A recent case report by Morton\(^1\) published in the journal Chiropractic & Manual Therapies screams for critical appraisal given the implications made by the author on the chiropractic care of pregnant women with a diagnosis of systemic lupus erythematosus (SLE). According to Morton\(^1\):

\[\text{"Immediately after receiving treatment the subject noted severe right sided anterior neck pain, and rapidly developed ipsilateral Horner’s syndrome. It was not possible to obtain exact information regarding the nature of the chiropractic treatment; though from the subject’s description it is likely that spinal manipulation was given. Magnetic resonance imaging (MRI) revealed extensive dissection of the right internal carotid artery..."}\]

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Morton described a 31-year-old woman pregnant at 16 weeks gestation with a history of bilateral occipital muscle tension headaches (HAs) since the age 14 years, an episode of migraine HA 6 weeks prior to chiropractic care and Systemic Lupus Erythematosus (SLE) diagnosed at 12 years of age. The SLE was complicated by renal involvement treated with azathioprine and prednisone. In addition, the patient was hypertensive and medically managed with labetalol, and suffered from episodes of deep vein thrombosis and pulmonary embolism. She was heterozygous for prothrombin gene mutation but did not have a lupus anticoagulant or anticardiolipin antibodies. Morton concludes with the warning that:

\[\text{"Practitioners should be aware of this possible complication of neck manipulation in pregnancy and the postpartum period, particularly in mothers with underlying medical disorders that may predispose to vessel fragility and arterial dissection."}\]
Morton is to be commended for raising the possible complications in the care of a pregnant woman with an autoimmune disorder. We are concerned however, that his case report should be misinterpreted that chiropractic care resulted in internal carotid artery dissection. The title alone implies such a scenario and Dr. Bruce Walker, DC, MPH, DrPH, Editor of Chiropractic & Manual Therapies and the involved peer-reviewers should have had more sense on the negative impact this may have on chiropractors, their patients and the chiropractic profession.

Case reports provide a unique opportunity to inform evidence-informed practice and a great vehicle for educating existing and future clinicians. We wish to expand upon certain aspects of the case presented by Morton. The chiropractic care of the pregnant woman requires special considerations. When a pregnant patient presents with an autoimmune disorder such as SLE, the clinical complexity of the case becomes, in some respects, elevated.

Chiropractic care is predicated upon a thorough history and physical examination to determine the appropriateness of care. This involves the detection for spinal subluxations and whether absolute or relative contraindications exist for certain chiropractic adjustments or adjunctive therapies. In the case reported by Morton, despite the absence of certain clinical information, enough information was provided for meaningful discussions. A number of salient features are revealed from the patient’s history. These include a history of headaches (i.e., occipital tension and migraine) as well as systemic lupus erythematosus (SLE).

Pregnancy, Systemic Lupus Erythematosus and Stroke

According to Egido and colleagues, the incidence of cerebral infarction and myocardial infarction is lower in females than in males, but only up to menopause. They attribute this to the protective role of natural estrogens during the fertile span of a woman’s life. The estrogens have anti-atherogenic and neuroprotective effects and, prior to menopause, account for a risk profile that is less atherogenic. Of interest in our discussions are the risk factors and indicators for stroke that are of important consideration for young women of childbearing years. As in the case presented, a pregnant woman suffering from migraines and SLE will be discussed in the context of risk for stroke and ultimately, the implications of the case reported.

The incidence, prognosis and causes of strokes associated with pregnancy or puerperium are not well understood. As will be discussed, migraine headaches are a risk factor for stroke and there exists a link between SLE and stroke but to what extent stroke occurs during pregnancy compared to the general female population of childbearing age remains to be fully elucidated. We qualify that, despite supporting literature indicating that pregnancy possibly increases the likelihood of cerebral infarction, particularly with certain etiologies associated with pregnancy, there are conflicting results. For example, Kittner and colleagues analyzed data from a large US inpatient population - from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality for female patients aged 15 - 44 years discharged in a 4 year period from 46 hospitals. The authors found that the postpartum period, but not pregnancy itself, was associated with an increased risk of cerebral infarction and, specifically, intracerebral hemorrhage.

Furthermore, most of the known causes of ischemic stroke in young women have also been reported during pregnancy. This raises the question of whether pregnancy is coincidental or plays a role in the occurrence of stroke. Additionally, etiologies specifically associated with pregnancy such as eclampsia, chorionicarcinoma, amniotic fluid embolism, etc. remain poorly understood. Hypercoagulability and vessel wall changes associated with pregnancy have been raised as a possible contraindication to SMT during pregnancy. We will address this more fully but at this point, the reality is - the role of these variables in the occurrence of idiopathic ischemic strokes is unknown in the pregnant patient population.

Systemic lupus erythematosus is characterized by global loss of self-tolerance with activation of autoreactive T and B cells. This leads to the production of pathogenic autoantibodies with resulting tissue and organ injuries. SLE affects primarily women of childbearing age, no cure exists and sadly, patients face lifelong suffering from the disease.

The incidence of the disease in women is highest at 15-44 years of age while maximal for prevalence at 45-65 years of age. Given the highest risk for women during their childbearing years, it is suggested that hormones play a key role in its etiology. In general, epidemiological and experimental data thus far strongly suggests that sex steroids are important modulators of genetic risk (i.e., for onset and/or perpetuation) in human autoimmune diseases like SLE. Estrogens are thought of as enhancers of the humoral immunity while androgens and progesterone (and glucocorticoids) act as natural immunosuppressors.

To determine whether there is an association between 32 different immune-mediated disorders (IMDs) such as SLE and first hospitalization for ischemic or hemorrhagic stroke, Zoller and colleagues examined all individuals in Sweden hospitalized with a main diagnosis of IMDs in a 1 year period. The investigators found the risk (ratio of the observed and expected) of hemorrhagic stroke with SLE was 8.65. Add the clinical condition of pregnancy and James and colleagues found the risk for stroke with pregnancy and SLE at an odds ratio of 15.2.

In other words, stroke occurred 15.2 times more often in pregnant patients with SLE. Interestingly, Morton reported that the patient was heterozygous for the prothrombin gene mutation indicating increased prothrombin levels for this patient and the propensity for blood clot formation. Not surprisingly, Morton also reported that the patient had a history of deep vein thrombosis and pulmonary embolism – collectively known as venous thromboembolism (VTE).

Interestingly, the patient did not have a lupus anticoagulant (actually a prothrombin agent) or anticardiolipin antibody (antibodies that attack cardiolipin, an important component of the inner mitochondrial membrane). Lupus anticoagulant and anticardiolipin antibodies, in addition to anti-β2 glycoprotein I antibodies constitute the antiphospholipid antibodies that target phospholipid protein complexes that lead to
antiphospholipid syndrome (APS), a risk factors for venous thrombosis.\textsuperscript{17} Given that antiphospholipid antibodies are a necessary feature of primary APS, how does one reconcile the findings of VTE in this patient given the unlikely scenario that this patient suffers from APS? Consider that approximately one-third of patients have APS secondary to systemic lupus erythematosus or SLE-like disease.\textsuperscript{18}

First, not all SLE patients who develop thrombosis have antiphospholipid antibodies.\textsuperscript{19} Second, no gold standard exists for the measurement of antiphospholipid antibodies and marked heterogeneity exists in the antibodies themselves rendering interpretation of laboratory testing challenging if not questionable. Third, other mechanisms may exist such as inflammation, acquired protein S deficiency\textsuperscript{20-21} and microparticles\textsuperscript{22} that predispose the patient with SLE patient for VTE.

These findings also lend credence to the idea that autoimmune diseases such as SLE should not be viewed solely as inflammatory disorders but also hypercoagulable disorders.\textsuperscript{23} Current understanding of the epidemiology of VTE and atherothrombosis is their share of common risk factors and pathophysiological characteristics such as inflammation, hypercoagulability, and endothelial injury.\textsuperscript{24-25} As chiropractors, we are well educated about the components of Virchow's Triad--blood flow conditions, blood components, and vascular walls - that contribute to the formation of pathological thrombi and ischemic stroke.\textsuperscript{20-28}

Autoimmune disorders have been linked to cerebrovascular diseases.\textsuperscript{20} Compared with the general population, patients with SLE are more likely to be hospitalized for the risk of ischemic stroke and intracerebral hemorrhage. Not surprisingly, SLE is a risk factor for stroke in pregnancy\textsuperscript{30} in and of itself, regardless of the application of the chiropractic adjustment.

Migraine and Stroke Risk

With respect to the patient’s history of migraine; migraine is a common, chronic-intermittent primary headache disorder affecting mostly women. It is beyond the scope of this paper to review the extensive literature on migraine pathophysiology but suffice it to say, it involves both the neuronal and vascular systems.\textsuperscript{31} A large body of literature supports an association between migraine and ischemic stroke, particularly in young women suffering from migraine with aura.\textsuperscript{32} However the precise mechanisms involved are not fully known. According to Pezzini and colleagues\textsuperscript{33} migraine may directly cause an ischemic event (i.e., migrainous infarct) through cerebral microcirculatory vasoconstriction (i.e., cortical spreading depression-related oligemia), intracerebral large vessels spasm, and vascular endothelium-related hypercoagulability.

Alternatively, migraine may predispose to cerebral ischemia outside of a migraine attack by affecting endothelial function, alone or in combination with traditional vascular risk factors, or by interacting with pre-existent stroke susceptibility conditions such as in patent foramen ovale or SLE. Finally, migraine and ischemic vascular events may be linked via genetic pathways. Certain genes play a role in these aforementioned conditions and influence their relation. The coexistence of ischemic stroke and migraine in the context of specific syndromes (i.e., autoimmune disorders) characterized by a peculiar phenotype, established genotypic background and chronic alterations of the wall of arteries suggests that migraine and ischemic stroke may be the end phenotype of common pathogenic mechanisms.

Indeed, the question is raised if the patient’s migraine symptoms are as a consequence of SLE or independent of it. Also as a final consideration, the migraine-stroke link may be the consequence of adverse events associated with migraine-specific drugs such as triptans or ergot alkaloids or with the azathioprine and prednisone that was prescribed to the patient. Insofar as we are aware, these types of pharmacological interventions were not indicated or refuted in the case presented. In an analysis of a large US inpatient sample, from the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality consisting of five to eight million hospital stays from approximately 1000 hospitals, Bushnell and James\textsuperscript{34} found a 15-fold increased odds of stroke in women with peripartum migraine (odds ratio 15.1; 95% CI: 8.3-27.4).

Pregnancy and Stroke Risk

Since the World Health Organization first considered that stroke is a life-threatening (or “near miss”) as an obstetric complication and as a co-morbidity that may deem unexpected pregnancies as an unacceptable risk,\textsuperscript{35} the problem has received much attention. Studies now indicate a growing proportion of women in industrialized countries with risk factors for stroke. Examples include hypertensive disorders\textsuperscript{36}, heart disease\textsuperscript{37}, and diabetes.\textsuperscript{38}

Furthermore, chronic diseases such as SLE are being managed and as in the case presented by Morton\textsuperscript{1}, women are entering pregnancies with increased risks for cardiovascular complications.\textsuperscript{39} In the United States, Kuklina and colleagues\textsuperscript{40} found that pregnancy-related stroke hospitalizations increased by 54% from 1994-1995 to 2006-2007. Furthermore, pregnancy-related stroke hospitalizations increased by 47% in the antenatal period and 83% in the postpartum. Based on their analysis of a large, US hospital discharge dataset, the authors found pregnancy-related stroke hospitalizations was 0.71 per 1000 delivery hospitalizations.

The incidence of stroke during pregnancy ranges from approximately 9 to 34 per 100,000 deliveries worldwide.\textsuperscript{41} With respect to specific risk factors, the hypertensive disorders were the leading cause of stroke. This is consistent with other studies\textsuperscript{42-44} and we remind the reader that the patient presented by Morton\textsuperscript{1} was hypertensive. There is a link between SLE and cardiovascular disease.\textsuperscript{45} It should also be noted that the impact of hypertension in the pregnancies from autoimmune patients is not fully defined despite the prevailing thinking among researchers and clinicians that autoimmunity seems to be associated with a higher risk of developing hypertension.\textsuperscript{46} Women with hypertension complicating pregnancy are six- to nine-fold more likely to have stroke.\textsuperscript{47-48}
Chiropractic Care During Pregnancy

To date, no study has examined in the clinical setting the prevalence and/or incidence of adverse events associated with the chiropractic adjustment or the totality of chiropractic care among pregnant patients.\(^4\)\(^5\) Stuber and colleagues\(^5\) performed a systematic review of the literature to examine adverse events associated with spinal manipulation during pregnancy and the post-partum period. The authors found two articles documenting adverse events associated with SMT in the post-partum period while 5 articles documented adverse events with SMT during pregnancy.

The adverse events were described as minor injuries such as increasing pain after treatment that resolved within a few days to more severe injuries including fracture, stroke, and epidural hematoma. In the case reported by Morton, the author claims that it was not possible to obtain exact information regarding the nature of the chiropractic treatment but hazards to guess that it involved spinal manipulation. In light of the caveat raised by Morton in the care of the pregnant patient with SLE and their possible risk for stroke, it is of paramount importance to determine the nature of the "spinal manipulation" prior to making such caveats. Did the spinal manipulation involve a high velocity, low amplitude type thrust or was it more characteristic of mobilization (i.e., low velocity, low amplitude)? Did it involve a drop table mechanism or an Activator or Torque Release adjusting instrument? Arguably, these different techniques have differing risk factors for stroke.

This is an important consideration when attributing possible risk or causality without first-hand knowledge or experience with the type of care rendered. As exemplified in a recent case report by medical physicians that attributed causality on the use of an Activator Instrument for a posterior rib fracture in an infant,\(^5\) their lack of knowledge of the Activator Instrument arguably paints them of sensationalism reminiscent of irresponsible journalism rather clinician-scientists. The brothers Alcantara\(^5\) addressed the controversy by pointing out that the dynamic bending (i.e., not biomechanical failure resulting in fracture) of the sixth and seventh ribs in children under the age of 14 years occurs at applied forces of 234N.

The peak forces applied by an Activator Adjusting Instrument has been measured to range from 116N-140N, depending on the force settings. Clearly such forces are not capable of causing a rib fracture in an infant. In the review article by Stuber and colleagues,\(^5\) the authors raised the possibility that the hormonal and coagulability state of pregnancy may be contraindicative to SMT. We would argue against this position given that pregnancy alone, exclusive of specific etiologies (i.e., SLE) does not increase the prevalence or incidence of stroke when compared to the general population of women as previously discussed.

A consideration not addressed by Stuber and colleagues and pointed out by the brothers Alcantara\(^5\) is the type of SMT rendered. A great deal of heterogeneity exists with the type of SMT performed by different professions that perform manual therapy as well as within the same profession. As such, appraisals of indications and contraindications and the risk of adverse event on the use of SMT during pregnancy must necessarily take this into consideration.

Thus far, risk has been discussed in terms of probability. In clinical practice, risk analysis goes beyond probabilistic terms (i.e., observed versus expected) and must account for the uncertainty, ambiguity and complexity of clinical practice. We respectfully are of the opinion that Morton did not address this sufficiently in the context of his recommendations and caveat for chiropractors.

Motivation for use of alternative therapies by pregnant women is to address a specific condition or conditions such as pregnancy-related low back pain as well as general wellness care.\(^5\) This is consistent with the findings by Alcantara and colleagues\(^4\) in the characterization and response to care of pregnant patients receiving chiropractic care within a practice-based research network. This should come as no surprise given chiropractic’s clinical and theoretical framework of patient-centered care - incorporating the principles of vitalism, holism, humanism, conservatism, naturalism, and rationalism.\(^5\)

Arguably, the care rendered to pregnant women vis a vis the detection and elimination of spinal subluxation go beyond beyond the framework of addressing pregnancy-related musculoskeletal complaints. In the chiropractic care of the pregnant woman with an autoimmune disorder such as SLE; due consideration for their pre-existing risk factors such as stroke should play a role in the decision for the type of chiropractic adjustment (i.e., HVLA versus non-force technique or the use of a drop table) and adjunctive therapies rendered.

In the case presented by Morton\(^1\), such advice should be heeded in light of the finding that the increased risks of VBA stroke associated with chiropractic and medical care visits are likely due to patients with headache and neck pain from VBA dissection and are seeking care before their stroke.\(^5\) In the case presented by Morton\(^1\), the author does not describe the presenting clinical symptom(s) for chiropractic care but it is our contention that a similar stroke scenario may have occurred. The outcome of the patient’s pregnancy was tragic. Many epidemiological studies document the potential adverse effects of autoimmunity disorders on nearly every aspect of reproduction, even in the absence of clinically manifest autoimmune disease.\(^5\) The importance of integrative medicine in this scenario cannot be overstated.

In closing, our commentary discussed the existing risk factors for cerebrovascular compromise in the patient described by Morton.\(^1\) The patient’s pre-existing condition of migraine headaches and SLE placed the patient at risk for cerebrovascular compromise, prior to and exclusive of chiropractic care. We acknowledge the temporal association of the undefined chiropractic care and stroke in the case report by Morton. However, as Morton himself commented, this is not sufficient to attribute causality. Given the patient’s pre-existing conditions and risk factors, it should serve as a consideration for the type of chiropractic care rendered rather than a contraindication for care.
References


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