INPLASY PROTOCOL

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Conflicts of interest:
None declared.

A systematic review and meta-analysis on GnRH antagonists with add-back therapy in management of heavy uterine bleeding secondary to uterine leiomyoma in premenopausal women

Ooi, SJ[1]; Binti Raja Kamarul Zaman, RNS[2]; Binti Zainal Abidin, N[3]; Chai, SW[4]; Sathiyaseelar A/P, S; Akl Hussein, H[5]; Teng, CL[6].

Review question / Objective: **The aim of this systematic review is to compare GnRH antagonists with add-back therapy and placebo in terms of efficacy and acceptability in the heavy uterine bleeding secondary to uterine leiomyomas in premenopausal women to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to reduce heavy uterine bleeding in premenopausal women with uterine leiomyomas, GnRH antagonists with add-back therapy or placebo?**
Condition being studied: **Uterine leiomyomas are benign tumors that are very commonly seen in women within the reproductive age group. They originate from the myometrium or uterine smooth muscle cells which are dependent on the levels of serum estrogen and progesterone for its growth. The common symptoms for uterine leiomyomas are heavy menstrual bleeding, characterized as more than 80ml blood loss, and painful menstruation. Less common symptoms such as chronic pelvic pain, dyspareunia, changes in bowel habits, including urinary symptoms, are considered as compressive symptoms of uterine leiomyomas. The gold standard in diagnosing uterine leiomyomas is through pelvic ultrasound, either transabdominal or transvaginal ultrasound to check for the pelvic organs, which is found to have high sensitivity of 92.1% and specificity of 91.7%.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 December 2021 and was last updated on 08 December 2021 (registration number INPLASY2021120047).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to compare GnRH antagonists with add-back therapy and placebo in terms of efficacy and acceptability in the heavy uterine bleeding secondary to uterine leiomyomas in**

premenopausal women to better inform clinical practice. To this end, the proposed systematic review will address the following question: Which is the best choice to reduce heavy uterine bleeding in premenopausal women with uterine leiomyomas, GnRH antagonists with add-back therapy or placebo?

Rationale: Uterine leiomyomas are benign tumors that are very commonly seen in women within the reproductive age group. The common symptoms for uterine leiomyomas are heavy menstrual bleeding, characterized as more than 80ml blood loss, and painful menstruation. Less common symptoms such as chronic pelvic pain, dyspareunia, changes in bowel habits, including urinary symptoms, are considered as compressive symptoms of uterine leiomyomas. It is important for women presenting with heavy uterine bleeding secondary to uterine leiomyomas to be treated immediately in order to prevent any acute complications like hypovolemic shock and anaemic symptoms secondary to heavy uterine bleeding, uterine torsion, venous thromboembolism and necrosis. The treatment options for uterine leiomyomas vary, and their main aim is to relieve the symptoms of the uterine leiomyomas and to prevent complications. One of the hormonal medical treatments, the Gonadotropin-releasing hormone (GnRH) antagonists has recently been found to be one of the most effective treatments in management of heavy uterine bleeding as it shrinks the uterine leiomyomas up to 50%. GnRH antagonists act by directly inhibiting the secretion of Luteinizing Hormone (LH) and Follicular Stimulating Hormones (FSH) which are secreted by anterior pituitary. This eventually reduces the blood concentrations of Oestradiol (E2) and Progesterone level within days and induces amenorrhea, controls the bleeding, alleviate patients' symptoms and shrinks the uterine leiomyoma through decreasing the oestradiol & progesterone level secreted from the ovary. Add-back therapy a hormonal therapy composed of oestradiol and progesterone is added to improve the drug induced pseudo menopausal effects of GnRH antagonists especially on the bone mineral density by minimising the hypo-oestrogenic effects of GnRH antagonists and to alleviate the vasomotor symptoms like hot flushes, sweating and mode swinging. A randomized controlled trial concluded that 300mg Elagolix, a GnRH antagonist, given twice daily orally with add-back therapy, 1.0 mg oestradiol/0.5 mg norethindrone acetate significantly reduce menstrual bleeding in women with heavy menstrual bleeding associated with uterine leiomyomas.Furthermore, the nature of its rapid and short half-life, GnRH antagonists, has allowed a faster recovery of normal hormone levels and menstruation. It leads to rapid recovery of fertility potential in comparison to GnRH agonists. Medical hormonal therapy is considered a crucial treatment in relieving the patient's symptoms, particularly heavy uterine bleeding secondary to uterine leiomyomas. Besides, it is also to enhance the well-being of patients and prevent the complications of the disease. However, studies comparing effectiveness of GnRH antagonists with other treatments are lacking. Hence, this systematic review and meta-analysis should be conducted.

Condition being studied: Uterine leiomyomas are benign tumors that are very commonly seen in women within the reproductive age group. They originate from the myometrium or uterine smooth muscle cells which are dependent on the levels of serum estrogen and progesterone for its growth. The common symptoms for uterine leiomyomas are heavy menstrual bleeding, characterized as more than 80ml blood loss, and painful menstruation. Less common symptoms such as chronic pelvic pain, dyspareunia, changes in bowel habits, including urinary symptoms, are considered as compressive symptoms of uterine leiomyomas. The gold standard in diagnosing uterine leiomyomas is through pelvic ultrasound, either transabdominal or transvaginal ultrasound to check for the pelvic organs, which is found to have high sensitivity of 92.1% and specificity of 91.7%.

METHODS

Search strategy: Online searches were done using electronic databases platforms: PubMed, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and ScienceDirect. We searched for any ongoing trials using the following trial register: ClinicalTrials.gov (www.clinicaltrials.gov). MeSH terms and text words were combined using the Boolean operators 'AND' and 'OR', in liaison with the rules of the respective databases proceeded with the selection of publication characteristics which limits to Randomized Controlled Trial. The employed sets of text terms are (Gonadotropin-releasing hormone/antagonist&inhibitor OR GnRH Antagonist* OR Relugolix OR Elagolix) AND (Leiomyoma OR fibroid*).

Participant or population: Premenopausal women who had a pelvic ultrasound-confirmed diagnosis of uterine leiomyomas with symptoms and suffered from moderate to heavy uterine bleeding will be included in the study. Women who are pregnant or with other coexisting gynecological conditions will be excluded from the study.

Intervention: Treatment with Gonadotropin-releasing hormone antagonists with add-back therapy.

Comparator: Placebo.

Study designs to be included: Randomised controlled trials.

Eligibility criteria: Randomised controlled trials which compare Gonadotropin-releasing hormone antagonists with add-back therapy to placebo will be considered in this study. The study must be published in English language between 2000 to 2021. Inclusion criteria for the randomised controlled trials must be GnRH Antagonist, premenopausal women, heavy uterine bleeding, uterine leiomyomas, uterine fibroids. Exclusion criteria for the randomised controlled trials must be pregnancy women, menopause women, women with other gynaecological problems.

Information sources: All of the information sources are electronic databases platforms, which are PubMed, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and ScienceDirect.

Main outcome(s): Control of heavy uterine bleeding by measuring the menstrual blood in millilitres and Pictorial blood loss chart.

Additional outcome(s): Patients' quality of life (pain score).

Data management: From each selected article which fulfilled the eligibility criteria, data regarding methodology, trials design, treatments, baseline parameters, volume of menstrual blood loss and quality of life will be extracted. RefWorks will be used in managing the data obtained from the articles. Two reviewers will be involved in selecting studies for inclusion. In the event of disagreement, the article will be examined by a third reviewer.

Quality assessment / Risk of bias analysis: Quality of study will also be assessed by using Cochrane Collaboration's tool.

Strategy of data synthesis: From each selected article, data regarding methodology, trials design, treatments, baseline parameters, volume of menstrual blood loss and quality of life will be extracted. Mean difference will be calculated for continuous data (volume of menstrual blood loss). Although quality of life or pain score is an ordinal data, it will be treated as continuous data and standardised mean difference will be calculated. Data collected will be merged and analysed statically by using Revman.

Subgroup analysis: If the included studies have significant heterogeneity, subgroup analysis will be performed based on different control groups.

Sensitivity analysis: To identify the robustness of the results, sensitivity analysis will be conducted according to the

following criteria: the quality of studies, sample size, and missing data. The meta-analysis will be repeated, and lower quality studies will be excluded.

Language: Only randomized clinical trials published in English will be considered for inclusion.

Country(ies) involved: Malaysia.

Keywords: GnRH antagonists; Heavy uterine bleeding; Uterine leiomyoma; Management; Add-back therapy.

Dissemination plans: Report will be completed and submitted in March 2022 and submitted for journal publication.

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