The Efficacy of Ultrasound Guided Posterior Sacroiliac Ligament Corticosteroid Injection in Pregnancy-Related Pelvic Girdle Pain: A Randomized Double Blinded Controlled Trial

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1. Protocol Synopsis

1.1 Study premise and specific research question

Premise: Pelvic girdle pain (PGP) in pregnancy is common with prevalence estimates of 45%.[1] It is defined as pain experienced between the posterior iliac crest and the gluteal fold, particularly in the region of the sacroiliac joint.[2] Pain may radiate in the posterior thigh and can also occur in conjunction with/or separately in the symphysis. In PGP, the endurance capacity for standing, walking and sitting is diminished. The diagnosis of PGP can be reached after exclusion of lumbar causes and must be reproducible by specific clinical tests. While various pain mechanisms including mechanical, hormonal, inflammatory, and neural have been proposed in the development of PGP, the etiology and pathogenesis is poorly understood. It is possible that musculoskeletal changes influenced by hormonal (Relaxin) elevation in pregnancy predispose pregnant women to acute musculoskeletal injury presenting clinically as PGP. An inflammatory response in other acute musculoskeletal injuries has been well described[3] and may also occur in pregnancy related PGP particularly given the musculoskeletal vulnerability during this time. Though PGP is common in pregnancy, no study to date has investigated the efficacy of anti-inflammatory treatment in pregnancy related PGP in order to better establish the contribution of inflammation in the etiology of pregnancy related PGP.

Specific research question:

Can pregnancy related PGP be more effectively treated with the use of injectable anti-inflammatory medication plus lidocaine compared with a saline with lidocaine active comparator injection?

1.2 Specific study objectives

Primary question and response variable:

Does ultrasound guided posterior sacroiliac ligament corticosteroid injection combined with lidocaine provide superior pain relief in pregnant women with PGP in the second or third trimester compared with a saline with lidocaine active comparator injection as measured by the pain Numeric Rating Scale (NRS) (0-10)?

Primary outcome variables: Pain NRS (0-10) (anchors: 0 = none, 10 = worst imaginable)

Secondary questions and response variable:

Does posterior sacroiliac ligament corticosteroid injection combined with lidocaine in pregnant women with PGP in the second/third trimester result in less disability and improved physical examination as compared with a saline with lidocaine active comparator injection?

Secondary outcome variables: Oswestry Disability Index (ODI), Pelvic Girdle Questionnaire (PGQ) and physical examination testing including the Patrick's Faber test, the Posterior Pelvic Pain Provocation test (PPPP or P4), long dorsal ligament (LDL) palpation, pubic symphysis palpation, the modified Trendelenburg test and the Active Straight leg raise (ASLR) test.

1.3 Summary of the study design

Study design: Randomized double blinded controlled trial.

Power calculation: Sample size (total and in each treatment group): A minimum of 50 participants, 25 in each treatment group would be sufficient to detect a treatment effect of a 2 point change in NRS at the 4 and 8 week follow-up period with 80% power at a 5% significance level (two tailed). 5 patients will be added to each group to account for a 10% loss to follow-up rate.

Population: Clinic-based patients seen at the at the Loyola University Medical Center, Gottlieb Hospital Obstetrics Clinics or patients referred from Chicagoland area hospitals or physical therapy practices

Intervention Group: Ultrasound guided posterior sacroiliac ligament corticosteroid plus lidocaine injection

Control Group: A saline with lidocaine active comparator injection

Follow-up: Conducted at 7 days, 4 weeks, 8 weeks and 6 weeks postpartum after intervention

Primary Outcome measure: Pain Numeric Rating Scale (NRS) (0-10)

Secondary Outcome measures: ODI, PDQ, and physical examination testing

2. Rationale

Pelvic girdle pain (PGP) often described by patients as "sciatica" is an important problem in pregnancy that can lead to significant functional disability[4], postpartum chronic pelvic pain[5], depression[6] and adversely affect future child-bearing decision making[7]. Current treatment utilizes physical therapy (PT) with stabilizing exercises and this is supported by the literature[8,9]. Clinically, however, there is often a group of severe pain patients (often those with pelvic girdle syndrome, i.e. bilateral sacroiliac joint and pubic symphysis pain) that do not respond to physical therapy alone and have the poorest prognosis[10,11]. These are the same patients who typically go on to persistent postpartum chronic PGP. Optimal pain relieving treatment in pregnancy could possibly prevent chronic PGP postpartum and the significant long-term disability associated with it.

2.1 Research to date

Randomized clinical trials on exercise/physical therapy interventions[12,13], acupuncture[14] and an educational intervention[15,16] have been performed in the study of PGP during pregnancy. There are currently no randomized clinical trials, however, evaluating the use of pain medications or corticosteroids for PGP in pregnancy. Torstensson et al performed a randomized double blind controlled trial evaluating the use of intravaginal corticosteroid injection at the ischiadic spine in postpartum women with persistent sacral pain. Slow release triamcinolone and lidocaine provided superior pain relief compared with saline and lidocaine alone.[17] Musculoskeletal ultrasound (US) has been widely utilized in other musculoskeletal joint disorders to diagnose pathology [18] and recently to identify the posterior sacroiliac joint ligamentous structures[19]. It has also been used to evaluate the sacroiliac joint in the non-

pregnant state for the purpose of diagnostic (anesthetic) joint injection with good success [20]. US is already routinely being performed for obstetrical use during pregnancy and is considered safe in pregnancy due to its lack of radiation exposure [21].

Glucocorticoids constitute one of the most frequently prescribed medications during pregnancy, used commonly in preeclampsia and for maternal inflammatory, dermatologic, and autoimmune disorders. Antenatal glucocorticoids are used for a multitude of reasons in pregnancy. Examples of use are asthma refractory to inhalant therapy (*National Asthma Education and Prevention Program: Full Report of the Expert Panel: Managing asthma during pregnancy: Recommendations for pharmacologic treatment – 2004 update. NHLBI, NIH publication no. 005-3279l*), autoimmune disorders[22,23] and for acceleration of fetal lung maturity for women at risk of preterm birth[24].

Although fluorinated glucocorticoids are known to cross the placenta readily, the majority of prednisone and methylprednisolone (non-fluorinated glucocorticoids) are inactivated in the placenta and do not reach the fetus in significant concentrations. Both of the latter are Category C agents in that animal studies show no risk but no definitive studies in humans have been done, and may be safely used as anti-inflammatory/immunosuppressive agents if indicated in pregnancy[25].

3. Protocol (See Appendix II and III)

Patients will be approached in their second or third trimester regarding the study in the Obstetrics or Rehabilitation clinics if they have PGP. They will be given a flyer regarding the study. If interested in participating, they will either proceed to study visit 1 (baseline), if time permits, or set up a separate time for study visit 1 to take place. Patients will be consented and evaluated for eligibility at this baseline visit. Eligible patient will be randomized to either the control or intervention groups at study visit 1. They will receive the injected medication at study visit 1. This study will require study visits total, study visit 1 will be at the time of randomization,

study visit 2 will be 4 weeks after injection, study Visit 3 will be at 8 weeks after start of intervention/after injection. and study visit 4 will be 6 weeks post-delivery. There will be one follow-up phone call between visit 1 and 2 on day 7 following intervention to inquire about any medication side effects or adverse events. Study duration is 8 weeks per patient, with an expected two year total recruitment and data collection time period. At study visit 1, patients will be randomized to receive the intervention medication or active comparator and undergo a physical examination of the external musculoskeletal pelvis and will complete the NRS for 'worst pain' and 'mean pain' during the latest 48 hours, a pain diagram, a personal health information questionnaire regarding their pregnancy, past medical history, activity level and restrictions. Disability as measured by the Pelvic Girdle Questionnaire (PGQ) and Oswestry Disability Index (ODI), Health-Related Quality of Life (HRQL) measured by the Wellbeing NRS and work ability will be measured with one question from Workability Index i.e. "Current work ability compared with the lifetime best".

Those randomized to the will receive either 40mg of a non-fluorinated injectable glucocorticoid, methylprednisolone acetate (1cc) combined with 1cc of 1% Lidocaine or 1cc f1% Lidocaine plus 1cc of normal saline. The injection will be performed unilaterally if pain is single sided or bilaterally if the pain is in both sacroiliac joint regions The injection will be ultrasound guided and performed by the PI Dr. Fitzgerald who is trained in musculoskeletal ultrasound and ligamentous injections as a specialist in physical medicine and rehabilitation. Dr. Fitzgerald and the participant will both be blinded to the type of injectate used. Study visits 2 and 3 will include the same questionnaires and physical examination and will document any change in the pregnancy status. Study visit 4 will occur 6 weeks post-delivery and will include the same questionnaires and physical examination to determine if any chronic pain remains. Patients will be allowed to utilize acetaminophen as needed and the amount utilized in each intervention arm will be recorded. Total study visit time is expected to be 60 minutes for study visit 1 and 30 minutes for visits 2-4. Standard physical examination maneuvers validated for the assessment

of pregnancy related PGP will be performed by the PI Dr. Fitzgerald and include pelvic pain provocation tests and functional stability testing. It will be noted with each maneuver whether the test was positive or negative. They will include:

a. *Patrick's Faber test*: With the patient in supine, the patient's leg is flexed, abducted and externally rotated so that the heel rests on the opposite kneecap. This test is positive with production of pain in the sacroiliac joint.

b. *Posterior Pelvic Pain Provocation (P4) test:* with the patient supine, the femur is flexed to be perpendicular with the table at 90 degrees and the knee is flexed at 90 degrees. A gentle force is applied to the femur in the direction of the examination table. The test is positive when the patient experiences pain in the gluteal region of that leg.

c. *Long Dorsal Sacroiliac Ligament (LDL) palpation test*: The subject lies on her side with slight flexion in both hip and knee joints. Specifically, the LDL is palpated directly caudomedially from the posterior iliac spine to the lateral dorsal border of the sacrum if palpation causes pain that persists five seconds after removal of the examiner's hand, it is recorded as pain. If the pain disappears within five seconds, it is recorded as tenderness. When the identical pain is felt directly in the vicinity, but outside the borders of the ligament, the test is not deemed as positive.

d. *Pubic Symphysis palpation test*: Examiners will palpate the subject's pubic symphysis joint while the patient is lying supine for tenderness. If palpation causes pain that persists five seconds after removal of the examiner's hand, it is recorded as pain. If the pain disappears within five seconds, it is recorded as tenderness.

e. *Modified Trendelenburg's test*: The standing woman stands on one leg and flexes the other at 90° (hip and knee). The test is considered positive if pain is experienced in the symphysis.

f. *Active Straight Leg Raise (ASLR) test*: performed with the patient supine with straight legs extended on the table 20 cm apart. The patient raises each leg one at a time 20 cm above the table without bending the knee. A) The test is positive when the patient describes a heaviness or difficulty in performing the task. B) In the second part of the maneuver, posterior

compression is applied and the patient is then asked to actively perform a straight leg raise. If there is greater ease in lifting the leg this is considered a positive test. The patient will be asked to score impairment (scoring inadequacy to raise the legs but not pain) on a 6-point scale: not difficult at all = 0, minimally difficult = 1, somewhat difficult = 2, fairly difficult = 3, very difficult = 4, unable to do = 5, the scores of both sides will be added so that the summed score can range from 0-10. Impairment is considered severe if the summed bilateral score is at least 4.

Personal Health Information to be collected The personal health information (PHI) items that will be collected during pregnancy will include: name, phone number; date of birth; BMI; height; age; race; education level; income level; number of previous pregnancies; number of previous deliveries; types of previous deliveries, past abdominal surgeries if any, current medications; history of other pain diagnoses, history of depression; history of neurological disease; history of anxiety; history of sexual abuse; previous low back injury; previous low back or pelvic pain; history of smoking; history of infertility; history of urinary or fecal incontinence; history of interstitial cystitis; history of arthritic conditions (osteoarthritis, rheumatoid arthritis, lupus); body parts affected by arthritic conditions; diabetes (Type I, Type II, gestational); gestational week of current pregnancy; due date of current pregnancy; number of babies expected; trimester/gestational week of onset of low back and/or pelvic pain (if applicable); current pregnancy complications; occurrence of miscarriage; activity and exercise types and levels during pregnancy; activity level restrictions; and duration for any previous physical therapy; previous home exercise program; and physical therapy descriptions and reasons for initiating therapy after enrollment in the study. Social history including marital status, support at home, and type of occupation will be documented.

3.1 Eligibility criteria:

- English speaking pregnant women presenting in their second or third trimester with posterior PGP. Trimester will be determined from date of last menses or ultrasound date.

- Women who have failed physical therapy for pain management (physical therapy, chiropractic management, aquatic therapy
- Pain NRS on average of greater than or equal to 5/10 at Visit 1
- Pain must be between the upper level of the iliac crests and the gluteal folds in conjunction with or separately from pain in the pubic symphysis and influenced by position and locomotion
- 2/4 positive physical examination tests on the symptomatic side including the P4 test, the LDL test, pubic symphysis palpation and the ASLR

3.2 Exclusion criteria:

- Non-English speaking pregnant women <21 or >50 years old
- Women presenting with PGP in the first trimester (<13 weeks gestation)
- Women with pubic symphysis (anterior) pain alone
- Women who have not yet received some form of physical therapy for their pain
- Pain above the upper level of the iliac crest
- History of lumbar or pelvic fracture, neoplasm, inflammatory disease, active urogenital infection or active gastrointestinal illness, current physical therapy or other therapies for PGP, or previous surgery of the lumbar spine, pelvic girdle, hip joint or femur
- History or signs of radiculopathy or other systemic neurologic disease
- Women with diabetes or gestational diabetes

3.3 Intervention

Experimental intervention: At the posterior sacroiliac joint ligament just inferior to the posterior superior iliac spine, 40mg of methylprednisolone acetate (1cc) combined with 1cc of 1% Lidocaine will be injected using a 1.5 inch 25 gauge needle. The medication with be injected unilaterally if pain is single sided or bilaterally for a total of 4cc of medication if the pain is in both

sacroiliac joint regions. The subject will subsequently receive once weekly physical therapy for 4 weeks.

Control intervention: At the posterior sacroiliac joint ligament just inferior to the posterior superior iliac spine, 2cc of saline with 1cc of 1% Lidocaine will be injected using a 1.5 inch 25 gauge needle. The medication with be injected unilaterally if pain is single sided or bilaterally for a total of 4cc of placebo saline if the pain is in both sacroiliac joint regions.

The subject will subsequently receive once weekly physical therapy for 4 weeks

3.4 Consent process

Patients will be identified when they arrive for a scheduled MD appointment at any point during their second or third trimester. They will be given a flyer with information about the study and will be asked to participate A separate study visit 1 time will then be scheduled. At study visit 1, if the patients meet eligibility criteria, a consent form will be read to them describing the nature of the trial and potential associated risks and benefits. They will be informed that neither participation nor refusal will influence the care received at either Loyola University Medical Center or Gottlieb Hospital. They will be asked a few questions afterwards to verify comprehension and then sign the consent form documenting their agreement to participate. A copy of the consent form will be given to them. Participation is completely voluntary and they may discontinue participation in the study at any time. Patients will complete the informed consent process at study visit 1. A study coordinator (Mary Tulke) or the PI (Dr. Fitzgerald) will consent all patients. The patients who consent to participate will be given a set of questionnaires at that time and asked to complete them during study visit 1. Consenting patients will undergo systematic examination procedures. These procedures will be performed by the PI. Patients will receive parking vouchers for each study visit.

3.5 Trial design

Randomized double blinded controlled clinical trial

3.5.1 Pre-Enrollment

Eligible participants will be informed about this trial during any second or third trimester visit when they complain or present clinically with PGP in the office. Special efforts will be made to increase enrollment in certain subgroups (minorities). No other medical or other documentation will required for determining eligibility. After assuring eligibility, patients may proceed to study visit 1 where consent and randomization will take place. With prevalence rates of PGP in pregnancy at 45%, there will be ample availability of eligible participants. Sixty total participants will be enrolled.

3.5.2 Randomization

Randomization strategy will be developed in collaboration with Loyola Biostatistics Department, using blocks of 3 stratified on pain location and allocation will be a 1:1 ratio of patients in the intervention and control groups. The randomization procedure will take place at study visit 1 after informed consent is completed and eligibility status is determined. A research coordinator (Mary Tulke) blinded to the study will give precoded identical envelopes with randomization assignments to the patients at the conclusion of study visit 1. This assistant and an independent Data and Safety Monitoring Board (DSMB) will have access to the randomization code.

3.5.3 Intervention administration

The injection intervention will be administered at study visit 1 following successful recruitment and consent. Since physical therapy is considered standard of care treatment in the management of pregnancy related PGP, all participants will need to have failed PT.

3.5.4 Follow-up

Patients will be instructed to contact the study nurse coordinator blinded to the study hypotheses with any side effects: flushing, nausea, vomiting, insomnia, and/or worsening pain at any time during the first week. The study nurse coordinator will then contact each patient by phone on day 7 after the injection regarding medication tolerance. After the four weeks of physical therapy, patients will return for a repeat questionnaire administration and physical examination. Questionnaires will be performed prior to physical examination so as not to

influence pain scores. During the course of physical therapy, they will be reminded by the physical therapist to follow-up with study visit 2 and reminder letters mailed the week prior to study visit 2. Study visit 3 will be performed eight weeks post injection to determine if the intervention has a lasting effect. Study visit 4 will occur 6 weeks post-delivery and will include the same questionnaires and physical examination to determine if any chronic pain remains.

3.5.5 Adverse event reporting*

The PI or the study nurse coordinator can be reached by pager or phone and will be on call for study patients 24 hours a day. Dr. Jean Goodman, chief Loyola Maternal Fetal Medicine will also be available for patient adverse reactions. Adverse events to be recorded will include excessive bleeding, infection, significantly worse pain at the 7 day post-injection phone check, fetal distress or demise, fall post injection, and/or maternal hospital admission. If the subject has persistent post injection side effects of flushing, nausea, vomiting or insomnia, this will be reported. If any other unanticipated adverse event occurs, this will also be immediately reported to the IRB. A data safety monitoring plan is detailed below in the section titled “Safety Monitoring Plan.”

3.5.6 Confidentiality

Following HIPPA guidelines, patient identifiable data will be coded to protect each patient’s identity. The data obtained from the patients will be entered onto electronic forms and imported into the database. We are familiar with using this technology from other studies. It is efficient to complete in a clinical setting and minimizes data entry errors. The data will be presented in peer reviewed manuscripts and other public presentations at the group level only. No individual patients will be identified.

3.6 Schedule of events

(Refer to Appendix I for schedule of events, Appendix II for study timeline and to Appendix IV for study forms, attached pdfs)

3.7 Sample size (Refer to Appendix III for calculations)

Sample size calculations are based on a 2-sided type I error rate of .05 and 80 % power. An additional 10% is added to account for loss to follow-up and for premature deliveries. Non-compliance is expected to be minimal given the short duration of the study medication intervention. The variance estimates are obtained from a previously reported RCT in pregnancy related PGP by Bastiaenen[16]. Approximately 50 participants will be needed to detect 2-point NRS effect size for 25 (exp) compared to 25 (control).

3.8 Analysis

Data will be analyzed using descriptive univariate statistics with STATA 11.0. In this population, there is evidence from current literature that pain and disability may not be normally distributed. If this is the case, the primary and secondary outcomes, pain and disability respectively, will be presented as median values and interquartile ranges. Comparisons between the intervention groups at follow-up will be performed using the Mann Whitney U test and change within groups from baseline to follow-up will be examined using the Wilcoxon signed-rank test. If data are sufficiently normally distributed and differences are found, multivariate analyses will be conducted. This will determine the need to control for group differences based on location of pain, history of low back pain or pelvic girdle pain, age, educational level, parity, and time from pain onset. Additional secondary analyses will examine the impact of the treatment group assignment on physical examination tests using chi-square test of proportions.

4. Risks and Benefits

The excellent overall safety and efficacy record of injectable corticosteroids is well established[26]. A prospective evaluation of intraarticular and periarticular injections with methylpredinisolone found a very low rate of complications[27]. Systemic effects of injectable corticosteroids are influenced by the agent used, dose, frequency and number of sites injected. Osteoporosis is found only with use of systemic/oral steroids and myopathy more commonly documented with oral fluorinated steroid use has not been reported with intraarticular injections. The ability of intraarticular injections to suppress the hypothalamic pirutitarty-adrenal (HPA) axis

is well documented[28] but has not been described with extraarticular or ligamentous injections. A corticosteroid induced increase in glucose synthesis is not seen in soft-tissue injections of methylprednisolone acetate[29].

Fetal Risk and Benefit

Glucocorticoids constitute one of the most frequently prescribed medications during pregnancy, used commonly in preeclampsia and for maternal inflammatory, dermatologic, and autoimmune disorders. Antenatal glucocorticoids are used for a multitude of reasons in pregnancy. Examples of use are asthma refractory to inhalant therapy (*National Asthma Education and Prevention Program: Full Report of the Expert Panel: Managing asthma during pregnancy: Recommendations for pharmacologic treatment – 2004 update. NHLBI, NIH publication no. 005-3279l*), autoimmune disorders[22,23]and for acceleration of fetal lung maturity for women at risk of preterm birth[24].

Although fluorinated glucocorticoids are known to cross the placenta readily, the majority of prednisone and methylprednisolone (non-fluorinated glucocorticoids) are inactivated in the placenta and do not reach the fetus in significant concentrations. Both of the latter are Category B agents in that animal studies show no risk but no definitive studies in humans have been done, and may be safely used as anti-inflammatory/immunosuppressive agents if indicated in pregnancy[25].

In light of this, the investigators feel that there is minimal risk to the fetus. Fetal exposure to systemic corticosteroids in pre-term labor and been proven safe and even advantageous to fetal lung maturity. There is no benefit in this study to the fetus aside from the potential long term benefit of better maternal pain control in the postpartum period that would influence maternal-child bonding and childcare.

Maternal Risk and Benefit:

The risk to the mother is also minimal. Mothers with moderate to severe pain have significant disability that affects current and future quality of life. The potential benefit of the pain

treatment outweighs the minimal risk. Both study groups will receive standard of care physical therapy (cost covered by their insurance), a proven treatment for pregnancy related pelvic girdle pain. For the intervention group that receives methylprednisolone, expected immediate side effects might include vasovagal reaction and delayed (2 days) side effects might include injection site soreness, sweating or facial flushing[30]. Toxicity at high levels and multiple dosing effects are not expected given that this is a low dose of corticosteroid injected locally. Infection rates associated with injection are low and typically seen in intraarticular not extraarticular injections[31]. A possible rare adverse effect might include allergic reaction. If an adverse reaction or side effect occurs, the subject will be seen by Dr. Goodman (maternal fetal medicine) at Loyola. This will also be immediately reported to the IRB.

The benefits of the intervention include the possibility of superior pain relief compared with placebo. Lidocaine has been safely and successfully used in pregnant women undergoing amniocentesis.[32] Oral steroids are used for other conditions in pregnancy such as asthma, rheumatoid arthritis, and severe sinusitis. They are also utilized in the treatment of pre-term labor to assist in the development of fetal lung maturity. Methylprednisolone is a class B drug and its well-established clinical utility in other diseases lends to the safety of its potential use in this debilitating pain condition (PGP) in pregnancy and warrants further study for the treatment of musculoskeletal pain.

I. Safety Monitoring Plan

a. Definition of adverse events, serious adverse events

i. An adverse event is defined as any symptom or medical problem experienced by the participant following consent to participate. All adverse events must be reported to the study physician and regulatory coordinator within three working days of discovery. All adverse events that occur during the trial will be recorded on the adverse event log. The investigator study physician will ask patients at each visit “Have you experienced any

symptoms or medical problems since your last visit?" and will subsequently record all events using the adverse event log.

ii. Serious adverse events must be reported to the University's IRB, Principal Investigator, Study Physician, and Regulatory Coordinator within 24 hours of discovery using the Serious Adverse Event Case Record Form. An SAE is defined as <u>any adverse drug experience</u> that results in:

1. Death

2. A life-threatening adverse experience

3. An important medical event

4. Inpatient Hospitalization (or prolonged hospitalization)

5. Persistent or significant disability/incapacity

6. A congenital anomaly or birth defect

iii. Finally, the principal investigator or her designee will record on the adverse event log: (1) A description of the event, (2) the start date of the event, (3) the stop date of the event, (4) the expected relationship to the study drug, (5) Whether any action was taken with the study drug, and (6) the primary outcome of the event. Additionally, the principal investigator or her designee will record any change in an ongoing adverse event.

b. What procedures will be used to monitor subject safety?

i. All participants will complete a general physical examination prior to randomization. Data will be recorded using the General Physical Case Record Form.

ii. Vital signs (weight, height, temperature, seated blood pressure, and seated heart rate) will be taken at each visit. Data will be recorded using the Vitals Case Record Form.

iii. [Description of labs used to monitor mother and child health, and how often those labs will be collected and evaluated. Also describe whether the participant will receive a copy of their laboratory results, and whether such a report will be given directly to them or sent to their personal healthcare provider].

iv. Participants are encouraged to report any (1) New adverse event, (2) whether any existing adverse events have worsened or resolved, (3) whether there are any changes to their concomitant medications, and (4) whether a medication was required to treat an adverse event. Such information is recorded on the adverse event log CRF and concomitant medication log CRF as necessary.

c. Who (list names) will identify, document, and report adverse events?

i. All named research members may receive information about an adverse event and, consequently, are required to report such events as described in this protocol.

ii. The principal investigator and/or study physician will evaluate (1) The expected relationship of the event with the study drug and (2) Whether any action should be taken regarding the study drug following an adverse event.

d. What is the frequency for review of summarized safety information and who will perform the review (e.g., safety monitoring board)?

i. The Principal Investigator or her designee will alert Loyola University Chicago Health Sciences Division IRB#1 *promptly* of all serious and any unexpected adverse events associated with the project (or the study supplement). **Associated** is defined as any adverse experience that is *possibly, probably, or definitely* related to the study drug. **Unexpected** is

defined as any untoward experience following informed consent that is not listed as a risk in the informed consent document.

ii. The Principal Investigator will also *promptly* report non-compliance with the activities described in the protocol, participant complaints, and any billing errors. Additionally, the PI will *promptly* report:

1. Serious adverse events (including events that produce injury or death, an event leading to hospitalization or lead to prolongation of a current hospital stay)

2. The enrollment of a patient on a study that is no longer enrolling participants

3. Any patient reporting a billing problem as a result of project participation

4. Any participant who has voiced a complaints about some aspect of the project or the consent document

5. Any unanticipated, untoward, or unexpected adverse event not covered above including rare adverse events or adverse events that occur at an unexpected rate

6. Protocol deviations

7. Investigational drug/device brochures and revisions

e. What are the stopping rules with regard to efficacy and safety?

i. A decision to stop the study may be made when there are documented serious maternal or fetal adverse events that can be possibly, probably, or definitely attributed to study drug exposure and are deemed to exceed the potential benefits of the study drug.

ii. The principal investigator, the Institutional Review Board, or United States Government Regulatory Authorities (e.g., the Federal Drug Administration or

FDA) may stop this study at any time. If this happens, the research team will be in direct contact with the Institutional Review Board and regulatory agency regarding participants' suspension or termination of study drug.

iii. The investigator may decide to stop a subject's participation in this trial at any time. This may happen, for example, if the participant fails to comply with the protocol activities or experiences an adverse event. If this happens, the research team will be in direct contact with the Institutional Review Board and will, with the participant's informed consent, continue to follow the participant off study drug for pregnancy outcome and fetal adverse events.

5. Importance of Clinical Research in Pregnant Women

In October 2010, the Office of Research on Women's Health (ORWH) convened a scientific research forum, *Issues in Clinical Research: Enrolling Pregnant Women* in partnership with several National Institutes of Health (NIH) institutes, centers, offices and the Food and Drug Administration (FDA), to address the ethical/ Institutional Review Board (IRB) and recruitment issues that investigators face in the conceptualization, initiation, and conduct of clinical research studies that enroll pregnant women. During this forum, the audience was challenged to address gaps in knowledge about medical treatment and pregnancy, to increase the evidence base on the inclusion of pregnant women in clinical research, and to conduct appropriate scientifically- and ethically-designed clinical research. Medical ethicists, clinical investigators, academic researchers, and those with an interest in and concern about clinical research in women provided information related to risk perception, risk reasoning, and the ethics of balancing risks and benefits in the clinical arena.

The NIH strategic plan for research on women's health identified six major goals for women's health research, one of which was the goal of increasing research to *"actualize personalized prevention, diagnostics and therapeutics for girls and women."* Among specific

objectives listed for the goal were two objectives that directly addressed pregnancy: 1) *"encourage research on safe and effective interventions for conditions affecting pregnant women";* and 2) *"expand research on pregnancy related conditions, such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring."*

The report from this forum (http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-EPW-Report-2010.pdf) made several poignant statements relevant to Dr. Fitzgerald's proposed project.

- "The current approach to treatment during pregnancy has resulted in significant knowledge gaps and harms. Pregnant women are left with two unacceptable options: either take a drug of unknown safety and efficacy or fail to treat a condition, with consequences. Pregnant women deserve better."
- "Only 12 drugs are explicitly approved by the FDA for use in pregnancy. These drugs are approved either to prevent premature labor or to ameliorate labor pain. All medicines used for non-obstetrical treatments with pregnant women are off-label. Pregnancy is the ultimate off-label condition. This lack of knowledge has led to a profound reticence to treat pregnant women when they do fall seriously ill, and it ends up harming the women and the babies."
- "What is needed in the case of pregnancy research is the development of a thoughtful, careful framework to address a scientifically and ethically challenging situation."

The PI (Dr. Fitzgerald) and co-investigators of this proposed project (Drs. Goodman, Loyola chief of maternal fetal medicine) and Dr. Stuge (scientific collaborator and international expert in pregnancy related PGP RCTs) feel strongly that the proposed study addresses a significant issue in pregnancy: disabling pelvic girdle pain that can lead to deleterious maternal consequences if left untreated. We feel the injectate proposed is safe and with ultrasound guidance will pose minimal risk to the mother and fetus. The potential significant maternal

benefit outweighs this minimal risk. The proposed study also is in response to the NIH call to action for clinical research in pregnancy. The study has already been peer reviewed by the American Academy of Physical Medicine and Rehabilitation Foundation and, given its potential significant scientific contribution, has already been funded with recruitment to start in 2014.

Appendix I: Schedule of procedures/ Study Schedule

Visit Number	1 (baseline) Day 0	2 Day 7	3 4 weeks	4 8 weeks	5 6 weeks postpartum
Consent	X				
Randomization	X				
Intervention	X	X			
Physical Exam	X		X	X	X
Questionnaires	X		X	X	X
Phone f/u		X			

Participation: 8 weeks per patient, anticipate one year of recruitment

Appendix II: Sample Size Calculations

Sample size was determined under the assumption that a difference of 2 on NRS would have clinical relevance. This was based on the previous work of Elden[14] in an RCT for acupuncture compared with sham for PGP in pregnancy. The 2 point difference on the NRS has also been used in other gynecologic RCTs in the measurement of pain.[33] The standard deviation of 25 mm was derived from the prior work of Bastiaenen[16] in an RCT comparing a specific educational physical therapy program to usual care in postpartum PGP. No standard deviations were available in the Elden paper or in any other literature on this topic. For the primary outcome of patient pain ratings (0-10 NRS) after 4 weeks of physical therapy with or without methylprednisolone, a sample size of 50 (25 in each group) will give the study 80% power to identify a 2 point difference on the NRS (with [alpha] of .05). The 4 week follow-up time period is used because the clinical effect of the study medication is expected within the 4 weeks. An additional 5 participants in each group is added to account for a loss to follow-up of 10% which calculates to then 30per treatment group. Power analyses were performed by using STATA

11.0. The basic formula for calculation is $\Delta/\sigma = 3.96/\sqrt{n}$, with Δ = effect size, σ = the standard deviation and n = number of patients needed.

Sensitivity analysis

Expected change in NRS (Effect size)	**N if Power 80%**	**N if Power 90%**
1	198 (99 per group)	264 (132 per group)
1.5	88 (44 per group)	118 (59 per group)
2	**50 (25 per group)**	66 (33 per group)
3	22 (11 per group)	30 (15 per group)

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