Effect of goserelin on the quality of life of women with benign gynecological disorders: a systematic review

Efeito da goserelina na qualidade de vida de mulheres com transtornos ginecológicos benignos: uma revisão sistemática

Efecto de la goserelina en la calidad de vida de mujeres con trastornos ginecológicos benignos: una revisión sistemática

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ABSTRACT

Objective: Goserelin reduces the estrogen levels and is approved for several hormonally sensitive benign disorders. There are few data about the quality of life of women using goserelin for benign disorders. The purpose of this article is to objectively assess the quality of life of these women. **Methods:** We searched from electronic databases as PubMed, Scielo, LILACS, among others. The inclusion criteria were RCTs which evaluated using validated questionnaires the quality of life of women with benign gynecological disorders treated with goserelin. **Results:** The five RCTs demonstrated improvement in quality of life after goserelin compared to the baseline. It was evidenced a temporary effect of the goserelin. Goserelin by itself or associated with another therapy improves the quality of life when compared to the baseline. Hot flushes are not an expressive cause of patient noncompliance. The temporary effect of goserelin is in accordance with literature. **Final considerations:** This systematic review suggests that goserelin is an effective treatment for benign gynecological disorders, but more studies are necessary to embark therapy choice.

Keywords: Chronic pelvic pain, Endometriosis, Goserelin, Menorrhagia, Quality of life.

RESUMO

Objetivo: A Goserelina reduz os níveis de estrogênio e é aprovado para vários distúrbios benignos hormonalmente sensíveis. Existem poucos dados sobre a qualidade de vida de mulheres em uso de goserelina para doenças benignas. O objetivo deste artigo é avaliar objetivamente a qualidade de vida dessas mulheres. **Métodos**: Foi pesquisado ECRs de bancos de dados eletrônicos como Pubmed, Scielo, LILACS, entre outros. Os critérios de inclusão foram ECRs que avaliaram por meio de questionários validados a qualidade de vida de mulheres com distúrbios ginecológicos benignos tratadas com goserelina. **Resultados**:

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Os cinco ECRs demonstraram melhora na qualidade de vida após goserelina em comparação com a linha de base. Foi evidenciado um efeito temporário da goserelina. A goserelina isolada ou associada a outra terapia melhora a qualidade de vida quando comparada à linha de base. Os fogachos não são uma causa expressiva de descumprimento do paciente. O efeito temporário da goserelina está de acordo com a literatura. **Considerações finais**: Esta revisão sistemática sugere que a goserelina é um tratamento eficaz para distúrbios ginecológicos benignos, mas são necessários mais estudos para embarcar na escolha da terapia.

Palavras-chave: Dor pélvica crônica, Endometriose, Goserelina, Menorragia, Qualidade de vida.

RESUMEN

Objetivo: La goserelina reduce los niveles de estrógeno y está aprobada para varios trastornos hormonales sensibles benignos. Hay pocos datos sobre la calidad de vida de las mujeres que usan goserelina para enfermedades benignas. El objetivo de este artículo es evaluar objetivamente la calidad de vida de estas mujeres. **Métodos:** Se realizaron búsquedas en ECA de bases de datos electrónicas como Pubmed, Scielo, LILACS, entre otros. Los criterios de inclusión fueron ECA que evaluaran, a través de cuestionarios validados, la calidad de vida de mujeres con trastornos ginecológicos benignos tratadas con goserelina. **Resultados:** Los cinco ECA demostraron una mejor calidad de vida después de la goserelina en comparación con el valor inicial. Se evidenció un efecto temporal de la goserelina.La goserelina sola o asociada a otra terapia mejora la calidad de vida en comparación con la línea de base. Los sofocos no son una causa importante de incumplimiento por parte del paciente. El efecto temporal de la goserelina está de acuerdo con la literatura. **Consideraciones finales:** Esta revisión sistemática sugiere que la goserelina es un tratamiento eficaz para los trastornos ginecológicos benignos, pero se necesitan más estudios para emprender la elección del tratamiento.

Palabras clave: Dolor pélvico crónico, Endometriosis, Goserelina, Menorragia, Calidad de vida.

INTRODUCTION

Menorrhagia, endometriosis, and chronic pelvic pain are major sources of psychologic morbidity and decreased quality of life. For example, women with endometriosis may experience psycho-social and sexual problems so menorrhagia may impact physical health, work health, psychologic health, family and social life (JONES GL, et al., 2002).

Therefore, it is particularly relevant that studies concerning these conditions evaluate not only uterine size or hemoglobin, for example, but also the quality of life with validated questionnaires. When choosing a treatment, it is important to considerate its capability to improve the patient's quality of life. Clinical trials evaluating the quality of life of women with benign gynecological disorders using goserelin are scanty (JONES GL, et al., 2002).

Goserelin is an analog of gonadotropin releasing hormone (GnRHa) that acts as a partial agonist of the gonadotropin receptors in hypophysis and leads to a down-regulation of the production of luteinizing hormone (LH), Follicle-stimulating hormone (FSH) and a resultant decrease in the estrogen levels (National Institute of Diabetes and Digestive and Kidney Diseases,2012). Hypoestrogenism may occasion adverse effects such as hot flushes, loss of libido and loss of bone mineral density (PERRY CM and BROGDEN RN, 1996). Goserelin is approved for use in advanced breast and prostate cancer and for several hormonally sensitive benign disorders, such as endometriosis and uterine fibroids (NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES, 2012). The therapeutic efficacy of goserelin has been documented in numerous clinical studies conducted since the late 1980s (PERRY CM and BROGDEN RN, 1996).

Uterine fibroids are benign estrogen-dependent tumors constituted of smooth muscle and connective tissue. Symptomatic women may present enlarged uterus and menorrhagia. As pretreatment of patients requiring surgery, goserelin leads to a decrease in fibroids and uterine volume. GnRHa are also used as an effective temporary alternative to surgery in the teatment of fibroids. It is particularly useful for women

approaching menopause in whom fibroids natural degeneration is imminent. Fibroid regrowth occurs 3 to 4 months after treatment discontinuation so it may not be helpful as monotherapy in younger women. Endometriosis is another estrogen-dependent gynecological disorder. It is caused by the presence of functioning endometrial tissue outside the uterus. Goserelin suppresses topic and ectopic endometrium and establishments amenorrhea. Dysfunctional uterine bleeding may also be treated with goserelin. The management of dysfunctional uterine bleeding often involves hysterectomy or surgical ablation and goserelin is an effective adjunctive surgical pretreatment because the drug decreases uterine volume and endometrium thickness (BROWN J and FARQUHAR C, 2014).

The hypoestrogenism may occasion adverse effects such as hot flushes, loss of libido and loss of bone mineral density (PERRY CM and BROGDEN RN, 1996). A Cochrane Review found an incidence of 55% of vasomotor symptoms for women with fibroids using goserelin (SANGKOMKAMHANG US, et al., 2020). In the short term, women usually experience significant vasomotor symptoms that may result in discontinuation of therapy (SOYSAL S, et al., 2004). Although the high incidence of hot flashes, a study that included 866 patients with benign gynecological disorders treated with goserelin had only 4% withdrew due to adverse effects during therapy and a further 4% after cessation of treatment (MILLER RM, et al., 1992).

There are extremely few data about the quality of life of women who uses goserelin for treatment of benign gynecological disorders. Although there are a great number of clinical trials using validated quality of life questionnaires to evaluate how people with breast and prostate cancer treated with goserelin lives, there are only five evaluating the quality of life of patients with benign conditions treated with goserelin. The concerns about tolerability and adverse effects of goserelin may limit its use by some physicians. The purpose of this article is to objectively assess the quality of life of women with benign gynecological conditions treated with goserelin. We aim to evaluate the real impact of its adverse effects on welfare and whether it expressively compromises patient compliance.

METHODS

This systematic review was registered a priori in the PROSPERO database (registration nº. CRD42022356750) and used the Cochrane Reviews of Interventions manual as a reference for its preparation. Unlike primary researchers, we did not collect personal, sensitive or confidential information from participants in our systematic review. We used only publicly accessible documents as evidence.

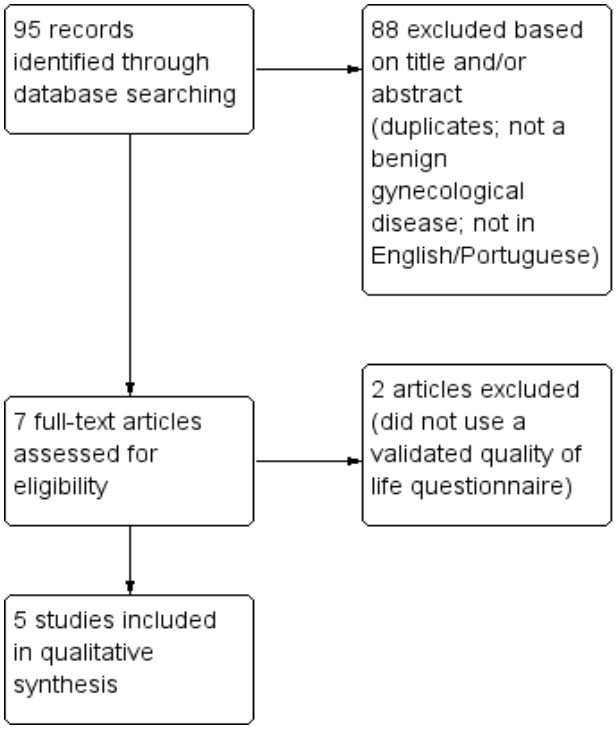
The protocol was determined by the authors before the review started. The authors searched trials independently and used only published literature. The following databases were searched for identification of studies: PubMed, Scielo, LILACS, EMBASE and the PROSPERO International Prospective Register of Systematic Reviews. The following Medical Subject headings (MeSH) terms were used: ‘goserelin’ and ‘quality of life’ or ‘goserelin’ and ‘physiological sexual disfunction.

The inclusion criteria were controlled trials which evaluated with validated questionnaires the quality of life of women with benign gynecological disorders treated with goserelin. It was chosen not to include trials with cancer patients to minimize potential confounding factors – adverse effects of chemotherapy, oophorectomy and psychological impact of a malignant disease diagnosis on the quality of life. The exclusion criteria were reviews, retrospective and observational studies, articles published after March 2021 and not written in English or Portuguese.

The titles and abstracts were screened by the authors, who discarded clearly ineligible studies but were overly inclusive to avoid losing possibly relevant studies. The copies of the seven full articles were assessed independently by each author to determine whether the studies met the inclusion criteria. The data of each eligible study was extracted and the results of trial selection were reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 1**).

It was performed an assessment of the included RCTs using the Cochrane ’risk of bias’ tool in accordance with the Cochrane Handbook for Systematic Reviews of Interventions criteria. The authors evaluated independently each element of potential bias of Cochrane tool for assessing risk as low, high or unclear risk of bias.

Figure 1 - Flow diagram of identified studies.



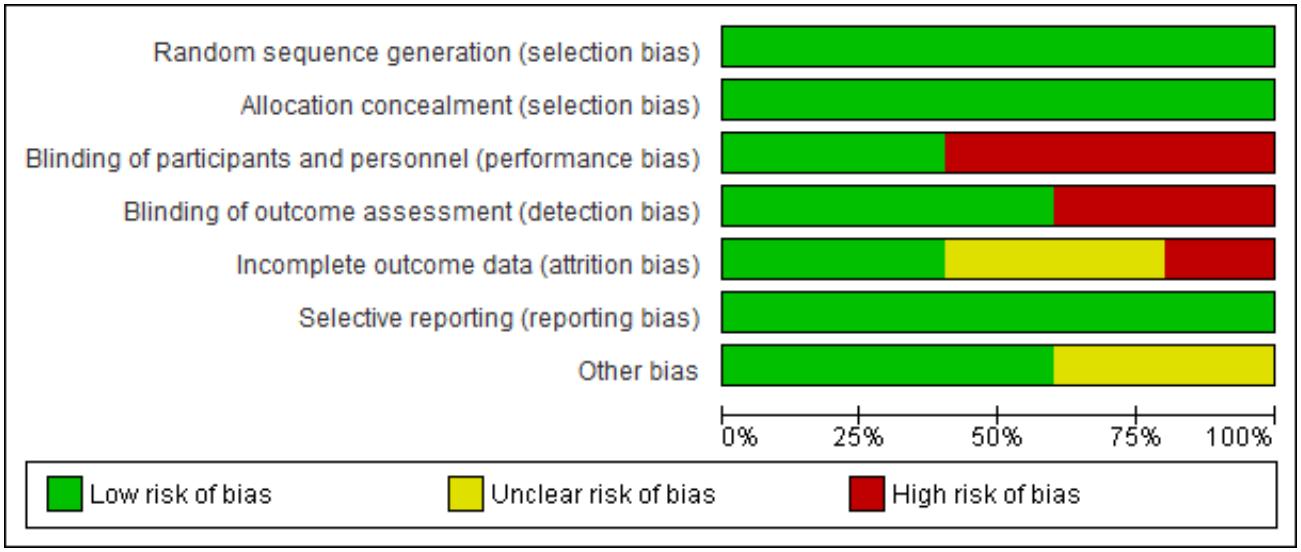
Source: Caetano IM, et al., 2023.

RESULTS

Study characteristics

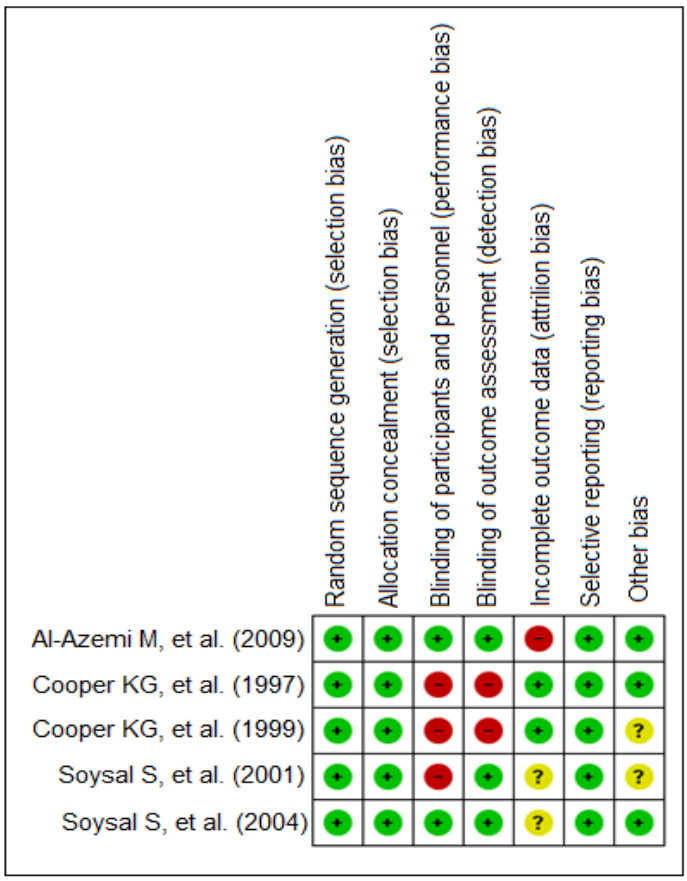
Figure 1 shows the flow diagram (PRISMA template) of the studies through the phases of the review. A total of 95 articles were identified through database searching and the ones which did not meet the criteria based on title and/or abstract were excluded. A total of 7 full-text studies were screened; two did not use validated quality of life questionnaires. The overall risk of bias is shown in **Figures 2 and 3**. **Table 1** shows the characteristics of the studies.

Figure 2 - Risk of bias graph: authors' judgements about each risk of bias item presented as percentages across all included studies. Low risk, unclear risk and high risk of bias, respectively.



Source: Caetano IM, et al., 2023.

Figure 3 - Risk of bias summary: authors' judgements about each risk of bias item for each included study. Minus sign: high risk of bias; plus sign: low risk of bias; question mark: unclear risk of bias.



Source: Caetano IM, et al., 2023.

Al-azemi M, et al. (2009) evaluated 38 premenopausal women with chronic cyclical pelvic pain by utilizing the Endometriosis Health Profile *Questionnaire* (EHP-30), Chronic Pain Grade Questionnaire (CPG) and Short-form McGill Pain Questionnaire (SF-MPG).

The participants were divided into two groups: the placebo group used goserelin and placebo over 6 months followed by goserelin and tibolone over 12 months; the hormone replacement therapy (HRT) group used goserelin and tibolone concurrently over 18 months. For the EHP-30, the HRT group showed a significant improvement in all domain scores (except for the emotions domain) from baseline to 6 months and this persisted until 18 months.

The placebo group also showed significant improvement in all domain scores from baseline to 6 and 18 months. A similar trend was observed for the SF-MPG and CPG questionnaires. There were significant differences between the two groups only on the EHP questionnaire. This was for the self-image domain and emotions domain between the baseline and 30 months: the HRT group did slightly better. But at 30 months, all scores were returning to the baseline levels (AL-AZEMI M, et al., 2009).

Souysal S, et al. (2004) divided 80 women with severe endometriosis into two groups. Group 1 used anastrozole and goserelin for six months after conservative surgery for endometriosis and group 2 used goserelin alone for six months after conservative surgery for endometriosis), using the Total Pelvic Symptom Score (TPSS).

The mean differences between the 6, 12, 18 and 24 months treatment regimens were shown to be significantly in favor of goserelin and anastrozole. Protocols that are effective in both TPSS compliance are confirmed (SOYSAL S, et al., 2004).

Soysal ME, et al. (2001) performed a clinical trial with 47 women with pelvic congestion syndrome. Some were treated with goserelin for 6 months and the others were treated with medroxyprogesterone acetate for 6 months.

The quality of life was accessed through Hospital Anxiety and Depression Scale (HADS) and Revised Stabbatsberg Sexual Rating Sacale (rSSRS). Although both agents were effective and induced HADS score reduction and rSSRS score improvement 12 months after the end of the treatment, goserelin was more effective than medroxyprogesterone acetate (MPA) in both scores (SOYSAL ME, et al., 2001).

Kevin GC, et al. (1999) evaluated 263 women with heavy menstrual loss through the Short Form 36 Health Survey Questionnaire (SF-36). Group 1 used microwave *endometrial ablation* (MEA) 5 weeks after goserelin and Group 2 was submitted to transcervical resection of the endometrium (TCRE) 5 weeks after goserelin.

The baseline SF-36 scores of both groups were lower than normative values in women of equivalent age in the United Kingdom. The follow-up was 12 months after treatment. Changes in score showed significant improvements for 6 out of 8 health scores after MEA. Seven items showed significant improvements after TCRE (COOPER KG, et al., 1999).

This same group did a clinical trial in 1997 with 197 women with heavy menstrual loss. The women were divided in two groups. The first one received medical treatment (progestogens, combined oral *contraceptive* [COCs], tranexamic acid, danazol or HRT) for a minimum of three cycles and the second one endometrial ablation five weeks after goserelin preparation.

The questionnaire was answered at the baseline and after a 4-month-follow-up. After medical treatment there were significant improvements in all parameters except for general health, but normal scores were not achieved in any of the eight parameters. In contrast, scores equal or better than normal for all eight Short Form 36 scales were observed after transcervical resection (COOPER KG, et al., 1997).

Table 1 - Descriptive data of included trials.

Study	Sample	Lost to follow-up	Scale	Intervention
Al-Azemi M, et al. (2009)	38 premenopausal women with chronic cyclical pelvic pain.	13 (group not specified. Three before and 10 after intervention)	EHP-30 CPG SF-MPQ	**Group 1:** goserelin and placebo over 6 months followed by goserelin and tibolone over 12 months. **Group 2:** goserelin and tibolone concurrently over 18 months
Soysal S, et al. (2004)	80 women with severe baseline Endometriosis.	Not specified	TPSS	**Group 1:** anastrozole and goserelin for 6 months after conservative surgery for endometriosis. **Group 2:** goserelin alone for 6 months after conservative surgery for endometriosis
Soysal S, et al. (2001)	47 women with pelvic congestion syndrome.	0	HADS rSSRS	**Group 1:** goserelin for 6 months. **Group 2:** MPA for 6 months.
Cooper KG, et al. (1999)	263 women with heavy menstrual loss.	13 from group 1 10 from group 2	SF-36	**Group 1:** MEA 5 weeks after goserelin. **Group 2:** TCRE 5 weeks after goserelin.
Cooper KG, et al. (1997)	197 women with heavy menstrual loss.	1 from group 1 0 from group 2	SF-36	**Group 1:** medical treatment (progestogens, COCs, tranexamic acid, danazol or HRT) for a minimum of 3 cycles. **Group 2:** endometrial ablation 5 weeks after goserelin.

Source: Caetano IM, et al., 2023.

Questionnaires

The main component of the Short-form McGill Pain Questionnaire (SF-MPQ) consists of 15 pain descriptors (11 sensory and 4 affective), rated from none to severe. It also includes a visual analogue scale (VAS) (MELZACK R, 1987).

The Endometriosis Health Profile *Questionnaire* (EHP-30) is the only questionnaire created and validated specifically for evaluation of patients with endometriosis. It is divided in five main areas: pain, control and impotence, emotional well-being, social support and self-image. The EHP-30 scores range from 0 to 100 and the lower the score, the better the health status (JONES GL, et al., 2001).

The Chronic Pain Grade Questionnaire (CGP) is simple and self-administered. It evaluates pain intensity and pain-related disability with numerical scales from 0 to 10 and the lower the absolute value, the lower the level of pain. According to the score, pain is classified into 5 levels, from pain free to highly limiting (VON KM, et al., 1992).

The Total Pelvic Symptom Score (TPSS) is obtained with the patient's subjective evaluation of dysmenorrhea, dyspareunia and pelvic pain associated with physical examination of pelvic in order to identify sensitivity to touch and presence of induration. Each of these items can be graded from 0 to 3 (zero means absence of pain and 3 means severe pain) (BIBEROGLU KO and BEHRMAN SJ, 1981).

The Hospital Anxiety and Depression Scale (HADS) is a screening test for psychiatric disorder and consists of 16 items: eight for assessing anxiety and eight for depression. They are graded from 0 to 4 on a severity scale (ZIGMOND AS and SNAITH RP, 1983).

The Revised Stabbatsberg Sexual Rating Sacale (rSSRS) is a self-administered questionnaire to assess sexual function with 16 questions, obtaining a score from 0 to 100. The lowest values represent less interest and/or less sexual satisfaction (GARRATT AM, et al., 1995).

The Short Form 36 Health Survey Questionnaire (SF-36) contains 36 items and evaluates health on eight multi-item dimensions: well-being, functional status and overall evaluation of health. It detects positive as well as negative states of well-being. In six dimensions patients rate their responses on three- or six-point scale rather than simply responding yes or no. For each dimension, item scores are summed and transformed in a scale from 0 (worst health) to 100 (best health) (BRAZIER JE, et al.,1992).

Synthesis of results

The included studies used different interventions and different questionnaires. Therefore, they cannot be compared through meta-analyses.

Al-azemi M, et al. (2009), Soysal S, et al. (2004) and Cooper KG, et al. (1999) used goserelin in both groups so we could not access the impact on the quality of life compared to other treatments. Both groups of each of these three studies had better welfare questionnaire performance than the baseline, demonstrating that treatment with goserelin improved quality of life of women with chronic pelvic pain, endometriosis and heavy menstrual loss, respectively.

Soysal S, et al. (2004) did not specify the number of dropouts and Cooper KG, et al. (1999) had only 8% over one year of follow-up. On the other hand, Al-azemi M, et al. (2009) had a significant number of dropouts - 34.2%. It may be partially explained by the length of the study, which lasted 30 months. The reasons of the dropouts reported by the participants were peripheral neuralgia, pruritis, chest pain, migraine, weight gain, calf cramps, joint pain and seeking pregnancy. It was observed that the most common adverse effects of goserelin (i.e., hot flushes, libido loss, hyperhidrosis and injection site reactions) apparently did not cause any withdrawal. Among the reported reasons of dropouts, only headache and weight gain are described in Zoladex label (Zoladex Label).

Soysal ME, et al. (2001). found that, although medroxyprogesterone acetate and goserelin are effective to improve quality of life of women with pelvic congestion syndrome, goserelin is more effective than medroxyprogesterone acetate. They had no dropouts.

Cooper KG, et al. (1997). demonstrated that medical treatment and endometrial ablation five weeks after goserelin preparation improved quality of life, but the improvement was more significative in the goserelin followed by endometrial ablation group. There was only one dropout, and it was in the group that did not use goserelin. The reason of the dropout was not described.

DISCUSSION

The systematic review found only five RCTs that evaluated using validated questionnaires the quality of life of women with gynecological benign disorders treated with goserelin. Altogether, the 5 RCTs had 621 participants and evaluated goserelin by itself and associated with other clinical and surgical therapies (e.g., tibolone, anastrozole, MEA and TCRE) (SOYSAL S, et al., 2004; SOYSAL ME, et al., 2001; KEVIN G, et al., 1997).

It is well established in the literature that goserelin is an effective treatment option for some benign gynecological conditions. As far as quality of life is concerned, this systematic review corroborates the literature. Aspects other than quality of life were not evaluated.

The benign gynecological conditions included were chronic cyclical pelvic pain, severe baseline endometriosis, pelvic congestion syndrome and heavy menstrual loss. It was observed an improvement in quality of life of women that used goserelin in all five RTCs when compared to the baseline. It was not possible to compare the different treatment options involving goserelin with each other to evaluate the most effective one (SOYSAL S, et al., 2004; SOYSAL ME, et al., 2001; KEVIN G, et al., 1997).

The longer RCT follow-up was Al-azemi M, et al. (2009), which lasted 30 months. A strong effect of time on all questionnaire domains was evidenced in this RTC. They found a trend of return to the baseline levels following the cessation of treatment. This finding is consistent with the temporary effect of goserelin reported in literature.

Hot flushes are one of the most common adverse effects of goserelin. None of the RCTs reported any dropout due to this symptom. Although sleep disturbance is specifically addressed in the questionnaires, it was not mentioned in the RCTs. These two symptoms are possible adverse effects of goserelin. Therefore, it would have been interesting to explicitly approach them in the RCTs (SOYSAL S, et al., 2004; SOYSAL ME, et al., 2001; KEVIN G, et al., 1997).

There are no new RCT about quality of life of women with benign gynecological disorders treated with goserelin since 2009. Considering that such RCTs were already scarce before 2009, it reinforces the need for new RTCs concerning this theme.

One of the strengths of this systematic review is that it followed the Cochrane Handbook of Systematic Review for Intervention closely. Our systematic review included all studies published to date on the topic and included 621 women.

It was neither possible to make a meta-analysis of a specific gynecological benign condition regarding quality of life questionnaires nor a specific treatment regimen including goserelin because none of the studies used the same intervention. Publication bias could not be assessed given the small number of studies included. Other limitations of our study are intrinsic to the limitations of the included RCTs.

FINAL CONSIDERATIONS

This systematic review suggests that goserelin is an effective treatment for chronic cyclical pelvic pain, severe baseline endometriosis, pelvic congestion syndrome and heavy menstrual loss regarding quality of life improvement. It also suggests that hot flushes, although quite common, are not a significative reason of therapy discontinuation. It was evidenced the temporary effect of goserelin, as reported in literature. There are extremely few studies concerning the quality of life aspect of benign gynecological disorders treatment and more studies are necessary to embark therapy choice.

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