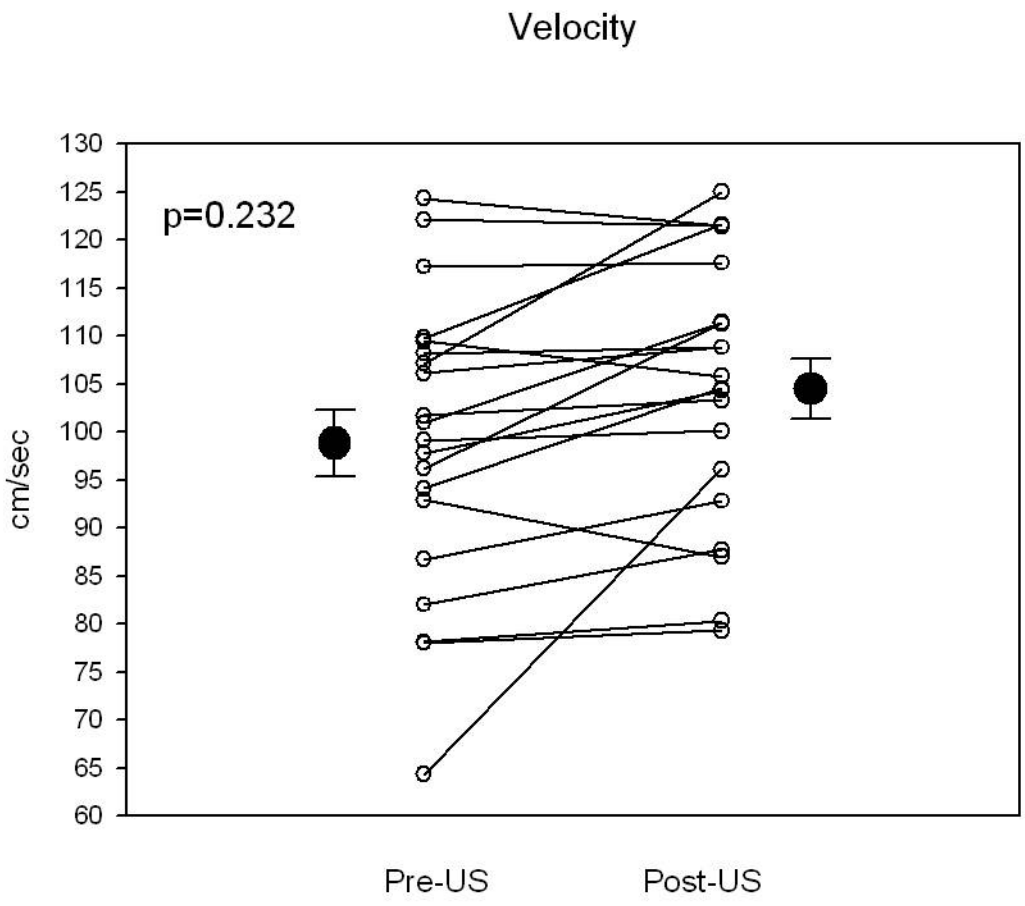

Figure 8: Velocity Before and After Placebo Ultrasound

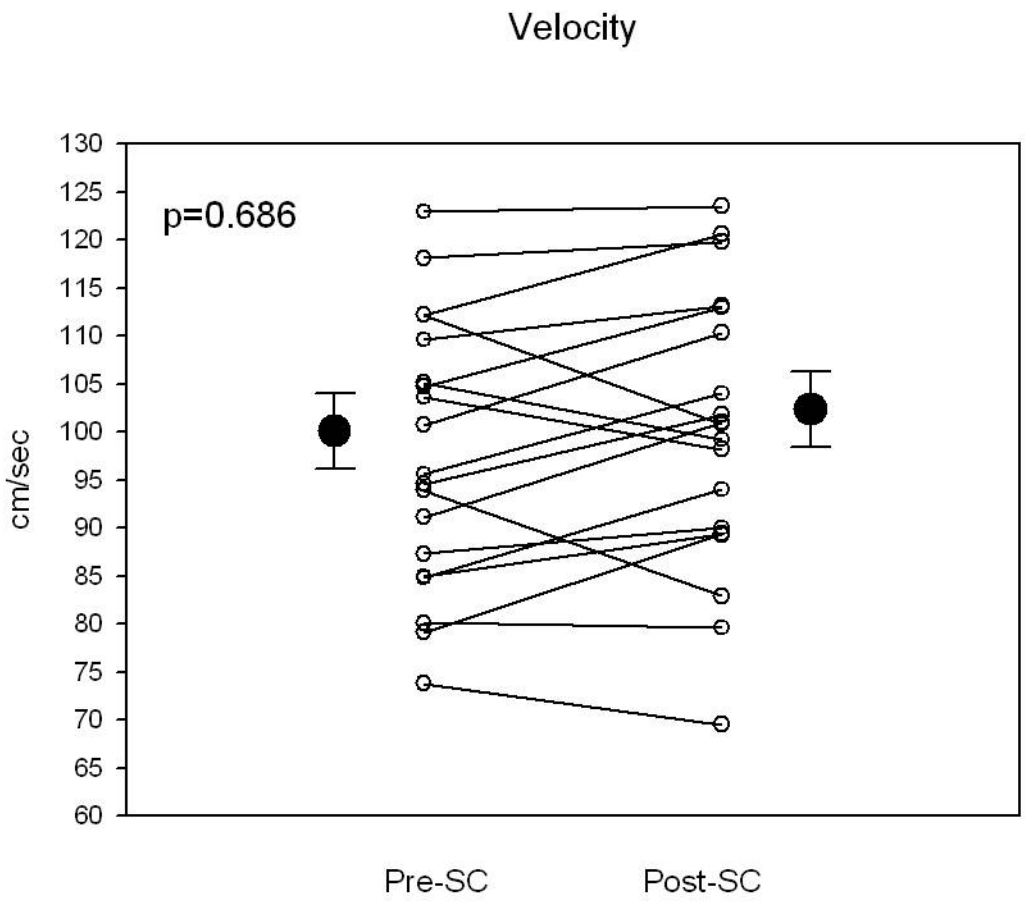

Figure 9: Velocity Before and After Standard Care Only

CHAPTER 7

FUTURE DIRECTIONS

The purpose of these two projects was to try to elucidate underlying mechanisms by which OMM may affect selected outcomes in pregnancy, labor, and delivery. The physiological and hemodynamic study demonstrated that an acute benefit of OMM is to enhance the venous return of blood to central circulation, thereby improving blood pressure control and decreasing heart rate. A current and future direction is to complete an ongoing longitudinal study of regular OMM treatments during the third trimester of pregnancy. In this study, the same measures described in this dissertation are being made at weeks 30 and 36 of pregnancy.

The lack of effect of OMM on the heart rate variability measures conflicts with a recent study of OMM on the indices of autonomic control of heart rate. This difference may relate to the fact that OMM was performed in an adjacent room and to where the experiments were conducted, necessitating the subject walking between rooms. This calls into question the duration of effects of OMM on autonomic control and merits further testing in both a non-pregnant and pregnant population. Future physiological studies may try to replicate Giles' data by gathering data in closer temporal proximity to the treatments.

A follow-up study to evaluate the gait and biomechanics changes throughout the third trimester of pregnancy is needed. It is possible that regular OMM treatments may improve structural function and mobility and enhance the reduced gait dysfunction that accompanies pregnancy in the third trimester. An ongoing study is designed to investigate these goals by repeating the gait analyses at weeks 30 and 36 of pregnancy.