Vaginal Estriol as adjunctive treatment for Relapsing Remitting Multiple Sclerosis.

Study Site(s):
Texas Tech University Health Sciences Center

Principal investigator
Name: Mirla Avila MD.
Department: Neurology
Phone number: 832 244 8072
Email address: mirlavila@ttuhsc.edu
Previous TTUHSC/TTU grants in the past three years:
Previous non-TTUHSC/TTU grants in the past three years: Laura Bush grant 2015.

Principal investigator/Co-Investigator
Name: Charles Thomposon MD.
Department: Gynecology ; Email address: Charles.thompson@ttuhsc.edu

Principal investigator/Co-investigator (select one)
Name: Alan Peiris MD, PhD
Department: Endocrinology ; Email address: alan.peiris@ttuhsc.edu

Total number of words: 1143

Vaginal Estriol as adjunctive treatment for Relapsing Remitting Multiple Sclerosis.

Background : Multiple sclerosis is an inflammatory, immune driven condition of the central nervous system. Characterized by inflammation, demyelination and eventually nerve cell damage. It is a common cause of disability in young adults, affecting approximately 450,000 patients in the United States and 2.3 million worldwide.[1] It is now well known that MS patients will have a decreased annualized relapse rate during pregnancy, with a statistically significant decrease in the third trimester. Additionally, in the 3 months postpartum, the rate of relapse increases significantly.[2] Estriol is the predominant estrogen of pregnancy. Estriol has been studied in animal models and has been demonstrated to have distinctly different modulatory actions on the immune system than estradiol [3]. We are also aware of the dramatic neurological improvement in one patient that did use Estriol. In regards to safety, a recent prospective cohort study, found that vaginal estrogen use did not increased associated risk for heart disease, stroke, of cancer among vaginal estrogen users versus non-users. [4]

Oligodendrocytes, or demyelinating cells of the central nervous system, continue to be generated by oligodendrocyte precursor cells (OPCs). The process of demyelination represents a major form of plasticity in the developing adult central nervous system. Previous studies have showed that pregnancy leads to an increase in oligodendrocyte precursor cells (OPC) proliferation, oligodendrocyte generation and the number of myelinated axons in the maternal CNS.[5]

Prolongation of the P100 latency of the visual evoked potential (VEP) has been used to detect subclinical demyelinating lesions in multiple sclerosis, it has also been a tool for researching evidence of remyelination in MS.[6]

Recent study with oral estriol showed a significant decreased in the relapse rate in MS patients.[7]. Oral estriol is associated with entero- hepatic recirculation which prolongs exposure due to recycling. Vaginal estrogen delivery has a regional benefit to the lower urogenital tract, is well absorbed as dose of 0.5 mg to 1 mg. Vaginal estriol is frequently used for management of urogenital symptoms in female patients, these symptoms are significantly common in MS patients. [6]

Purpose/specific aims

1.To determine if vaginal estriol, as adjunctive therapy provides additional benefit to the standard management of Relapsing Remitting Multiple Sclerosis (RRMS)

2. To asses if vaginal estriol improves MRI changes, in patients with RRMS.

3.To evaluate improvement in visual evoked potentials in patients with RRMS with adjunctive use of vaginal estriol.

3. To evaluate the improvement of urogenital symptoms with vaginal estriol in patients with RRMS.

Methodologic Summary: Novel Prospective study which objective was to evaluate the role of vaginal estriol (1 mg daily) as an adjunctive therapy in patients with relapsing remitting MS. Objective measurements included bladder questionnaire, quality of life questionnaire, visual evoked potentials, Ocular coherence tomography (OCT) and 3Tesla MRI . Inclusion criteria included menopausal (either by hysterectomy or natural) female patients with RRMS who were experiencing symptoms suggestive of neurogenic bladder (frequency, urgency, retention, incontinence). A total of 21 patients were included, informed consent obtained. An established urogenital (BLCS) questionnaire will be given to all participants at 6 months and 12 months. Key exclusion criteria were patients with progressive multiple sclerosis, patients with personal history of breast cancer, uterine or ovarian cancer. Patients who were unable to undergo an MRI will also be excluded.

Initial study designed included evaluations at baseline, month 3, 6 and 9. This study was conducted between the summer of 2019 and 2020, due to the COVID 19 pandemic we had to revise the study protocol and decided to modify it and include baseline and 9 month data. IRB approved this amendment.

Study design: Pilot study at TTUHSC department of neurology, MS clinic. Adjunctive vaginal estriol (1mg) was offered to patient with RRMS. VEP and OCT obtained at baseline and 9 months. Multiple sclerosis quality of life-54(MSQOL-54) mental and physical were performed at first encounter and 9 months. Vaginal estriol is absorbed more naturally, levels of FSH, estriol and LH were done at baseline and 9 months. Bladder questionnaire was performed at baseline, month 3, 6 and 9.

All patients received a brain MRI w/wo contrast (in patients with normal renal function) 3Tesla scanner, at baseline and after completing the study. Between 9 to 12 months.

21 patients were included, due to COVID 19 pandemic 9 patients were unable to continue follow up, 12 patients completed the protocol, no side effects were reported.

Results

Estriol in RRMS patients regarding bladder disfunction outcomes:

Improvement of bladder disfunction symptoms were observed among all participants at 6 and 9 months. Statistically significant improvements were observed for BCLS Questionnaire ($p = 0.001$*) as well as in quality of life questionnaire MSQoL 54 Physical ($p = 0.009$*), and MSQoL 54 Mental ($p = 0.042$*). Statistically significant improvements were observed for Urinary urgency ($p = 0.008$*), Urinary frequency ($p = 0.002$*), and Frequent UTI ($p = 0.016$*).

Estriol in RRMS patients regarding remyelination outcomes:

Statistically significant improvement observed for VEP Left Eye ($p = 0.031$), OCT MRNFL Left Eye ($p = 0.005$), Flair Lesions ($p = 0.018$), MSQoL 54 Physical ($p = 0.009$), and MSQoL 54 Mental ($p = 0.042$). were observed after 9 months of estriol. Diminished burden of disease was appreciated in MRI brain at 12 months, no significant changes in T1 black holes. Statistically significant improvements of MSQol-54 quality of life mental and physical were observed after 9 months of vaginal estriol.

Discussion:

Urinary tract dysfunction is seen in 80% of the MS patients. Symptoms include urinary frequency, urgency, incontinence, retention and frequent urinary tract infections. Bladder dysfunction interferes with daily activities and has a major impact in the patient's quality of life.

Oral estriol is associated with entero- hepatic recirculation which prolongs exposure due to recycling. Vaginal estrogen delivery has a regional benefit to the lower urogenital tract. This study showed a statistically significant benefit in urogenital symptoms and quality of life of MS patients treated with vaginal estriol. In our study adjunctive vaginal estriol (1mg) significantly improved bladder disfunction symptoms and quality of life in RRMS patients.

In regards to remyelination, there is scientific evidence that remyelination in MS is incomplete and inadequate, understanding the mechanism of regeneration failure are one of the main focus in MS therapies. Estriol has anti-inflammatory properties, facilitates remyelinating process through enhancing oligodendrocyte precursor cell regeneration.

Prolongation of the P100 latency of the visual evoked potential (VEP) has long been used to detect subclinical demyelinating lesions in MS. Optical coherence tomography (OCT) offers a non-invasive measurement if the retinal nerve fiber layer thickness, both have been used in previous studies to evaluate remyelination outcomes.

In our study adjunctive treatment of vaginal estriol showed beneficial effects in remyelination and improved functional outcome in relapsing remitting multiple sclerosis patients.

Conclusion:

Vaginal estriol as adjunctive therapy showed significant improvement in bladder disfunction as well as evidence of remyelination in patients with relapsing remitting multiple sclerosis.