

RESOLVING ENDOMETRIOSIS-INDUCED PAIN

utilizing a
LOW GLYCEMIC DIET

by

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ABSTRACT of the THESIS

Resolving Endometriosis Induced Pain Utilizing a Low Glycemic Diet

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This single-blinded clinical study was designed to determine if a diet consisting of foods having low glycemic indices (GI), with an emphasis on reduction of simple sugars, is an effective tool for reducing symptoms of endometriosis. Chronic inflammation may be the primary activator of endometrial tissue migration and adhesion. Studies suggest that the high levels of sugar (i.e. USDA reports 150 lbs per person a year) promote chronic inflammation. Thus, it was proposed that if there was a reduction in dietary simple sugars (i.e. low glycemic index/load), there would be a concomitant reduction in the painful symptoms of endometriosis. All subjects received healthy dietary guidance according the United States Department of Agriculture (USDA) food pyramid. The experimental group was asked to eliminate all simple sugars throughout the study.

There were no statistically significant differences in the mean Endometriosis Symptom Scores (ESS) or Glycemic Indices between the control and test groups. However, the subjects (n=9) who followed

through with the trial for the entire six weeks (C=Continuers), maintained higher mean compliance scores, with intermediate Glycemic Load (GL) values, and experienced a significant decrease in endometriosis induced pain as evidenced by the substantial drop in their ESS values, compared to those who dropped out of the study (n=4).

This preliminary study did not show a significant difference in the mean glycemic indices (GI) between the Control and Test groups. However, the mean GL was significantly lower in the Continuers than in the Dropouts.

Acknowledging the fragility of reproducible results due to the small sample size, the data shows that lowering the GL of the diet reduced pain in subjects with endometriosis.

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TABLE OF CONTENTS

Abstract of the Thesis.....	ii
Acknowledgements.....	iv
Chapter 1. Introduction/Overview	
1a. Glycemic Index.....	1
1b. Glycemic Load.....	1
1c. Endometriosis.....	2
1d. Research Purpose.....	7
Chapter 2. Literature Review	
2a. The Inflammatory Cascade.....	9
2b. Inflammation and Endometriosis.....	9
2c. Inflammation-Simple Sugars Connection.....	11
2d. The Glycemic Index/Glycemic Load.....	13
Chapter 3. Methods	
3a. Study Design, Figure 1.....	15
3b. Differentiated Group Treatment.....	16
3c. Confidentiality and Informed Consent.....	17
3d. Baseline Values.....	17
3e. Blinding.....	17
3f. Exclusion Criteria.....	18
3g. Inclusion and Recruitment.....	18
3h. Compliance Assessment.....	19
3i. Glycemic Index and Glycemic Load Determination	20
3j. McGill Pain Questionnaire.....	20
3k. USDA Food Guide Pyramid.....	21

Chapter 4. Data Analysis	
4a. Dietary Assessment–Glycemic Index/Glycemic Load determination	23
4b. Endometriosis Pain Assessment.....	23
4c. Compliance Assessment.....	23
4d. Stress/Activity Assessment.....	25
4e. Characteristics of Participants.....	25
Table 1.Participant Data.....	25
4f. Statistical Analysis.....	26
Chapter 5. Results.....	27
Table 2. GI/GL, Pain Scores and Compliance for Control and Test Groups.....	28
Table 3. GI/GL, Pain Scores and Compliance for Dropouts and Continuers.....	28
Table 4. GI/GL, Pain Scores and Compliance for Continuers....	29
Table 5. Stress and Activity Levels for Dropouts and Continuers.....	30
Chapter 6. Discussion.....	31
Chapter 7. Study Limitations	
7a. Group Size.....	35
7b. Examining Inflammation.....	35
Chapter 8. Implications for Future Research.....	37
Chapter 9. Conclusion.....	40

Appendices

A. List of Abbreviations.....	41
B. Subjects Assessed for Eligibility.....	42
C. Glycemic Index Meal Planner Program.....	43
D. Endometriosis Symptom Questionnaire.....	44
E. Informed Consent Form.....	45
F. Stress and Activity Assessment Logs.....	47
G. USDA Food Pyramid.....	48
H. Sample Menu for Test Group.....	49
I. Sample Menu for Control Group.....	50
J. Sample Food Journal Page.....	51
K. Sample GI/GL International Table Food Listings.....	52
L. Short Form – McGill Pain Questionnaire.....	53
M. Support Personnel.....	54
N. Anecdotal Subject Reports.....	55
References.....	56

Resolving Endometriosis-Induced Pain Utilizing a Low Glycemic Diet

1. Introduction/Overview

1a. Glycemic Index

Dr. David Jenkins, a professor of nutrition at the University of Toronto created the Glycemic Index (GI) in 1981. The goal was to support diabetics in choosing the most appropriate foods to maintain normal blood sugar levels. Subsequent clinically reproducible low GI dietary evaluations demonstrated benefits conferred on individuals with diabetes, heart disease^{1,2} and appetite control issues.

These GI values allow comparisons between various carbohydrates for the purpose of blood sugar regulation. Excessive blood sugar fluctuations (e.g., hypoglycemia) have been found to promote systemic inflammation, possibly portending the development of certain diseases (e.g., diabetes, cancer)³.

GI values are derived from physiological measurements of the immediate effects of carbohydrates on blood glucose levels 2 hours post prandial, measured in 15 minute segments. A 50g load of glucose is used as the reference carbohydrate. (Glucose = 100 on the GI scale). Thus, foods can be ranked based on 50 g of their carbohydrate content. Jenkins' GI values were divided into the following three categories:

High GI scores ≥ 70 , Intermediate GI scores = 56 – 69. Low GI scores ≤ 55

1b. Glycemic Load

In 1997, Harvard University researchers⁴, having observed that the Glycemic Index (GI) did not account for the amount of carbohydrates in a particular food actually eaten, devised a more accurate means of expressing the glycemic effect (GE) named the Glycemic Load (GL)⁴. The GL values also provide a ranking mechanism to evaluate the

GE of a variety of foods by utilizing the GI value as well as the amount of carbohydrate in 100g of a food termed the *standard portion*. Thus, the GL reflects not only the GI of a particular food, but the amount of carbohydrates consumed in a serving. The researchers devised the following algorithm:

$$\text{Glycemic Load (GL)} = \text{GI} \times \text{carbohydrate per serving (in grams)} / 100$$

In subsequent clinical studies, Harvard researchers observed strong correlations between high GL diets and risk of disease. Thus, they determined the following categories:

$$\text{High GL} = 20+, \text{ Intermediate GL} = 11-19, \text{ Low GL} \leq 10$$

The Glycemic Load allows individuals better dietary management, since the glycemic effect can be minimized if the portion size of a high GI-ranked food is appropriately reduced, which reduces the carbohydrate content yielding lower resulting blood sugar levels and its corresponding insulin level.

1c. Endometriosis

Description

Endometriosis is defined as a condition in which endometrial cells from the lining of the uterus are found in abnormal locations (e.g., ovaries, Fallopian tubes, and various sites in the abdominal cavity). Implanting on non-endometrial surfaces, these cells nest and grow to varying sizes, forming adhesions between structures, often referred to as implants or nodules. The four levels of endometrial classification, referred to as “staging”, range from minimal (1) to severe (4), are determined by the size and depth of the nodules. Endometrial implants are most commonly found on the ovary⁵. Other sites include adhesions of vaginal wall lesions and the bladder anterior and posterior to the rectum. Other anatomical targets due to contiguous invasions include the sigmoid colon,

the ileum, cecum and appendix, which can lead to rectal bleeding and intestinal blockages. Endometriomas found in the kidneys and ureters in the thoracic cavity are much less common but have been documented.

Morbidity

The chronic non-menstrual pain, which accompanies this tissue migration, is apparently due to the twisting and/or rupturing of these abnormal cysts and growths. Additionally, they become distended and engorged with blood during menstruation, increasing the severity of cramps and leading to the formation of a new layer of scar tissue each month in response to the accumulating pockets of unshed blood. Progressive endometriosis can become debilitating, leading to such problems as sterility, painful intercourse, heavy menstrual bleeding with thick clots, increased duration of menses, irregular menses, bowel obstruction, urethral obstruction, internal bleeding along with incapacitating, unremitting lower abdominal pain ⁶.

Frequency and Diagnosis

Endometriosis affects approximately 10% of fertile women, and has been found to occur in 20% to 50% of infertile women.^{7,8} Endometriosis can affect any woman during their reproductive years, however, the presenting age is between 25 and 29 years.⁹ Although asymptomatic women accounted for 50% ¹⁰, up to 80% of women with debilitating chronic pelvic pain are diagnosed with endometriosis ¹¹.

Endometriosis is diagnosed primarily by laparoscopy, where the displaced tissue can be seen directly. This procedure is generally recommended after two pelvic exams, one during menstruation and the other at mid-cycle, indicating the possibility of migrating uterine tissue.¹² Due to the invasive nature of laparoscopy, some

gynecologists prefer to pay close attention to patient history, patient presentation and patient assisted anatomical pain mapping in lieu of this procedure.¹³ Confidence in this non-invasive method of diagnosis is high due to the significant correlation of chronic pelvic pain and endometriosis. MRIs have displayed high degrees of sensitivity and specificity (i.e. 90-92% and 91-98%) in differentiating endometrioma (i.e., adhesions) from other masses¹⁴. Chronic pelvic pain associated with the menstrual cycle is generally the primary indicator of possible endometriosis warranting further diagnosis.

Conventional Medical Treatment

Current medical treatment offers a varied range of options; however they all can incur short and long term side effects. Commonly prescribed drugs fall under the category of gonadatropin-releasing hormone (GnRH) which causes temporary cessation of the menstrual cycle. These GnRH analogs (Lupron, Zaladex) are derived from male hormones¹⁵. Other prescribed drugs with similar actions are Danazol¹⁶ and Gestrinon. Side effects from all these medications include depression, acne, weight gain, hirsutism, hot flashes, fluid retention, irregular bleeding, amenorrhea and teratogenic effects.¹⁷

Hormonal Regulation is achieved via administration of oral contraceptives. High dosages of medroxyprogesterone acetate (Provera), which effectively suppresses endometrial pain and menstruation, can be delivered orally or through injections.¹⁸ Metrorrhagia (breakthrough bleeding), weight gain and depression are some of side effects¹⁷.

Often, the removal of adhesions and cysts require performing a laparotomy. This is considered conservative as it attempts to remove endometrial implants leaving healthy tissue undamaged. However, endometrial reoccurrence is common¹⁹. Cauterization of

small implants can be performed utilizing expanded laparoscopy²⁰, combining diagnosis with treatment. Lasers are also used to perform endometrial nodule ablation and lyse adhesions²¹. A hysterectomy is recommended for those women suffering from unremitting pain, unrelieved metrorrhagia leading to severe anemia and irreparably damaged ovaries. Symptomatic recurrences have been recorded following this procedure²².

Anti-inflammatory steroids (e.g., prednisone), have been shown to halt the progression of endometrial implantation. Side effects, however, can be severe (e.g., diabetes, kidney failure, vision deterioration)¹⁶.

Etiology

From a biomedical standpoint, the etiology of endometriosis is unknown, although several theories have been developed. Sampson proposed the ‘reflux menstruation theory’²³, more recently referred to as retrograde menstruation, suggesting that menstrual fluid backs through the fallopian tubes into the peritoneal cavity²⁴. However, researchers found a significant shortcoming to this theory since “nearly all women of reproductive age exhibit some degree of retrograde menstruation” so other factors must initiate the endometriosis²⁵. Nothnick makes a strong case for expanded treatment options for endometriosis. His comparative research exposes similar characteristics between endometriosis and other autoimmune diseases (e.g., Crohn’s) such as elevated systemic cytokines with concomitant increased inflammation²³.

Another explanation links the spread of endometrial tissue via blood and lymph vessels²⁶ which could explain the existence of endometrial implants at extra-peritoneal sites. Given that only 10% of women of reproductive ability have endometriosis, some

researchers theorize that genetic alterations in the immune system may initiate the migration of endometrial tissue²⁷ via these portals.

In an effort to explain endometriosis found in women *after* a total hysterectomy and who are not following a regimen of hormone supplementation, researchers have proposed the possibility that mutation of coelomic (colon) epithelium into tissue similar to endometrium may be in response to an unknown estrogen mimic. The pervasive practice of inserting steroids that induce estrogenization into a large segment of our food source, may account for some of the increase in estrogen influence on tissue receptors.^{28,29, 30} Coelomic (intestinal) metaplasia may explain the abnormal locations where endometrial implants have been found³¹.

A new approach to determining the etiology of endometriosis may support the blood and lymph channel theory, the autoimmune theory and the fallopian tube menstrual backflow theory. Research demonstrates that the inflammatory process produces not just pain, but mitochondrial damage (e.g., excessive chemical oxidant production within the Electron Transport System (ETS)) leading to abnormal cellular behavior^{32, 33}. Research has also shown that intestinal inflammatory responses that occur in the presence of a food allergen, promotes an increase in GI mucosal production of pro-inflammatory prostaglandin E₂ (PGE₂), nitric oxide (NO) and superoxide radical production³⁴. This excessive and possibly prolonged oxidative stress can cause extensive damage to local tissue, which could extend to include endometrial tissue. Reproducible tests have demonstrated the occurrence of mitochondrial uncoupling due to high levels of NO during the inflammatory process, resulting in poor energy production, which may contribute to the fatigue noted by many women suffering with endometrial pain^{35,36}.

1d. Research Purpose

This author attempted to determine if consumption of a diet with low GI or GL, with an emphasis on the elimination of simple sugars, would decrease the severity of endometriosis symptoms. The plethora of studies attempting to determine the causes of endometriosis, have focused primarily on various biochemical and physiological processes. As important as these findings are, there are few studies focusing on the initial activators of the inflammatory processes that promote and perpetuate this painful, debilitating disease³⁷. However, although a few studies make a retrospective connection with allergies (e.g., food, airborne) and endometriosis³⁸, none actually investigate the food allergy –endometriosis connection directly. Research has shown that the intake of excess simple sugars overwhelm homeostatic biochemical functions which can lead to a toxic immune response and a subsequent gastrointestinal inflammatory process³⁹. This resultant faulty immunologic cascade, which can promote systemic circulation of inflammatory mediators, can lead to altered cellular function. This biochemical process may be an important link between the dramatic rise in simple sugar intake and the increased incidence of endometriosis as well as other autoimmune diseases.

This author proposes that a low-glycemic diet that primarily restricts intake of simple carbohydrates may reduce and/or eliminate the chronic pain of endometriosis. Attempting to integrate studies that have demonstrated the inflammatory component of endometriosis, with the studies confirming the sugar-gut inflammatory process, a low glycemic diet may reduce systemic inflammation enough to halt the progression of endometriosis in women with inadequate or faulty biochemical resources or physiological integrity to maintain appropriate homeostatic cellular function due to the current average

American intake of simple sugars at .5 lb daily⁴⁰. It is hypothesized that pain associated with ruptured endometrioma should greatly diminish or cease altogether, when simple sugars are eliminated from the diet. Exceptions to total elimination of endometrial related pain would possibly be due to the existence of intractable adhesions attaching the bladder or rectum to the vaginal wall, which would require surgical intervention.

This preliminary study was designed in an attempt to determine the feasibility of implementing a specific dietary treatment protocol, the extent of change in the outcomes measured and the length of time to improvement.

2. LITERATURE REVIEW

2a. The Inflammatory Cascade

Biochemical responses due to tissue injury, often initiated by free radical activity, cause the release of chemotactic substances (e.g., mast cells) to attract assistance from phagocytizing neutrophils, among other leukocytes. During phagocytosis, numerous Reactive Oxygen Species (ROS) are released (e.g., superoxide, hydrogen peroxide, hydroxyl radical) expanding the inflammatory cascade. Histamines and other proinflammatory substances (e.g., PGE₂) which promote vasodilation⁴¹, may facilitate the retrograde menstrual flow⁴².

2b. Inflammation and Endometriosis

Cytokines, the inflammatory mediators which are released into systemic circulation by activated lymphocytes, induce local and distant alterations in cellular function. This biochemical cascade is thought to be involved in, or initiate, endometriosis⁴³. Various symptoms due to the acute phase reactions initiated by cytokines (e.g., Tumor Necrosis Factor Alpha (TNF α), interleukin IL-1, IL-6, IL-8) include headaches, arthralgia, malaise and hyper-metabolism. Furthermore, once activated, this inflammatory cycle is perpetuated due to IL-6 production by endometrial stromal cells stimulated by hormones and immune activators⁴⁴.

Investigators have determined that cytokines stimulate the production of inducible nitric oxide synthase (NOS) which controls the formation of nitric oxide (NO). Nutritional studies in which NO production was modulated via inducing NOS with L-arginine supplementation demonstrated the ability to influence estrogen's effects on the uterus, thus, referred to as uterotrophic⁴⁵. A possible mechanism by which NO could

influence the upregulation of estrogen might be due to the fact that excess NO has an inhibitory effect on the Krebs cycle enzyme, cis-aconitase, resulting in excess amounts of acetyl-CoA⁴⁶. This glycolytic pathway intermediate could be shuttled to the cholesterol pathway, possibly increasing levels of estrogen, which could promote hyper-mitosis of the stratum basalis resulting in an excessive growth of the stratum functionalis. This stratum excess coupled with higher tissue porosity, due to the inflammatory cascade, could set the stage for tissue migration via blood backflow⁴⁷.

Of particular interest, Bergvist noted that “IL-6 is a multifunctional cytokine that stimulates cell proliferation and is involved in the creation of adhesions”⁴⁸. IL-6, secreted from endometrial tissue, is hormonally regulated and is located in both stromal and epithelial cells⁴⁸. TNF α inhibits and stimulates proliferation effecting angiogenesis and immunomodulation⁴⁹. Production of IL-1 and other growth factors are induced by TNF α .

Harada reports that “recent studies suggest that the peritoneal fluid of women with endometriosis contains an increased number of activated macrophages that secrete various local products, such as growth factors and cytokines.”⁴³. This finding in women with endometriosis may indicate “a possible pathogenic mechanism linking cytokines with endometriosis.” Cytokines have also been found to stimulate formation of pro-inflammatory prostaglandins, which would, in turn, promote more macrophage activation³⁹.

An autoimmune phenomenon appears to play a major role in the perpetuation of endometriosis. Weed and Arquembourg⁵⁰ proposed this hypothesis to explain low fertility rates after “observing IgGs and complement or circulating immune complex

(CIC) deposits in the eutopic endometrium” in women suffering from endometriosis. Their hypothesis was verified by Mathur⁵¹, who rendered the first description endometrial autoantibodies in those women with this syndrome. Chronic inflammatory state within the pelvic and abdominal cavities as evidence by increased IgGs, may set the stage for “defective immunosurveillance” which can promote ectopic endometrial tissue.

Numerous studies support the theory that food, airborne, viral and/or chemical allergens can lead to autoimmune activation by overwhelming the antigen load on the Gut Associated Lymphoid Tissue which damage gut mucosa and pathologically alter the intestinal flora ecosystem⁵². Since approximately 60% of the immunological activity occurs within the lymphoid tissue, immunologic alterations prompting release of pro-inflammatory activators, can easily become systemic due to increased CICs, extensive gut lymph tissue and mesentary lymph nodes. This observed inflammatory activation strongly indicates a relationship between chronic gastrointestinal dysfunction and systemic inflammation⁵³. Antigen insults activate humoral and cell-mediated immunity, which initiates lymphocytic inflammatory related activities. The resulting cytokine cascade can easily become systemic, promoting subsequent cellular alteration and hyper-metabolism of endometrial tissue leading to endometriosis⁵⁴.

2c. Dietary Simple Sugars-Inflammation Connection

Results from recent studies suggest that systemic and chronic inflammation is positively associated with foods found to have high GI and high GL values. Free radical activity has been shown to be initiated by ingestion of simple sugars (e.g., fructose, sucrose, dextrose)⁵⁵. Studies have also shown that these sweeteners can stimulate the production of ROS⁵⁶ which, left unchecked can cause chronic tissue damage⁵⁷. Mineral

usage by enzymatic reactions necessary to contain inflammation, are also compromised by intake of simple carbohydrates⁵⁸. Furthermore, minerals necessary for cell membrane integrity may be marginal due to intake of mineral depleted processed foods. Thus it is probable that the addition of the USDA estimated 0.5 lbs. per capita American intake *per day*, may decrease mineral intake below healthy levels^{59, 60, 61}.

Other studies have shown that increased dietary sucrose in healthy individuals is directly associated with increase fasting levels of glucose, impaired glucose tolerance and reduced insulin sensitivity.^{62,63,64,65} A correlation between dietary intake of simple sugars and inhibition of macrophage activity has also been documented⁵¹.

Several studies have confirmed a direct association between high dietary levels of simple carbohydrates (e.g., sucrose, honey, malt, orange juice) and immune suppression. In one in vivo study, 100 grams of simple carbohydrates decreased neutrophils capacity to engulf bacteria, where as the same amount of complex carbohydrates did not exhibit that effect.⁶⁶ Nutrients necessary for maintaining the integrity of healthy tissue (e.g., adrenal, endometrial, pancreatic β -cells) and their parenchymal functions (e.g., enzymatic reactions, hormonal secretions) are depleted by the high intake of sweeteners.⁶⁷

The USDA reported in 1995 that Americans were consuming approximately 150 lbs. of sugar per year⁶⁸, a substantial increase from 7 lbs. yearly only 100 years ago. Studies show that these high levels of sugar intake can lead to a disturbance of mineral interactions as well as mineral deficiencies such as: copper, chromium, calcium, magnesium, zinc, B vitamins and manganese.^{60, 69, 70} Studies have shown that proper mineral ratios confer stability upon the hundreds of cellular enzymatic function, and, in particular, menstrual cycle integrity. Balanced calcium ratios are integral to a healthy

menstruation process.^{71 72} Future studies are needed to assess mineral status in terms of levels and proportions, to determine if the mineral imbalances, caused by sweetener intake, contribute to initiating or escalating the deleterious processes that promote endometriosis.

2d. Glycemic Index

Clinical utility of the GI system of food classification is not without controversy. Opposing concerns revolve around “methodologic variables”⁷³ (e.g., food portion size, standard food) that can substantially modify GI values as well as glycemic feedback interpretation. These variables include: food-portion size, choice of standard food, repeated testing of standard food, as well as the food form, particle size, food processing and the nature of the starch. However, some recent studies do support the clinical utility of the GI, demonstrating improved blood glucose regulation in both diabetics and non-diabetics.

High quality epidemiological studies and randomized controlled trials demonstrate that daily consumption of foods with high GI values are significantly linked to a variety of disease processes. A cross-sectional observational study from the Framingham Offspring Study, which included 2,834 adults, supports a connection between GI and insulin resistance. Results showed that the chance of developing metabolic syndrome was significantly reduced for those regularly consuming cereal fiber and whole grains. Conversely, there was a statistically significant increased possibility of glucose dysregulation in those participants reporting high GI diets. There was no significant association between GL and syndrome X.⁷⁴

Data gleaned from the Nurses' Health Study and the Health Professionals Follow-up Study, suggests a significant association between elevated GL plus high intakes of sucrose and fructose, promoting hyperinsulinemia, and heightened risks of colorectal cancer among men but not women.⁷⁵ A population-based case-controlled study of 916 mothers was designed to determine if there was any association between high GI dietary values in foods consumed during pregnancy and the risk of neural tube defects (NTDs). Results demonstrated increased risks of NTD-pregnancy development in participants consuming high amounts of sucrose, irrespective of folic acid intake.⁷⁶ The Health Professionals Follow Up 12 year study demonstrated strong associations of increased risk of gall stone disease in men with high GI and GL diets. Male participants (n=1810) reported new gall stone symptoms, confirmed by radiology during the cross-sectional study. There was also a positive association between gall stone symptoms and high intakes of sucrose and fructose.⁷⁷

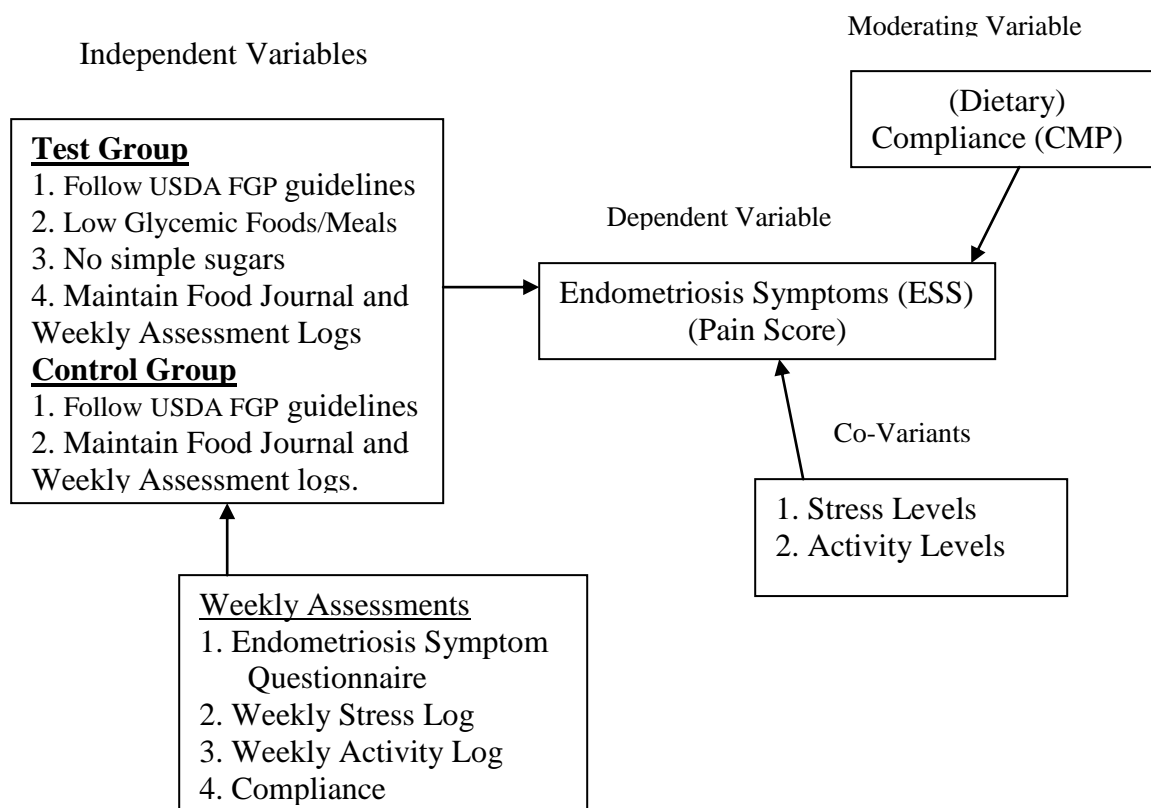
Together these studies provide strong evidence that diets containing foods with higher GI and GL values, contribute to a wide variety of diseases. This has vast implications for clinicians when advising patients on dietary and lifestyle habits for improved health outcomes.

To date, however, there are no studies involving the development of endometriosis in association with high GI/GL diets, with a focus on the high consumption levels of simple sugars. This clinical trial attempted to bridge that void.

3. METHODS

3a. Study Design

Figure 1
Research Clinical Study Model



This single blinded study utilized a randomized controlled clinical trial format of women with medically diagnosed endometriosis placed in two groups: control and test. Both groups were screened for specific characteristics as defined under § 3g Inclusion and Recruitment. All participants had been diagnosed by a state licensed medical doctor. Both test and control groups were given nutritional counseling for a healthy diet based on USDA guidelines. Each participant received basic nutritional advice concerning the benefit of each food group and USDA recommended daily amounts⁷⁸. There was a

recruitment goal of approximately 15 women in each group. However, that goal was not reached, despite vigorous outreach activity. Participants in all groups:

1. underwent either an MRI, ultra sound, laparoscopy or physician guided pain mapping recorded on their medical form to with a diagnosis of endometriosis.
 2. maintained an initial dietary questionnaire for one week to determine consumption levels of simple sugars and approximate dietary GI and GL.
 3. permitted the medical doctor and the assistant investigator (AI) (Appendix M), access to identifiable information (e.g., age, weight, height) in their files of information pertaining only to their medical presentation, test results and past treatment of endometriosis. The Primary Investigator (PI) was only given non-identifiable information.
 4. maintained a daily journal of food intake, weekly activity, stress levels for the duration of the study, divided into two three week segments.
 5. completed a weekly Endometrial Symptom Assessment concerning degree, type and frequency of pain based on McGill Pain Questionnaire (MPQ).⁷⁹
 6. were given a healthy food plan based on the USDA pyramid food guidelines.
- This information was accompanied with meal plan instructions (e.g., serving size) and sample meals (Appendix I). The Control group was allowed up to 19g. of simple sugars in their diet. The Test group was not allowed any simple sugars.

3b Differentiated Group Treatment

Both the control group and the test group received dietary advice based on the USDA Food Guide Pyramid. Food types and portions, as described in the USDA FGP

instructions, were explained by the AI (Appendix G). The Test group received a listing of some foods with low GI/GL values, as form of intervention (Appendix K). They were instructed to consume a predominance of the low GI foods and to eliminate simple sugars from their diet. Artificial sweeteners were eliminated from diets of both groups due to scientific controversy regarding safety concerns.^{80 81 82 83}

3c. Confidentiality and Informed Consent

Each participant signed the RU-IRB approved disclosure form (Appendix E) for their protection and was assigned an alpha-numeric identifier to protect their privacy. This consent form was verbally discussed to insure the participant understood the document. Only non-identifiable medical information such as age, history of endometriosis and current clinical status were made available to the PI.

3d. Baseline Values

Each participant's pre-trial GI and GL, calculated from all foods consumed during one week, pre-study Endometriosis Symptom Scores (ESS) and initial medical evaluations (e.g., height, weight, age, endometrial status) reviewed by the medical investigator, were recorded as each participant began the study.

3e. Blinding

Final evaluations were performed by the PI, who was blinded to the assignment of participants in each group as well as the group's designation (i.e., control or test). The researcher had no access to any subjects' identifying information. All participants were given numeric identifiers and assigned to either group on a random basis. Only the AI and the gynecologist know the identities of the participants. Only the AI knew their

respective group assignments. Food journal information was input into the Glycemic Index Meal Planner (GMP) program to obtain the GI and GL values. This program is a product from the Glycemic Diet Software Company, Stinson Beach, California.⁸⁴ The assessment questionnaires were scored by the PI.

3f. Exclusion Criteria

In accordance with Federal Policy 45 CFR 46.111, no pregnant women, prisoners or individuals with other serious disease processes or mental problems were recruited. Potential subjects with medically diagnosed disease states (e.g., diabetes, hypertension, autoimmune diseases, cancer) were excluded. Individuals taking pharmaceutical drugs for any health issue, with the exception of over-the-counter (OTC) pain medication, were also excluded.

3g. Inclusion and Recruitment

Inclusion was determined by the following characteristics: age, history of endometriosis-induced pain, and endometriosis medical history. Participants were between 21 and 47 years of age and had menstrual cycles ranging 27 to 29 days with appropriate Follicle Stimulating Hormone (FSH) levels (below 10mIU/ml) for non-pre and/or non-menopausal women. The medical investigator assigned the endometriosis stage values (i.e., level of severity). Participants were recruited through outreach to 60 gynecologists, emails to 500 women medically diagnosed with endometriosis (all members of the Endometriosis Association), and brief appearances to hand out approved information to women's professional, social and church groups. Although approximately 640 women were informed about the clinical trial, only 46 contacted the

AI. From that group, 26 women actually attended an initial meeting. Ultimately, only 13 women participated for at least 3 weeks, nine (9) women completed the full six weeks.

Participants were not paid. (Appendix B)

3h. Compliance Assessment

Based on the Health Belief Model,⁸⁵ the participants were scored on their perceptions concerning the severity level of Endometriosis-related pain (i.e., Endometrial Symptom Questionnaire) on a weekly basis. They were encouraged to contact the AI, for any questions or any issues that surfaced during the study. She contacted each participant at least once during each three week segment to provide encouragement and reminders to maintain compliance with all aspects of the study (e.g., diet, food journals) and provide an opportunity for the participant to voice any concerns, which were promptly addressed.

In order to increase compliance, all subjects were asked to bring their completed food journals and assessment questionnaires (e.g., Endometriosis Symptoms, Stress Levels, Activity Levels) to a one hour meeting at the end of the third week with the AI. This meeting was utilized to provide the subjects with feedback, guidance, encouragement and to receive their second three-week food journal package. The AI also assessed their compliance levels after reviewing their three week food journals, which was also reassessed by the PI as the food journal information was input into the GMP program. Out of the thirteen remaining subjects, four voluntarily dropped out after the first three week meeting. These dropouts were still in severe endometriosis related pain with three of them having gone to a local emergency ward for pain relief. The fourth, experiencing severe endometriosis-induced pain followed by extreme anemia from

mettorhagia, was advised to see her physician immediately for medical assistance.

3i. Glycemic Index and Glycemic Load Determination

Each subject's dietary GI values were assessed using the GMP program which included the exact physiologically measured GI values currently agreed upon by experts in the field of nutrition and reported in the International table of GI and GL values⁸⁶. The average daily GI and GL were calculated from weekly food intake.

Glycemic Index values are divided into three categories:

Low ≤ 55 , Intermediate = 56-69, High = 70+

Glycemic Load values are divided into three categories:

Low ≤ 10 , Intermediate = 11-19, High = 20+

3j Endometriosis Symptom Scoring

Endometriosis Symptom Scores were based on the McGill Symptom Questionnaire (Appendix D) scoring methods. The total of all values are categorized in the following manner:

Low ≤ 20 , Intermediate = 21-39, High = 40+

3j. McGill Pain Questionnaire (MPQ)

MPQ Historical Development

The MPQ was developed at the McGill University by Melzack, in 1975⁸⁰, who was able to elicit a wide range of descriptors, from the clinic's patients' experience of chronic pain.

Pain characteristics fell into four predominant categories: sensory (e.g., pulsing, throbbing), affective (e.g., exhausting, punishing), evaluative (e.g., annoying, miserable)

and miscellaneous (e.g., nagging, radiating). The last category (i.e., misc.) suggests a predictive correlation associated with the second qualitative dimension of the primary pain descriptor. The specific pain descriptions have been shown to be significantly helpful in developing improved pain management strategies for patients with chronic pain. Numerous clinical trials have been performed that have verified the accuracy and utility of the MPQ⁸⁷.

The Endometriosis Symptoms Questionnaire (ESS) (Appendix D) was designed utilizing the MPQ format to allow for a more expanded expression of pain and discomfort by the women suffering from endometriosis to be readily quantified for statistical integrity. The ESS, the endometrial pain indicator, was used to determine the level of effectiveness a low-glycemic diet may provide women suffering with endometriosis.

3k. USDA Food Pyramid Guidelines

The United States Department of Agriculture, USDA, introduced the Food Guide Pyramid (FGP) in 1992 (Appendix G), subsequently undertaking a comprehensive review in 2000 after an intensive period of gathering technical and consumer research along with professional input. The scientific basis of the development of the FGP is grounded in the following three components.

1. Recommended Dietary Allowances (RDA's) published by the National Academy of Science, which have now been replaced by Dietary Reference Intakes (DRI)
2. Recommendations from the Dietary Guidelines for Americans (DGA)
3. Actual food consumption patterns of Americans based on food surveys.

The 2000 FGP update was to determine that the current recommendations accurately meet nutritional standards. Nutritional composition of foods is also updated as information becomes available. The FGP was found to be a useful mode of communication with the public. The USDA currently provides an interactive FGP for kids and adults on the Internet⁸⁸.

FGP Dietary Guidelines for Trial Participants

The subjects were shown the USDA FGP (Appendix G) and were instructed to consume the minimum amounts in each food group each day. The AI carefully explained serving sizes for each food group. For example: one slice of bread or ½ c. of cooked rice or pasta is equivalent to one serving from the bread/pasta/cereal group. One half cup of cooked or raw vegetables is equivalent to 1 serving.

The menus were carefully developed to comply with the FGP. However, maintaining a low GL meal was a challenge when creating menus for the Test group (Appendix H), particularly when recommending foods from the bread/cereal group. Several days' menus only contained four or five servings from the bread/cereal group to maintain low GL diet integrity.

4. Data Analysis

4a. Dietary Assessment - Glycemic Index/Glycemic Load

The GI values were assessed utilizing the Glycemic Index Meal Planner program (Appendix C) which allows input of a wide variety of foods replicating those found in the “International Table of Glycemic Index and Glycemic Load values”⁸⁶. Foods and beverages were entered into the program which automatically assesses the GI and GL values for each food. Foods not found in the GI/GL International Tables were input by their separate components (e.g., knish, input as wheat and potatoes). Amounts (in grams) of “component” foods were estimated by the PI, according to information found on that particular food’s standard portion. The software provides a daily average value for the GI for all foods and beverages consumed throughout the entire day. The software added the GL values associated with each meal and snack for the day but did not calculate an average as it did for the GI values. The PI averaged each day’s GL using a calculator (Total GL of the day’s meals + snacks/ # of meals + snacks eaten that day). The average weekly GI and GL values were calculated by the PI using a calculator. Calculated values were rechecked by the AI.

4b. Endometriosis Pain Assessment

Pain due to endometriosis was assessed utilizing the scoring method developed by the McGill Pain Assessment Model. On a weekly basis, the participants scored each relevant characteristic describing their endometriosis symptoms (ESS) using a scale from 1 to 5 (Appendix D).

4c Compliance Assessment

Compliance assessment measures how closely the subjects followed the USDA Food Guide Pyramid (FGP). Each participant was asked to assign themselves a

compliance score weekly. Upon review, these self assessments were found to be inaccurate. Subsequently, the PI and AI calculated the compliance based on food journals completed by the subjects. Scores ranged from 0 to 100 points and were determined by the following criteria for each level of the FGP by food group and number of servings:

1. grains, cereals (6-11 servings) = 20 points (pts.)
2. vegetable group (3-5 servings) and fruit group (2-4 servings) = 20 pts. per food group
3. dairy group and meat, poultry, fish, beans, nuts group (both 2-3 servings) = 20 pts. ea.
4. 2.5 pts off for each incidence of consuming sweets, fats and oils above allowable levels.
 - 4a. Control group levels: 19g simple sugars, 114g. oil and/or fat per day
 - 4b. Test group levels: 0g simple sugars, 114g. oil and/or fat per day

The PI and AI reviewed daily food journal entries to determine if both the Control and Test group were consuming at least the minimum required servings of each food group daily. Some flexibility was given in determining points. If over the course of the week a subject averaged at least three vegetable servings a day, she was given the full 20 points, even if one day she had only 1.5 servings but another day had 4 or 5. Totals were rounded up (ex. 79.5 to 80). The Control group was allowed up to four teaspoons (19g) of sugar per day (e.g., sweeteners added to a beverage or pastry). Any amount of sugar over that allotment resulted in 2.5 points deducted from the daily total. The Test group

was asked to eliminate all simple sugars from their food plan. Any sugar added to food or snack incurred a 2.5 point deduction from a total of a possible 700 points per week/7.

4d. Stress and Activity Level Assessment

Stress levels were self-reported by participants using a rating scale from 1 to 10 (low to high) evaluated daily. Activity levels, also recorded daily, included the duration and type of activity performed. Subjects were provided with a list of acceptable aerobic activity: Some were: power walking, jogging, running, rope-jumping, dance and biking. Average daily activity was calculated based on hours of exercise per week.

4e Characteristics of the Participants.

Table 1 provides age, surgical history, disease stage (level of severity), OTC pain medication usage and weeks of the clinical trial completed.

TABLE 1 Endometriosis/Diet Intervention Study - Participants' Data
A=Control Group B=Test Group

Subjects N=13	Age	# of Surgeries Due to Endo	OTC Pain RX Y/N	Stage of Disease ^a	Weeks Completed
1-A	22	2	Y	3	3
2-A	33	1	Y	3	6
3-A	35	1	Y	3	6
4-A	44	1	Y	4	6
5-A	44	0	Y	2	3
1-B	45	1	Y	4	3
2-B	32	1	Y	3	6
3-B	24	1	Y	3	6
4-B	26	0	Y	1	6
5-B	47	2	Y	3	6
6-B	27	1	Y	2	6
7-B	38	1	Y	4	3
8-B	26	0	Y	2	6

^a Stage of disease was assessed and ranked, from mild (1) to severe (4), by a medical doctor.

Forty-six women expressed a desire to participate in this clinical study. Twenty six actually presented for an initial meeting (ethnicity: 16 white, 9 Black, 1 Philippino). Of these, 13 dropped out within the first week. Of the remaining 13 subjects the ethnic

spread was: 8 Black, 4 white and 1 Philippino. All of the women were taking OTC pain medication on a regular basis, with 6 subjects consuming their pain medication four to five times daily during menstruation. This level of endometriosis pain correlated with the medically assessed stages of severity.

Stage 4, n=3

Stage 3, n=6

Stage 2, n=3

Stage 1, n=1

Eleven women described their menstrual flow as heavy, often causing varying levels of anemia. All subjects expressed an earnest desire in resolving their chronic pain through natural means, and were hopeful of the possible benefits of this original study. Eight of the women indicated that they had done some research of their own and had tried other diets without success. Interestingly, 75% of women over the age of 38 were not compliant and dropped out. (Table 1 - mean age of Dropouts = 37.3 vs. mean age of Continuers = 32.7).

4f Statistical Analysis

Statistical comparisons between the control (n=5) and test (n=8) groups for continuous variables were performed using independent t-tests. Comparisons of subjects at various time periods were done using paired t-tests. Data were examined by comparing results of subjects who continued (C) on the protocol and those who dropped out (D) at the end of three weeks. These groups were also compared by t-tests. T-tests were performed utilizing the SPSS software.

5. Results

This clinical study was undertaken to determine if a low glycemic diet, particularly one in which simple sugars were excluded, would reduce the painful symptoms of endometriosis.

Comparison of mean values for the control and test groups by t-test revealed no statistically significant differences in: GI, GL, Endometriosis Symptom (Pain) Scores, Dietary Compliance (Table 2), Activity and Stress levels (Table 4). Also, no correlation was found between the GI and the Pain Scores. However, when the subjects were re-grouped according to whether or not they continued in the study beyond three weeks, statistically significant differences were found between Dropouts and Continuers (Table 3).

Interestingly, both groups ate foods classified in the upper level of the low Glycemic Index range (GI =45-55) regardless of whether they were in the control or test group. While the mean GI for the dropouts was a few points higher, statistical significance was not reached. However, comparing the mean GL values of each group, Dropouts maintained a mean GL in the highest range (mean of weeks 1-3, $GL_D=24.9$, Table 2) while the mean values for Continuers decreased from a high baseline ($GL_C=26.6$) to the medium range ($GL_C=14.4$) and experienced a concurrent improvement in their pain scores (Table 3).

Table 2 Glycemic Index, Glycemic Load, Endometriosis Symptom (Pain) Scores and Dietary Compliance Scores of Subjects in Control and Test Groups

	Control (n=5)					Test (n=8)			
	Base-line	Week 1	Week 2	Week 3		Base-line	Week 1	Week 2	Week 3
Glycemic Index	57.4 ^a ±2.7	49.1 ±4.4	50.2 ±4.8	51.0 ±5.5		57.0 ±3.3	44.9 ±6.5	48.2 ±9.1	45.2 ±8.8
Glycemic Load	29.4 ±3.2	19.5 ±3.8	20.0 ±6.9	19.4 ±5.2		25.0 ±2.6	15.9 ±6.1	17.3 ±8.1	16.1 ±7.5
Pain Score	57.9 ±6.0	53.8 ±10.0	40.6 ±16.0	37.6 ±16.7		58.6 ±4.3	51.0 ±8.8	42.3 ±11.8	37.5 ±17.5
FGP Compliance		66.0 ±11.4	66.0 ±12.9	69.0 ±8.3			70.4 ±20.1	75.6 ±19.4	78.8 ±21.8

Values are mean ±SD. No statistically significant differences from baseline were found by a paired t-test.

Table 3 Glycemic Index, Glycemic Load, Endometriosis Symptom (Pain) Scores (ESS) and Dietary Compliance Scores of subjects who dropped out after 3 weeks, and subjects that completed 6 weeks

	Dropouts (n=4)					Continuers (n=9)			
	Base-line	Week 1	Week 2	Week 3		Base-line	Week 1	Week 2	Week 3
Glycemic Index	56.3 ^a ±2.1	48.6 ±1.4	51.9 ±7.9	50.8 ±7.4		57.6 ±3.3	45.6 ±7.0	47.6 ±7.5	45.9 ±8.1
Glycemic Load	26.6 ±4.2	24.9 ±2.7	26.9 ±3.9	24.8 ±3.2		27.0 ±1.4	14.4* ±4.8	14.6* ±5.3	14.0* ±4.8
Pain Score	57.3 ±6.3	52.3 ±8.5	54.5 ±8.4	52.7 ±9.8		58.8 ±4.3	52.0 ±9.7	35.9* ±10.3	30.8** ±14.2
FGP Compliance		53.8 ±4.8	50.0 ±4.1	52.5 ±9.6			81.7*** ±8.7	81.7*** ±7.1	82.2*** ±8.7

^aValues are mean ±SD. Asterisk* and ** indicates a significant difference from baseline within groups (*P=.01, **P<.02) as determined by a paired t-test. GL and Pain Scores were significantly lower for Continuers at weeks 2 and 3. Asterisk *** indicates a significant difference between compliance values for the Dropouts and Continuers (***P < .01) as determined by an independent t-test.

The t-test showed a statistically significant inverse relationship between FGP Compliance (CMP) and Endometriosis Symptoms (ESS) of Dropouts versus Continuers (Table 3).

The results also indicated a significant inverse relationship between CMP and GL by the end of week 2 for the Continuers.

Also demonstrated was a significant inverse relationship between high CMP and low GL, yielding reduced endometriosis pain scores for the Continuers, as originally hypothesized (Table 3).

Table 4 Glycemic Index, Glycemic Load, Endometriosis Symptom (Pain) Scores (ESS) and Dietary Compliance Scores of subjects who completed 6 weeks

Continuers

	Base-line	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Glycemic Index	57.6 ^a ±3.3	45.6 ±7.0	47.6 ±7.5	45.9 ±8.1	42.8 ±5.7	39.8 ±9.1	39.2 ±6.5
Glycemic Load	27.0 ±1.4	14.4* ±4.8	14.6* ±5.3	14.0* ±4.8	13.8* ±4.2	13.9* ±4.5	13.1* ±3.5
Pain Score	58.8 ±4.3	52.0 ±9.7 r = 0.06	35.9* ±10.3 r = 0.58 ⁺	30.8** ±14.2 r = 0.64 ⁺⁺	28.8* ±13.5 r = 0.61	26.9* ±15.3 r = 0.83 ⁺⁺⁺	22.9* ±8.1 r = 0.12
FGP Compliance		81.7 ±8.7	81.7 ±7.1	82.2 ±8.7	83.3 ±9.6	83.9 ±11.7	90.6 ±3.0

^aValues are mean ±SD. Asterisk* and ** indicates a significant difference from baseline within Continuers (*P=.01, **P<.02) as determined by a paired t-test. GL and Pain Scores demonstrate a significant decrease from baseline for weeks 1 through 6 and 2 through 6 respectively. Compliance remained high from week 1 through 6. r values indicate a significant correlation (⁺P<.04, ⁺⁺P<.02, ⁺⁺⁺P<.01) between the GL and Pain Scores for the same week.

Table 5 Self-Reported Activity and Stress Levels by Subjects who dropped out after 3 weeks or continued to complete 6 weeks.

	Dropouts (n=4)				Continuers (n=9)		
	Week 1	Week 2	Week 3		Week 1	Week 2	Week 3
Activity (hours per week)	6.1 ^a ±3.5	2.5 ±0.3	4.3 ±2.1		4.7 ±4.5	4.5 ±3.9	1.5 ±3.4
Stress Level (1=none,10=unbearable)	4.4 ±1.2	4.0 ±1.1	3.8 ±1.4		3.6 ±1.9	3.6 ±0.9	4.3 ±2.4

^aValues are mean ±SD. No significant differences were found between the groups.

The self-reported Stress Levels and Activity Levels, according to a t-test, showed no correlation to the subjects' pain scores as quantified by the ESS. The level of activity in both groups was low, precluding any meaningful comparison.

6. Discussion

To date, no other study has attempted to determine if diet has any effect on endometriosis. This preliminary study is an effort to bridge that gap. The hypothesis asserted that a low-glycemic diet would reduce the painful symptoms of endometriosis that the subjects were experiencing. This study is the logical next step to demonstrate a significant association between low-glycemic diet and reduction of inflammatory – induced symptoms. There is also an emerging body of information gleaned from numerous recent studies consistently suggesting that chronically elevated blood sugar levels, post prandial, activates an inflammatory response that could lead to a variety of disease process⁶⁵. Numerous studies have confirmed the inflammatory environment perpetuates endometriosis^{43, 44}. The effective use of strong anti-inflammatory medications (e.g., prednisone), has also supported this finding.

Taking into account the small sample size, this clinical trial has demonstrated, for these participants, the benefits of utilizing a low-glycemic diet with an emphasis on maintaining a daily low glycemic load, by reduction in monthly or constant pain these women were experiencing within three weeks. Interestingly, it made no difference whether or not the participants were instructed to consume mostly foods with a low GI, mostly because the subjects' food choices, in both groups, were predominantly associated with low GI values (Table 2). Those subjects in the control group, who adhered to the USDA FGP, were as successful in reducing their endometriosis-induced pain as were those in the test group who adhered to the FGP. Thus, avoidance of simple sugars, as recommended by the FGP, resulted in a reduction in the daily average GL.

The subjects, from both groups, who decided to complete the entire six weeks of the study reported noticeable decrease in endometriosis-induced pain by the second week which continued decreasing throughout the clinical trial. The three women in the control group did not have any instruction about ways to lower their dietary GL or choose foods associated with low GI values. However, they rigorously followed the USDA food pyramid guidelines, verified by their compliance scores (Table 3), which clearly states that a healthy diet contains very low levels of sugars. These subjects' food journals showed a substantial reduction in their simple sugar intake which unknowingly, led them to consume a low GL diet, and thus no longer displayed characteristics of the control group. Notably, the Continuers' GL was markedly reduced by the end of the first week (Table 3). The fact that the reduction in their pain scores was delayed until the second week may have been due to the time required to reduce the level of inflammatory cytokines and ROS below the critical mass needed to produce and or initiate the inflammatory process^{42,43,44}.

There was a marked improvement in the Continuers' diet from baseline. A review of the food journals belonging to those subjects from the control group showed a substantial increase in the amounts of green leafy vegetables they consumed daily. They had also increased the amounts of dietary fiber which supports lower GL values by decreasing the rate at which sugar enters the blood⁸⁹.

These results may indicate that the GL may be, to some degree, a more useful tool than the GI, since this trial showed no statistical correlation between the GI values and the endometriosis symptoms. Instead, portion control (e.g.. ½ banana) of foods with medium to high GI values plus appropriate food combining may be a more important

dietary component since individuals are able to eat a wider variety of foods while maintaining low GL levels. Notably, all subjects ate foods with similar GI values. The statistical difference in the pain scores was achieved by those subjects who lowered their respective GL scores (all Continuers, Table 3). The Dropouts maintained a high GL diet and did not experience any improvements in their endometriosis symptoms. Also, the three subjects from the Control group, who followed the USDA guidelines closely, reduced their dietary GL, achieving significantly reduced pain scores. This outcome suggests that all simple sugars do not have to be eliminated, but kept at minimal intake levels, as advised by the FGP, to achieve improved health status. The subsequent benefit, at least for those participants who completed the entire six weeks, was a significantly improved menstrual experience with relief from chronic endometriosis-induced pain.

Comparative Review

Comparable improved outcomes were reported in a recent randomized controlled trial which utilized a low GL diet to improve symptoms in acne vulgaris patients.⁹⁰ Significant reductions in the Test's group GL (49%) correlated with acne improvement which was measured by the 51% drop in total lesions. Inflammatory lesions also showed a significant decrease of 45% in the Test group over the trial period. Whereas GL reduction for the Control group (who took acne medications) was only 4%, lesions were reduced by 30% and inflammatory lesions by 23%.

Another study utilizing an ad libitum low GI/GL diet, focused on weight loss, with 40-45% of energy from carbohydrates and 30-35% from fat vs. a conventional diet which restricted fat intake (<30% of energy) and overall caloric intake (240-400 kcal/d). Both groups experienced significant decrease in body weight, however there was a

significantly greater mean decline in plasma triacylglycerols for the experimental diet group (-37.2%) than the conventional diet group (-19.1%)⁹¹, suggesting that a low GL diet has broader implications for plasma lipid control.

Results from this clinical study utilizing a low GL diet to reduce endometriosis induced pain, were consistent with the above mentioned studies. This preliminary trial showed a 47% decrease from the Continuer's mean baseline GL to the mean GL of week two, accompanied by a 39% decrease in their mean pain scores (Table 3). Where as the Dropouts, whose food journals revealed no decline in mean GL, had no reduction in their pain scores.

7. Study Limitations

Group Size

The small sample size in this clinical trial may render the results unreliable. However, in as much as this study only included subjects whose medical and anecdotal history clearly described women who had gone to extreme lengths (e.g., multiple surgeries) to reduce and/or eliminate the endometriosis-induced pain, it may offer a template for studies with a more statistically acceptable sample size to determine if these beneficial results can be replicated. It has been argued, however, that studies with small sample sizes may be documenting a cause and effect that only pertain to a sizeable subpopulation (i.e. 10% of women between ages of 21-45), thus the degree of confidence that can be attributed to the results of a study containing a small sample size may be considered more reliable for that subgroup⁹².

Examining Inflammation

It is evident that this preliminary study did not examine inflammation directly. There was no pre- or post blood work to determine c-reactive protein levels or an organic acid test utilizing a substrate to determine levels of free radical activity, both indicators of inflammation, due to a lack a funding and time constraints. However, numerous studies^{45, 64, 70} have demonstrated sufficient evidence to strongly suggest that systemic inflammation creates an environment where a wide range of disease process can be initiated or perpetuated. Frequent daily insulin spikes can initiate and sustain an inflammatory cascade.

High glycemic index/load diets, over time, can create chronically high blood sugar levels. This process generates increased insulin spikes, which can, eventually,

initiate or promote increasing systemic inflammation. Studies have revealed increased levels of free radicals, ROS⁶¹, adhesion initiating cytokines (i.e. IL-6)⁵², in women suffering from endometriosis. These results confirm that endometriosis is an inflammatory induced process as evidenced by the pain relief experienced by those patients given anti-inflammatory medications such as prednisone. It must be noted, however, that other dietary factors, which may have changed as a result of adhering to the FGP, may have been involved in the decreased endometriosis pain scores.

8. Implications for Future Research

Due to the small sample size of this original study, researchers, clinicians and women suffering from endometriosis may not have the highest confidence levels that the positive outcomes achieved by those subjects who completed all six weeks of this study, can be replicated. To that end, future trials will require a larger sample size for statistical significant outcomes with a high degree of confidence. In order to reduce attrition and improve dietary compliance, the subjects' levels of fear, surrounding the return of endometriosis induced pain without access to their prescription pain medications, must be addressed up front, according to results from the Health Belief Model study⁹³. The intervention group should be informed about the beneficial outcome experienced by those subjects who completed this preliminary study to broaden new recruits' perception of options available to them that have a high probability of reducing their chronic debilitating pain.. Becker's study also suggests that the investigator discusses the subject's "prior experiences and present health beliefs in order to modify those perceptions likely" to prevent compliance⁹⁴. Being aware that other women who experienced similar endometrial pain were successful in reducing that pain by following a medication-free dietary regimen, may increase retention and compliance. Other studies have demonstrated improved compliance utilizing three of the strategies that were employed in this study: educating subjects in portion control, providing suggested menus, and maintaining regular communications for questions and support⁹⁵

The Control group should *not* follow the USDA FGP, but maintain their current diet as is. Otherwise, they should also be instructed to follow the same procedures as the Test group. Thus, the Control group should maintain a detailed food journal, complete

all weekly assessment questionnaires and/or logs (level and degree of pain, type and amounts of medications taken) and immediately inform the appropriate investigator of any hospitalizations and emergency surgeries. The investigator should meet with this group at regularly agreed upon intervals to collect and monitor all assessment questionnaires or logs as well as discuss their issues revolving around endometriosis. A useful area for the investigator(s) to explore with the Control group is to inquire as to their reasons for making certain unhealthy food choices, although the “unhealthy” descriptor would not be used. Their responses may provide insight for designing food plans for those individuals who find it difficult to follow a healthy diet.

Stress and activity levels should be included as baseline values. It is recommended that an effort be made to find more participants with high activity and stress levels providing adequate contrast within the groups to effectively determine if there is any significant impact on the participants’ endometriosis symptoms.

Initial and final study blood work should be performed containing C-Reactive Protein values along with free radical testing of organic acids to determine pre- and post levels of inflammation. Post trial ultra sound, medical infrared thermal imaging⁹⁶ and/or other non-invasive medical scans should also be performed to determine any significant change in the post study endometriosis staging levels. Current menstrual characteristics such as duration, amount of blood loss (e.g., heavy, moderate, light), pre-menstrual symptoms (e.g., bloating, irritability, fatigue, food cravings), color of blood, the presence of clots, amenorrhea or menstrual irregularity should also be noted as baseline information.

Including a means of rating the level of food choice satisfaction for the subjects in both groups, may possibly assist with improved menu choices to limit attrition. Lastly, using the McGill short form (Appendix L) would require less paper work for the subjects and may contribute to improved participant retention.

If the health benefits of following a food plan having a low-glycemic load are consistently reproducible, this may be one of the most useful tools a clinician can offer their patients for improved gynecological health and/or the prevention of any reoccurrence of endometriosis.

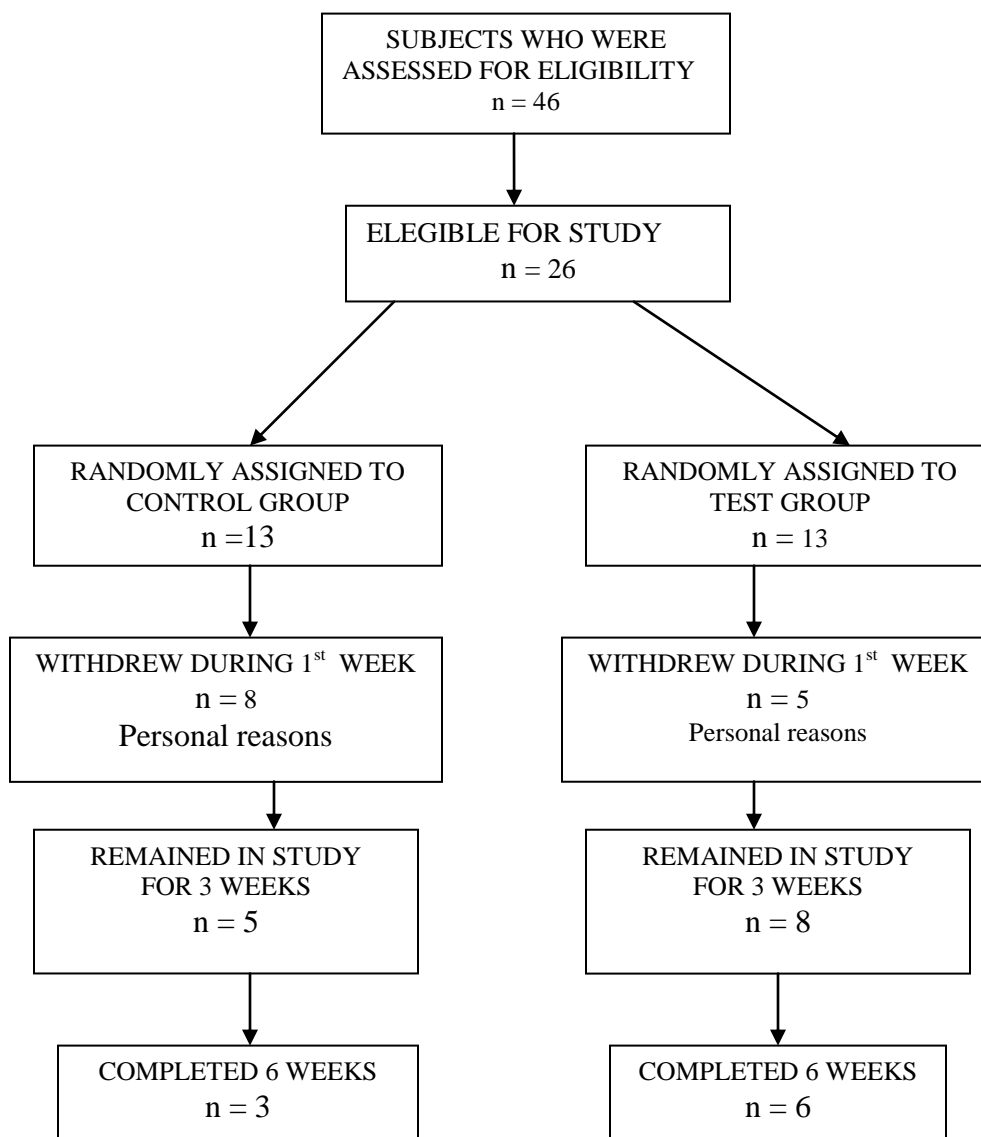
9. Conclusion

This preliminary clinical trial, albeit small, continues to support the growing number of studies demonstrating the significant association between low glycemic diets and improved health outcomes. Specifically, studies where health improvements have reached statistical significance include: endometrial cancer⁹⁷, neural tube defects⁷⁷, diabetes⁹⁸, cardiovascular disease risk⁹¹, obesity⁹⁹, pancreatic cancer¹⁰⁰ and now, possibly endometriosis.

Results from this study suggest that a reduction in mean GL values from the initial high scores at baseline, decreasing to medium and low GL values with a concurrent decrease in pain scores, may also diminish the level of systemic inflammation. Improved outcomes in this study, clearly point to the utility of abiding by a food plan emphasizing low glycemic loads. This would also suggest that future studies focused on a low glycemic diet and any disease state, may achieve significant improvement if the clinical trial's dietary requirements are based on the USDA FGP guidelines.

Appendix A**LIST OF ABBREVIATIONS**

1. AL Activity Levels
2. BS Blood Sugar
3. C Continuers
4. CIC Circulating Immune Complex
5. CMP Compliance
6. D Dropouts
7. ESS Endometriosis Symptom Scores (i.e. Pain Scores)
8. FGP Food Guide Pyramid
9. GE Glycemic Effect
10. GI Glycemic Index
11. GL Glycemic Load
12. IL Interleukin
13. MPQ McGill Pain Questionnaire
14. NO Nitric Oxide
15. RCT Randomized Control Trials
16. SL Stress Levels

Appendix B

DROPOUTS: PERSONAL REASONS

- I. Diet too regimented
- II. Unwilling to reduce or eliminate sweets
- III. Refused to eliminate Rx
- IV. Other

Appendix C

Glycemic Index Meal Planner Program

Glycemic Index Meal Planner - Day

File Info

8/5/2007 Low GI<56, Medium GI 56-69, High GI>69

Click on a Meal Row below

	Meal Name	Glycemic Index	Glycemic Load	Carbs (g)	Calories	Saturated Fat (g)	Fat (g)	Protein (g)
	Brkfst	35	7	22	216	3	8	12
	Snack1	36	6	16	443	21	31	25
	Lunch	40	6	15	460	21	32	28
	Snack2	0	0	0	0	0	0	0
	Dinner	35	16	45	880	1	4	166
▶	Snack3	0	0	2	8	0	0	0

Day Calculations: 36 8,5 100 2007 46 75 231

Saturated Fat % of Total Fat - 61

Calorie breakdown: Carbohydrates - 19 % Protein - 46 % Fat - 33 %

Display History Log Exit

This screen shows the average GI and GL for one day's food consumption.

Appendix D**Endometriosis Symptom Questionnaire⁸⁴**

Participant's ID: _____ **Date:** _____ **Time** _____ **am/pm**
(circle one)

Input the Symptom Frequency (0-5) next to each symptom.

Symptom Frequency: 0-never, 1-rarely, 2-occasionally, 3-weekly, 4-daily, 5-continuous

1. Flickering __	2. Pulsing __	3. Throbbing __	4. Pounding __
5. Shooting __	6. Stabbing __	7. Boring __	8. Pricking __
9. Sharp __	10. Pinching __	11. Gnawing __	12. Pressing __
13. Cramping __	14. Tugging __	15. Pulling __	16. Electric __
17. Hot __	18. Burning __	19. Searing __	20. Scalding __
21. Stinging __	22. Tingling __	23. Smarting __	24. Tender __
25. Dull __	26. Sore __	27. Aching __	28. Heavy __
29. Tiring __	30. Exhausting __	31. Fearful __	32. Sickening __
33. Radiating __	34. Grueling __	35. Cold __	36. Freezing __
37. Annoying __	38. Miserable __	39. Intense __	40. Unbearable __
41. Tight __	42. Drawing __	43. Squeezing __	44. Tearing __
45. Nagging __	46. Nauseating __	47. Tortuous __	48. Agonizing __
49. Brief __	50. Momentary __	51. Transient __	52. Rhythmic __
53. Periodic __	54. Intermittent __	55. Urgent __	56. Constant __

Comments: _____

Please place an X on the line in the box indicating the area where you are experiencing any endometrial-related symptoms.

<i>Upper Abdomen – Left</i>	<i>Upper Abdomen – Right</i>
<i>Lower Abdomen – Left</i>	<i>Lower Abdomen – Right</i>

If there are any endometrial-related symptoms in any other area, describe it (the area) here.

Appendix E

Informed Consent for Participants in Clinical Trial

Project: Effect of Dietary Carbohydrates on Endometriosis

You are being asked to participate in a study to determine if endometrial pain can be substantially reduced and/or eliminated by following a specific diet. This clinical study is being organized and administered by Courtney Witherspoon, Doctor of Oriental Medicine (D.O.M), a graduate student of Nutritional Sciences at Rutgers University.

At the beginning and end of this clinical study, you will be asked to complete an endometrial symptom questionnaire that should take about 5 minutes. For the next six weeks you will be following specific healthy dietary guidelines, recording your daily food and drink intake as well as any endometrial symptoms. This healthy diet carries no risks. It is imperative that Ms. Katheryn Boyce-Piper, RN., be informed of any food allergies you are aware of so that they can be excluded from your recommended food plan. The main possible benefit is that any chronic pain or discomfort due to endometriosis may subside.

Your permission is requested to review all information on your medical records pertaining to endometriosis. Your signature on this document confers that permission to the investigator of this study. All personally identifiable information of the study will be kept private. You will not be identified in any publication or presentation of the study findings. Only numerical scores and endometrial symptom changes will be reported. All documents from this study will be kept confidential in a locked file in the office of Dr. Husami and at Rutgers University Nutritional Science Department. All confidential information will be shredded December 2009.

If you decide to participate, you are free to withdraw at any time. Dr. Husami will continue to provide medical intervention as deemed necessary. The investigator or your doctor may also choose to withdraw you from this study if your endometrial symptoms are not improving. Whether you receive medical treatment or not, it is important to maintain the same diet throughout the six week study. Those participants randomly selected to be in the test group will not receive medical treatment for endometriosis. However, over the counter pain medications (e.g., motrin, alleve) for endometrial discomfort are allowed if needed.

You are encouraged to call Ms. Boyce-Piper, RN, (212-252-4741) or Dr. Witherspoon, DOM, (212-592-3994) with any questions regarding this clinical study. The Institutional Review Board (IRB) of Rutgers University has approved recruitment of participants for this research. Any questions regarding the rights of research participants can be directed to Humansubjects@orsp.rutgers.edu., or call 1732-932-0150 x2104. If you wish to find

out the results of this study you may call the Nutritional Science Dept at 1-732-932-9845 during or after December 30th, 2007.

SIGNED AGREEMENT

I understand that:

- (a) My signature indicates that I voluntarily agree to be a part of this research study.
- (b) By signing this form I do not waive any legal rights
- (c) I can withdraw from this study at any time.
- (d) I will be randomly assigned to the control group or the test group.
- (e) The test group receives no medical intervention for endometriosis, only diet changes.
- (f) I have given permission for Ms. Kathryn Boyce-Piper and Dr. Witherspoon, DOM, to have access to my medical history regarding endometriosis, age, ethnicity, FSH levels, standard CBC and CRP values.

I fully understand this Consent Form and choose to participate in this six week clinical study. I am signing this document of my own free will.

Date:

Signature of Participant

I believe that the participant fully understands this Consent Form and has freely given their informed consent.

Signature of Witness - Katheryn Boyce-Piper, R.N.

Signature of Primary Investigator
Courtney Witherspoon, D.O.M.

Date _____

Appendix F**WEEKLY ACTIVITY LOG****Dates: From** / / **to** / /

Please input the amount of exercise performed in the Duration column, as minutes. Some acceptable exercise activities include: biking, hiking, jumping rope, jogging, swimming, Pilates, martial arts, basketball, roller blading or skating, brisk walking, choreographed aerobics. Strolling is not considered exercise.

Days	Duration	Activity (exercise/sport)
Monday		
Tuesday		
Wednesday		
Thursday		
Friday		
Saturday		
Sunday		

STRESS LOG

Please enter your stress level (if any) in the column below. 1 = none, 10 = unbearable

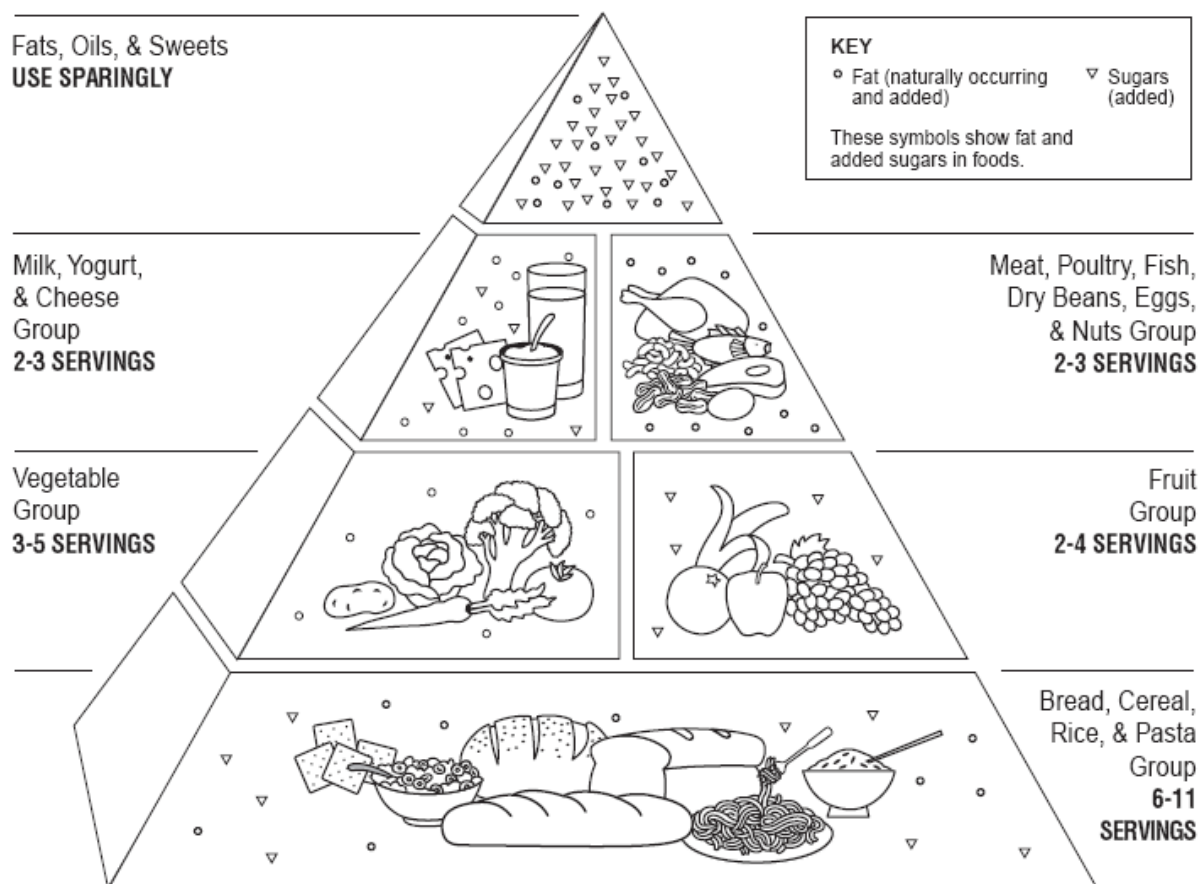
Days	Stress Level 1-10
Monday	
Tuesday	
Wednesday	
Thursday	
Friday	
Saturday	
Sunday	

Appendix G

USDA Food Pyramid

Food Guide Pyramid

A Guide to Daily Food Choices



Source: U.S. Department of Agriculture/U.S. Department of Health and Human Services, August 1992

Use the Food Guide Pyramid to help you eat better every day...the Dietary Guidelines way. Start with plenty of Breads, Cereals, Rice, and Pasta; Vegetables; and Fruits. Add two to three servings from the Milk group and two to three servings from the Meat group.

Each of these food groups provides some, but not all, of the nutrients you need. No one food group is more important than another—for good health you need them all. Go easy on fats, oils, and sweets, the foods in the small tip of the Pyramid.

Appendix H

Sample Menu for Test Group

3 meals, 3 snacks per day using USDA Food Pyramid Guidelines

Breakfast

2 slices whole grain toast with 2 tbs. almond butter
 ½ red grapefruit or fruit of choice

AM snack

1 C. vanilla yogurt

Lunch

½ c . three bean chili
 kidney, black and chick peas
 ½ cup chopped onion
 2 cloves garlic
 ½ chopped green & red bell pepper
 2 tsp olive oil; 1 tsp cumin
 1 c. crushed tomatoes

1 small corn tortilla
 1 ½ oz shredded cheddar cheese
 1 c. mixed green salad with oil and vinegar

Mid-Afternoon snack

1 medium pear or fruit of choice
 Small handful nuts of choice

Dinner

1 baked stuffed red bell pepper
 ½ c. cooked brown rice
 2 oz ground turkey sautéed in 2 tsp olive oil with
 4 tbs. chopped onion, celery, garlic
 1 c. chopped onion, celery, garlic
 1 c. chopped steamed collard greens, ½ tsp. grated ginger, 4 drops toasted sesame oil
 ½ c. carrot raisin salad
 shredded carrots
 1 tbs. raisins
 1 tsp. balsamic vinegar, 1 tsp olive oil, dash cayenne

PM Snack

3 slices papaya

Appendix I

Sample Menu for Control Group

3 snacks, 3 meals per day using the USDA Food Pyramid Guidelines

Breakfast

Whole wheat English Muffin toasted, topped with 2 slices Swiss Cheese and grilled 1 C. sliced kiwi fruit or strawberries or blueberries. Drizzle 1 level tbs. heavy cream mixed with 1 tsp. pear juice over fruit.

Herb tea (1 C.) with 1 tsp. agave nectar.

AM Snack

1/3rd C almonds-walnut mix

Beverage of choice (1 C.)

Lunch

Garden tuna avocado salad sandwich - 3oz water packed tuna – drained
1/2 C. finely chopped celery, carrots, onion,
parsley

2 tbs. mashed avocado

2 slices multigrain bread

Cucumber Salad – 1/2 sliced cucumber

1 tsp. olive oil

1 tbs. fresh lemon or lime juice

dash cayenne pepper

Mid-Afternoon Snack

1/2 C. skim yogurt with fruit and granola

Dinner

Spagetti Squash with meat sauce –

1 C. spaghetti squash

2oz ground turkey sautéed with 1/4 clove garlic in 2 tsp. olive oil

1 tbsp. finely chopped onion

1 tsp. finely chopped black olives

1/2 C. crushed tomatoes

Steamed broccoli flowerets – 1 C.

Mixed Green Salad - 1 C. with 3 tsp. apple cider vinegar and olive oil dressing

Arugula, romaine, red tipped lettuce, shredded carrots

PM. Snack

1/2 baked apple with cinnamon. Drizzle 1 level tsp. agave nectar over fruit.

Appendix J**Sample Food Journal****DAILY FOOD JOURNAL**

Monday (Date) _____

MEALS	FOODS & Condiments	Qty .	<i>DRINKS</i>	DETAILS:
Breakfast <u>Time:</u>				Restaurant?: _____ _____ Homemade?: _____ How Prepared? _____ _____ _____ _____
Snack <u>Time:</u>				Restaurant?: _____ _____ Homemade?: _____ How Prepared? _____ _____ _____ _____
Lunch <u>Time:</u>				Restaurant?: _____ _____ Homemade?: _____ How Prepared? _____ _____ _____ _____
Snack <u>Time:</u>				Restaurant?: _____ _____ Homemade?: _____ How Prepared? _____ _____ _____ _____
Dinner <u>Time:</u>				Restaurant?: _____ _____ Homemade?: _____ How Prepared? _____ _____ _____ _____

Your diligence in maintaining this Food Journal is greatly appreciated.

Appendix K**Sample Low Glycemic Food List**

Food	Serving Size	GI	GL
Whole wheat bread	1 slice	73	10
White (flour) bread	1 slice	70	10
Con Agra 7 grain bread	1 slice	55	8
Natural Oven English Muffin	½ muffin	77	11
Kellogg's All Bran Cereal	1 oz. (dry)	38	9
Nabisco Bran Chex	1 oz (dry)	58	11
Oatmeal	1 c.	75	17
Kellogg's Raisin Bran	1 oz (dry)	61	12
Sweet Corn	4oz	22	15
Long grain white rice	3.5oz	58	15
Brown rice, steamed	4oz.	50	16
Puffed Rice Cakes	½ piece	82	9
Whole milk	1 c.	27	3
Skim milk	1 c.	32	4
Apple (any)	1	40	6
Yellow Banana	½ piece	51	13
Cherries	4oz.	22	3
Kiwi	4oz	58	7
Orange	1	48	5
Black-eye Beans (cooked)	5oz.	33	10
Butter Beans (cooked)	5oz.	36	7
Chickpeas (cooked)	5oz.	28	8

Appendix L

Short Form – McGill Pain Questionnaire

Study #:	
Date:	

Short-Form McGill Pain Questionnaire:

I. Pain Rating Index (PRI):

The words below describe average pain. Place a check mark (✓) in the column that represents the degree to which you feel that type of pain. Please limit yourself to a description of the pain in your pelvic area only:

		None	Mild	Moderate	Severe
▲ Throbbing	0	1	2	3	
▲ Shooting	0	1	2	3	
▲ Stabbing	0	1	2	3	
▲ Sharp	0	1	2	3	
▲ Cramping	0	1	2	3	
▲ Gnawing	0	1	2	3	
▲ Hot-Burning	0	1	2	3	
▲ Aching	0	1	2	3	
▲ Heavy	0	1	2	3	
▲ Tender	0	1	2	3	
▲ Splitting	0	1	2	3	
▲ Tiring-Exhausting	0	1	2	3	
▲ Sickening	0	1	2	3	
▲ Fearful	0	1	2	3	
▲ Punishing-Cruel	0	1	2	3	

II. Present Pain Intensity (PPI)–Visual Analog Scale (VAS). Tick along scale below for pelvic pain:

No pain		Worst possible pain
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III. Evaluative overall intensity of total pain experience. Please limit yourself to a description of the pain in your pelvic area only. Place a check mark (✓) in the appropriate column:

Evaluative	
0 No pain	
1 Mild	
2 Discomforting	
3 Distressing	
4 Horrible	
5 Excruciating	

IV. Scoring:

	Score
I-a S-PRI (Sensory Pain Rating Index)	
I-b A-PRI (Affective Pain Rating Index)	
I-a+b T-PRI (Total Pain Rating Index)	
II PPI-VAS (Present Pain Intensity-Visual Analog Scale)	
III Evaluative overall intensity of total pain experience	

Appendix M

Support Personnel

Nabil Husami, MD

Dr. Husami, a reproductive endocrinologist, runs a private practice, American Fertility Services, PC, in NY. He also serves as Medical Director of the Columbia Presbyterian Endometriosis Center. Dr. Husami served as the primary gynecologist to determine the necessary medical scoring of endometriosis for each participant.

Katheryn Boyce-Piper, RN, CINC – Assistant Investigator

Ms. Boyce-Piper has been licensed as a Registered Nurse in NY State since 1968. She graduated from the Jewish Hospital of Brooklyn School of Nursing. Ms. Boyce-Piper also is a Certified Integrative Nutritional Consultant (CINC), received from the School of Integrative Nutrition in NY. She acted in the capacity of the Assistant Investigator (AI), meeting with the participants, assigning them numeric identifiers, familiarizing them with all records they were asked to maintain, collecting dairies, questionnaires, being available to subjects by phone for questions and concerns, and maintaining data collection sheets.

Kell Julliard

Mr. Julliard is currently Assistant Vice President of Research at Lutheran Medical Center in Brooklyn where he mentors Internal Medicine, Family Practice, Dentistry and Podiatry residents in research projects, including methodological consultation and statistical analysis. He also serves as administrator of the Lutheran Medical Center Institutional Review Board. Mr. Julliard holds an MS from the University of Louisville. He is serving as the statistical consultant for my thesis.

Appendix N

Participants' Anecdotal Accounts

Post Endo Study – participant 9B

Received 8-1-07; forwarded to me from Ms Boyce-Piper

Since the study and beginning on the "no-sugar" eating plan, much has changed for me. Before the study, I was in daily pain due to the endo that I have, despite a number of surgeries. On the eating plan, my daily pain was dramatically reduced, I even had days with no pain. I have had two periods since beginning the eating plan, both without incident. Prior to this change, I would miss 2 to 3 days from work each month, due to the pain from my endo and more often than not, I would end up in the ER or my doctor's office, requiring heavy pain medications. I happily report that I have not been to the doctor or the ER since being on this eating plan, due to endo symptoms. I have also noticed that I have more energy during the day and have been sleeping better at night. I frequently have a difficult time sleeping throughout the night, but while following this plan, I have had fewer incidents of this. My step-son commented the other day that I didn't need to "take a break" during a rather busy day out. My suffering with endo impacts my daily life, so much so that my 11 year old step-son notices when "mommy's having a good day". When I get home from work, I am able to help make dinner, do the dishes and spend time with my family, which is such a different story than before. Prior to my change in eating habits, I was lucky to make it through dinner before taking my heating pad to bed and pray for sleep. There are days in which, now, I slip up and have sugar ... and let me be honest, those days I pay for!!! I am so sluggish and miserable when I have sugar that despite the study being done, I am doing my best to continue with the daily guidelines. For me, this has made a world of difference and I am grateful for being given this opportunity.

Another subject (i.e., age 34) had amenorrhea for three months prior to entering the clinical trial. She wrote on her third week Endometriosis Symptom Questionnaire that her menses had finally returned, however any association with the diet cannot be made.

Three other subjects noticed a reduction in menstrual blood flow, from heavy to moderate, as well as a shorter duration by the fourth week of the study. Although a direct association with the trial study cannot be determined, these reported menstrual changes may be indicative of a reduction in inflammation and free radical activity.

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