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REVIEW

Roles of Goserelin in Gynecological Disorders

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Abstract: Goserelin is a gonadotropin-releasing hormone (GnRH) agonist with a long history of clinical application and well-established efficacy and safety profile. Its mechanism of action centers on sustained GnRH receptor desensitization, leading to pituitary downregulation, ovarian suppression, and reduction of estradiol and progesterone to postmenopausal levels; this forms the basis for its efficacy in hormone-dependent gynecological conditions. Over the past three decades, the use of goserelin has been expanded to an increasing number of indications and clinical scenarios. Approved gynecological indications of goserelin include endometriosis, uterine fibroids, usage as an agent for endometrial thinning, and usage as an agent for ovarian downregulation prior to assisted reproduction. More recent research continues to explore the use of goserelin in gynecological diseases such as adenomyosis and different types of female cancers. Goserelin may also be a useful tool in clinical scenarios where gynecologic management is required as part of multi-disciplinary therapy. This review consolidates the established and emerging roles of goserelin across the broad spectrum of benign and malignant gynecological conditions, underscoring its remarkable clinical versatility and the breadth of evidence that support its continued expansion of utility in contemporary practice.

Keywords: goserelin, gonadotropin-releasing hormone agonist, benign gynecological disorders, female cancers

Introduction

Goserelin is a gonadotropin-releasing hormone (GnRH) agonist with a long history and a wide geographic span of clinical application, whereby its efficacy and safety have been well proven. Goserelin is on the Essential Medicines List published by the World Health Organization.[1] Administered subcutaneously in the form of a biodegradable lactide-glycolide co-polymer rod, goserelin depot is available in two dosages, namely 3.6 mg once a month and 10.8 mg once every 3 months.[2]

The past three decades have seen the use of goserelin in an increasing number of indications. Although first approved and still an important treatment for prostate cancer, goserelin has found wider applications as an important therapy in breast cancer and gynecology.[2] Approved gynecological indications of goserelin include endometriosis, uterine fibroids, usage as an agent for endometrial thinning, and usage as an agent for ovarian downregulation prior to assisted reproduction. More recent research continues to explore the use of goserelin in expanded gynecological diseases, such as adenomyosis and female cancers. Over the course of long clinical application, new experience has been gained about the optimal use of goserelin. For example, alternative administration schedules different from the conventional timing of days 1–5 of the menstrual cycle have been explored, with the additional benefit of reduced uterine bleeding demonstrated in certain scenarios. Moreover, goserelin may be a versatile and useful tool in clinical scenarios where gynecologic management is required as part of multi-disciplinary therapy.

This article will take inventory of the use of goserelin in gynecological disorders, both in the traditional indications and in the newly established and/or emerging therapeutic areas. The subsequent discussions on goserelin refer to the 3.6 mg formulation, unless otherwise specified.

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Mechanism of Action and Pharmacological Profile of Goserelin

Mechanism of Action

The classical mechanism of pituitary-ovarian gonadal axis downregulation underlies the wide-ranging utility of goserelin in hormone-dependent conditions. Continuous administration of goserelin induces the desensitization of pituitary GnRH receptors and the downregulation of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]), which in turn leads to ovarian function suppression and reduces estrogen and progesterone to postmenopausal levels.[2]

In benign gynecological conditions, the local overexpression of inflammatory cytokines has been implicated in the pathogenic processes of cell proliferation, angiogenesis and accumulation of extracellular matrix. Goserelin can reduce the levels of pro-inflammatory cytokines and growth factors such as IL-8, PAPP-A, glycodelin-A and midkine, and effect a regression of the inflammatory microenvironment.[3] Some evidence suggests that such anti-inflammatory effect may arise from direct interactions with local GnRH receptors, over and above the effect of a hypoestrogenic state.[4] Recent molecular docking studies in endometriosis identified transcription factors and immune-related proteins as potential targets of goserelin, including the proinflammatory CXCL12, SCG2,[5] AEBP1 and HOXB6,[6] as well as the anti-inflammatory KLF2 and RORB,[6] although these remain to be validated biochemically.

Some molecular pathways have been identified for mediating direct anti-tumor effects of goserelin. In vitro and xenograft model studies showed that goserelin could promote apoptosis by upregulating the expression of FOXO1 through the PI3K/AKT pathway in epithelial ovarian cancer cells,[7] and can inhibit the growth of prostate cancer cells by attenuating EGFR signaling.[8]

Pharmacological Properties

The native GnRH is a decapeptide folded around the flexible glycine at position 6 (Gly6) when bound to the GnRH receptor.[9] Replacing Gly6 with a D-amino acid improves the conformational stability of the decapeptide, thereby enhancing its binding affinity to GnRH receptors and resistance to enzymatic degradation: this has formed the principle underlying the development of all GnRH agonists such as triptorelin, leuprorelin, buserelin, and goserelin (Figure 1).[9] In goserelin, the amino acid at position 6 is a D-Ser(tBu); additionally, the glycine at position 10 of the native GnRH is replaced by an aza-glycine (azaGly10) in goserelin. Compared to buserelin, which similarly has D-Ser(tBu)6 but with Pro9-nET instead of Pro9-azaGly10, goserelin is considered at least 5 times more potent as measured by induction of ovulation.[10]

Dose-ranging studies using goserelin depots of 0.9 mg, 1.8 mg and 3.6 mg revealed a dose-proportional serum concentration profile of goserelin.[2] The 3.6 mg depot has a release rate of 120 µg/day, which is sustained consistently over the course of 4 weeks.[2] Successive dosing of goserelin 3.6 mg depot at a 4-week interval yielded consistent serum

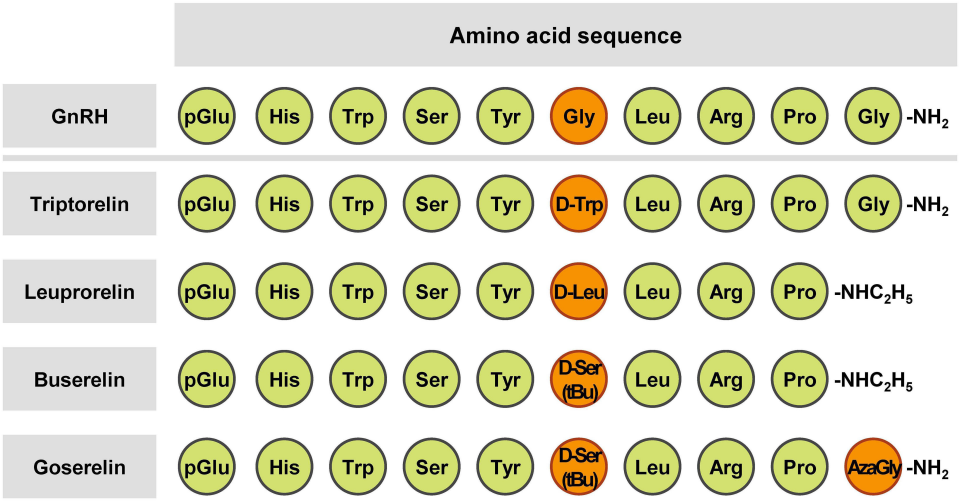

Figure 1 Amino acid sequence of GnRH and selected GnRH agonists. *GnRH* gonadotropin-releasing hormone. Adapted from Millar et al (2004),[9] copyright 2004 The Endocrine Society.

concentration profiles between doses; comparisons of the area under the concentration-time curve (AUC) values of goserelin between the aqueous and the depot formulations indicate a 100% relative bioavailability of goserelin from the 3.6 mg depot and a complete goserelin release from the depot over 4 weeks.[11]

In hepatically impaired individuals, the plasma elimination half-life and clearance of goserelin (in a research aqueous formulation), as well as the bodyweight normalized AUC, were not significantly different from those in age-matched healthy volunteers.[2] For patients with several renal impairment (investigated in prostate cancer patients), the body clearance of goserelin (in a research aqueous formulation) was reduced (1.9 L/h, vs 8 L/h with normal renal function) but still sufficient to avoid drug accumulation.[2] Thus, no dose adjustment of goserelin is required in patients with renal or hepatic dysfunction.

In females, following the injection of a goserelin 3.6 mg depot, the serum LH and FSH levels rise sharply before rapidly decreasing to below baseline level by day 3, and remain markedly suppressed from day 8 onward.[11] The levels of estradiol show a transient rise 3 days after goserelin depot administration, decrease to postmenopausal levels by week 1, and remained suppressed with successive administration of goserelin depot. Similarly, serum progesterone level peaks 2 days after administration of goserelin depot and becomes complete suppressed by day 14.[11]

Use of Goserelin in Benign Gynecological Disorders

Endometriosis

Endometriosis is an estrogen-dependent, inflammatory disease characterized by ectopic presence of functional endometrial tissue, affecting approximately 5%–10% of women of reproductive age worldwide.[12] Patients with endometriosis frequently experience the symptoms of dysmenorrhea and pelvic pain, and often face the problem of infertility. By suppressing estrogen synthesis, GnRH agonists can impede the growth of ectopic endometrial tissue, and pituitary downregulation by GnRH agonists may improve reproductive outcomes in patients with endometriosis. Furthermore, GnRH agonists have been investigated for facilitating and/or enhancing the outcomes of surgical treatment in endometriosis. According to guideline recommendations (Table 1), [13–19] the drug class of GnRH agonists, to which goserelin belongs, can be used for reducing

Table 1 Guideline Recommendations on the Use of GnRH Agonists in Endometriosis

Guideline	Treatment of Endometriosis-Associated Pain	Treatment for Patients Who Desires Fertility	Preoperative Use	Postoperative Use
ESHRE 2022[13]	Recommended for reducing endometriosis-associated pain (strong recommendation, moderate evidence) Second-line (GPP expert opinion)	A specific protocol for ART cannot be recommended; Both GnRH agonist and antagonist protocols can be offered based on patients' and physicians' preferences (weak recommendation, very low evidence) Extended administration prior to ART not recommended (strong recommendation, very low evidence)	–	Postoperative hormone treatment may be offered to improve the immediate outcome of surgery for pain, if the patient does not desire immediate pregnancy (weak recommendation; low evidence)
JSOG 2022[14]	Second-line (I-B) Effective for reducing pain associated with deep endometriosis (II-B)	A higher likelihood of achieving pregnancy can be expected by GnRH agonists followed by ART (III-C)	Not enough evidence	Not enough evidence
KSE 2018[15]	Recommends GnRH agonists for treatment of endometriosis related pain (grade A)	Recommends the use of GnRH agonists for 3–6 months before ART (grade B)	Prescription of hormonal therapy for pain control before surgery not recommended (grade A)	Recommends not to prescribe adjunctive short-term (<6 months) hormonal therapy for pain after surgery (grade A)

(*Continued*)

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Table 1 (Continued).

Guideline	Treatment of Endometriosis-Associated Pain	Treatment for Patients Who Desires Fertility	Preoperative Use	Postoperative Use
NICE 2017[16]	Hormone treatment, no specific mention of GnRH agonists	–	For deep endometriosis involving the bowel, bladder or ureter, consider 3 months of GnRH agonists before surgery	–
ASRM 2014[17]	First-line (no information about evidence strength)	–	–	May result in greater improvement in pelvic pain and longer interval before symptom recurrence
WES 2011[18]	Second-line treatments could include GnRH agonists, which should be used with add-back HRT, routinely (weak)	GnRH agonists administered for 3–6 months prior to IVF/ICSI (strong) Insufficient evidence for GnRH agonist treatment before IUI (weak)	Second-line treatment with GnRH agonists with add-back HRT may be considered prior to surgical diagnosis and treatment, whilst awaiting laparoscopic surgery (weak)	–
ACOG 2010[19]	Recommends 3-month GnRH agonist as second-line treatment (level B) When pain relief from GnRH agonist treatment supports continued therapy, add-back therapy is recommended (level A)	Medical suppressive therapy with GnRH agonists considered ineffective for endometriosis-associated infertility (level A)	–	–

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ART, assisted reproductive technology; ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology; GnRH, gonadotropin-releasing hormone; GPP, good practice points; HRT, hormone replacement therapy; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; JSOG, Japan Society of Obstetrics and Gynecology; KSE, Korean Society of Endometriosis; NICE, National Institute for Health and Care Excellence; WES, World Endometriosis Society.

endometriosis-associated pain (mostly as second-line therapy). Recent evidence has also led to the addition of a recommendation in the European Society of Human Reproduction and Embryology (ESHRE) 2022 guidelines for post-operative hormone therapy, which would include the drug class of GnRH agonists, for improving the immediate surgery outcome of pain management.[13]

Goserelin in Endometriosis

A series of non-comparative and comparative studies in the 1990s (as reviewed by Perry and Brogden)[2] established that goserelin confers both objective improvements (eg, reductions in the revised American Fertility Society [rAFS] endometriosis classification score) and subjective responses (eg, relief of pelvic symptoms such as pain and dyspareunia) in patients with endometriosis of various stages and severity. Particularly, in several randomized trials, goserelin demonstrated similar or numerically greater efficacy when compared with danazol[20,21] and low-dose oral contraceptive therapy.[22]

For the relief of endometriosis-associated pain, a Cochrane review of 72 studies involving 7,355 patients concluded that compared with placebo, 3-month treatment with GnRH agonists may reduce overall pain, and 6-month GnRH agonist treatment may reduce pelvic pain and pelvic induration slightly more than danazol treatment.[23] In a prospective study conducted in 28 centers from four Scandinavian countries, patients with symptomatic endometriosis treated with 6-month goserelin (n=113) showed a highly significant reduction of 45% in total pain score, with the prevalence of pelvic tenderness on palpation and pelvic induration reduced by 49% and 41%, respectively.[24]

In line with the recent ESHRE recommendation for postoperative hormonal therapy to enhance the immediate pain-relief outcome, a randomized controlled trial (RCT) in 70 patients with stage III/IV endometriosis reported that goserelin

initiated 3–5 days postoperatively was equally efficacious as that initiated on days 1–5 of menstruation, with the added benefit of reduced bleeding time and bleeding rate during the first treatment cycle.[25]

Although definitive benefit of preoperative medical therapy including GnRH agonists in endometriosis is not yet established, a systematic review (including 33 studies) and meta-analysis indicate that GnRH agonists can effectively reduce endometrioma sizes,[26] a feature potentially useful for facilitating laparoscopic cystectomy of ovarian endometriomas.[27] For goserelin specifically, an analysis published in 1996 of 814 patients with large ovarian endometriomas (>3 cm) reported that 3-month goserelin treatment, administered after drainage and first-look laparoscopy, facilitated the subsequent surgery by reducing the mean cyst diameter by 50% and reducing the internal wall thickness.[28] In a more recent prospective study, 35 patients with at least one endometrioma >4 cm received 4-month preoperative goserelin (1.8 mg) treatment, which significantly reduced the mean total size of endometrioma (from 93.6 mm to 82.4 mm); there was no recurrence of ovarian endometrioma >2 cm at 12-month follow-up.[29]

Postoperative GnRH treatment may also reduce the risk of symptom/disease recurrence, either alone[30] or in combination with oral contraceptives or progestins.[27,31,32] In a large RCT comparing postoperative 6-month goserelin treatment with expectant management in 269 patients with mild to severe endometriosis, goserelin significantly delayed the symptom recurrence over 2-year follow-up (recurrence rate 23.5% vs 36.5%).[33] A randomized study in 40 patients with severe endometriosis compared postoperative 6-month goserelin with levonorgestrel-releasing intrauterine system (LNG-IUS); significant reductions in pain scores were maintained 1 year post-treatment for goserelin, while the pain scores in the LNG-IUS group had returned to pretreatment levels.[34] Another randomized study in 80 patients with severe endometriosis reported that compared to postoperative goserelin alone, 6-month goserelin plus anastrozole significantly prolonged the pain-free interval and reduced symptom recurrence over 2-year follow-up.[35]

For patients with endometriosis and desiring pregnancy, appropriate medical therapy after conservative surgery and before pregnancy constitutes an important dimension of disease management. In this context, GnRH agonists may help improve fertility outcomes, as a meta-analysis of 17 studies involving 2,485 patients concluded that postoperative GnRH agonist treatment slightly raised the pregnancy rate (based on all 17 studies) and significantly shortened the time to pregnancy (based on 4 of the studies included).[36] A retrospective study investigated 3–6-month postoperative goserelin treatment in 108 patients with severe ovarian endometriosis, and reported high overall 5-year pregnancy and live birth rates, with 57.3% of all the natural pregnancies (55/96) attained within year 1.[37] In a prospective study, patients with ovarian endometriosis receiving 3-month postoperative goserelin treatment achieved a significantly higher pregnancy rate (57.1%, 12/21) than those without postoperative medication (36.8%, 7/19), with a numerically shorter mean interval from surgery to pregnancy.[38]

Goserelin in Extra-Pelvic Endometriosis

Extra-pelvic endometriosis is a rare form of endometriosis occurring in sites distant from gynecological organs. As high as 84% of reported cases of extra-pelvic endometriosis were managed by non-gynecologic clinicians,[39] highlighting the need for a multi-disciplinary approach in managing this condition. The most documented subtypes of extra-pelvic endometriosis are abdominal wall endometriosis (AWE) and thoracic endometriosis (TE).[40]

In cases of AWE, although surgical resection is considered the first choice for treatment, both preoperative and postoperative use of goserelin has been documented for symptom relief or recurrence prevention. For a patient with cutaneous endometriosis too large for excision on the perineum, 3-month goserelin treatment significantly shrank the lesion while providing symptomatic relief, enabling successful surgical excision 1 month later.[41] In a case of recurrent inguinal tumor with appendicular endometriosis, 9-month goserelin treatment was administered after reoperation and followed by a monophasic contraceptive, with no further recurrence reported.[42]

In case reports of TE, goserelin has been used either as pharmacotherapy alone for relieving symptoms such as chest pain and pneumothorax,[43] or postoperatively for 6–12 month for reducing the recurrence.[44,45] A case series highlighted the usefulness of timely postoperative goserelin in preventing recurrence: three of four patients initiated 6-month goserelin treatment 3 weeks postoperatively and had no recurrence through a mean follow-up of 33 months (max 45 months), while the remaining patient with delayed postoperative treatment experienced recurrence 6 weeks after surgery, 2 days before the scheduled initiation of goserelin treatment.[45]

Successful treatment with goserelin is also seen for cases of other rarer forms of extra-pelvic endometriosis. In a case of ureteric and pulmonary endometriosis[46] and a case of presumed cerebral endometriosis with catamenial epilepsy,[47] 3–6-month goserelin treatment effected symptom relief and lesion remission/shrinkage.

Adenomyosis

Adenomyosis is characterized by the presence of endometrial tissue in the myometrium with hyperplasia of adjacent smooth muscle, resulting in uterine enlargement and other signs and symptoms including menorrhagia, dysmenorrhea, and infertility.[48] Adenomyosis often coexists with endometriosis and/or uterine fibroid, and is likewise estrogen-dependent.[49] Although a system for assessing disease severity based on sonographic uterine features have been proposed,[50] a universally accepted diagnostic modality and classification scheme is still lacking.[51] As reflected in the current guidelines (Table 2), [52–56] GnRH agonists like goserelin are among the commonly used conventional medical therapies for adenomyosis, with effects reported for relieving the symptoms of dysmenorrhea and menorrhagia, shrinking adenomyotic lesions and the enlarged uterus, and potentially improving fertility outcomes.

In a prospective study, premenopausal female with symptomatic adenomyosis were randomized to receive goserelin (n=16) or letrozole (n=15) treatment for 3 months.[57] In the goserelin group, qualitative symptom improvements were reported by 100% of the patients experiencing dysmenorrhea and menorrhagia, and by 75%–92.8% of the patients experiencing chronic pelvic pain, metrorrhagia and dyspareunia. These percentages were numerically higher than those in the letrozole group.[57] A more recent study of similar design reported significant relief of quantitatively-assessed

Table 2 Guideline/Consensus Recommendations on the Use of GnRH Agonists in Adenomyosis

Guideline	Management of Symptoms Associated with Adenomyosis	For Patients Desiring Pregnancy
SOGC 2023[52]	Can be considered as a second-line agent for management of pain and heavy menstrual bleeding from adenomyosis; addback hormones should be initiated if treating for longer than 6 months (strong, low)	For patients with adenomyosis undergoing in vitro fertilization, GnRH agonist downregulation for 2–4 months may be considered before transferring fresh or frozen embryos (weak, low)
ASEA 2023[53]	GnRH agonists are effective in reducing adenomyosis-associated pain (1b-B)	–
CNGOF 2023a,[54]	For women with AUB-A who require conservative surgical treatment and no desire for future fertility, endometrial resection or ablation combined with hormonal therapy (including GnRH agonists) is suggested (weak recommendation, low quality of evidence)	–
CSOG 2022a,[55]	GnRH agonists as second-line treatment for AUB-A Patients with AUB-A with a uterus >8-week size and no immediate desire for pregnancy can be treated with GnRH agonists to shrink the uterus before LNG-IUS placement	Young patients with AUB-A desiring pregnancy can be treated with 3–6 months GnRH agonist and then consider ART based on patient condition
COGA 2020[56]	GnRH agonists can effectively and rapidly alleviate adenomyosis-associated pain and menorrhagia and reduce uterine sizes For patients with a large uterus or anemia, GnRH agonists can be used as preoperative adjunct or postoperative consolidatory treatment For patients with a very large uterus or severe anemia, GnRH agonists can be used as a pretreatment before the placement of LNG-IUS	For patients with adenomyosis undergoing in vitro fertilization, GnRH agonist pretreatment for 2–6 months is recommended before undergoing frozen embryo transfer. For patients <35 years old with good fertility, or for patients unwilling to received ART following repeated embryo transfer failure and conservative surgery, natural pregnancy can be attempted after 3–6-month GnRH agonist treatment

Note: [a]Guidelines focusing on AUB.

Abbreviations: ART, assisted reproductive technology; ASEA, Asian Society of Endometriosis and Adenomyosis; AUB, abnormal uterine bleeding; AUB-A, abnormal uterine bleeding associated with adenomyosis; CNGOF, French National College of Gynaecologists and Obstetricians; COGA, Chinese Obstetricians and Gynecologists Association; CSOG, Chinese Society of Obstetrics and Gynecology; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; SOGC, Society of Obstetricians and Gynaecologists of Canada.

dysmenorrhea and menorrhagia by both goserelin (n=77) and letrozole (n=79) after 3-month treatment, with goserelin demonstrating a more rapid effect, whereby near-maximal symptom relief was already achieved as early as month 1.[51]

In prospective studies, 3-month goserelin treatment achieved approximately 50% reduction in uterine volume, reducing the median or mean uterine volume from the range of 200–260 cm^3 at baseline to approximately 110 cm^3 at month 3.[57,58] Furthermore, 3-month goserelin treatment was shown prospectively to reduce adenomyoma sizes,[51,57] effect sonographic improvements in diffuse adenomyosis (in both myometrium and junctional zone) and focal adenomyosis (in junctional zone), as well as ameliorate asymmetric thickening of the myometrium.[51] The goserelin 10.8 mg formulation demonstrated comparable effects as the 3.6 mg formulation in symptom relief, uterine volume reduction, and cancer antigen 125 level reduction.[58] Goserelin's ability to rapidly reduce uterine volume is particularly useful for patients with uterine volumes >12 weeks gestational size, who cannot be effectively treated by other commonly used pharmacotherapies such as LNG-IUS (due to high expulsion rates)[59] or dienogest (which tends to be less effective for reducing uterine volume).[60,61] In a study of 21 such patients, 3–4 cycles of goserelin treatment reduced the uterine volume from 311.4±32.3 cm^3 at baseline to 220.6±17.2 cm^3, successfully reducing all patients' uterine lengths to ≤10 cm (cutoff for implanting LNG-IUS).[59]

By rapidly controlling menorrhagia, goserelin treatment helps restore the hemoglobin levels in anemic patients and reduce intraoperative bleeding; goserelin's fibroid shrinking effect also makes operation easier by decreasing pelvic congestion; together these features make goserelin a suitable preoperative adjunct therapy.[62] A recent prospective observational study in 214 patients found added value of preoperative use goserelin (n=41) in relieving acute postoperative pain for patients with adenomyosis.[63]

For patients with adenomyosis and desiring pregnancy, GnRH agonist treatment for 3–6 months before attempting natural pregnancy is considered beneficial.[56] In a case report, three women with a history of >5 years of infertility and adenomyosis received conservative microsurgical therapy followed by goserelin treatment (six courses in two patients, two courses in one patient), and all three patients conceived within 12 months after surgery and delivered viable infants.[64] There has also been a report of 6-month goserelin treatment before laparoscopic surgery in a patient with adenomyosis and infertility, who then successfully conceived and delivered a healthy infant.[62]

Uterine Fibroids

Uterine fibroids are benign growth near the muscle wall of the uterus. It is estimated that up to 25% of women of reproductive age experience symptomatic uterine fibroids.[65] Hysterectomy constitutes definitive treatment for uterine fibroids, but for patients desiring to preserve their uterus and the fertility, pharmacological therapies can be used either on its own or as pretreatment before conservative surgery. By the 1990s, there had been multiple reports on the efficacy of GnRH agonists in shrinking uterine fibroids. Currently, GnRH agonists are best established as preoperative adjunct treatments for uterine fibroids, whereby GnRH agonists provide symptom relief and facilitate the surgical procedure by reducing the uterine and fibroid sizes, restoring hemoglobin levels in anemic patients, and reducing intra-operative blood loss (Table 3). [54,55,66–73] According to a Cochrane review of data up to June 2017 including 38 RCTs (3,623 women), GnRH agonist treatment before hysterectomy for uterine fibroids significantly reduces the duration of surgery, intraoperative blood loss, and incidence of postoperative complications, while evidence in myomectomy is less certain apart from for reducing intraoperative blood loss.[74] If GnRH agonists are used as the sole therapy, fibroid regrowth has been observed after treatment cessation, and concerns over side effects, particularly on bone mineral density (BMD), limits their long-term use, as reflected in some of the guidelines for managing uterine fibroids (Table 3).

Goserelin in Uterine Fibroids

In patients with uterine fibroids, goserelin can effectively correct menorrhagia by inducing amenorrhea in majority of patients after approximately 1–2 months, and in patients with severe anemia resultant from menorrhagia, the levels of hemoglobin and hematocrit can be restored to normal after 3 months of treatment.[75] A Phase III RCT reported that in women with symptomatic uterine fibroids and iron-deficiency anemia, a single dose of preoperative goserelin 10.8 mg plus oral iron tablets (n=54) was more effective than iron monotherapy (n=56) in raising patients' hemoglobin levels (difference of least squares mean 1.17 g/dL, $P<0.001$) and reducing the incidence of uterine hemorrhage (9.3% vs

Table 3 Guideline Recommendations on the Use of GnRH Agonists in Uterine Fibroids

Guideline	Management of Symptoms Associated with Fibroids	Infertility Associated with Fibroids	Preoperative Use
CNGOF 2023a,[54]	–	–	In women with AUB-L associated with one or more type 3 (or higher) fibroids <10 cm and a planned hysterectomy: • Treatment by GnRH agonists for 3 months is suggested to reduce the laparotomy rate and facility the surgery (weak recommendation, low quality of evidence) • Treatment by GnRH agonists for 3 months is recommended to improve preoperative blood hemoglobin before surgery (strong recommendation, low quality of evidence)
CSOG 2022a,[55]	–	For patients with AUB-L and desiring pregnancy, 3–6 months GnRH agonist treatment can be considered, before attempting natural pregnancy or ART after fibroid shrinkage and amelioration of bleeding symptom	–
NICE 2021a,[66]	–	–	For patients with AUB-L with fibroids of 3 cm or more in diameter, pretreatment with a GnRH analogue before hysterectomy and myomectomy should be considered if uterine fibroids are causing an enlarged or distorted uterus
ACOG 2021[67]	GnRH agonists with or without addback hormonal therapy are recommended for short-term treatment of AUB-L and uterine enlargement associated with uterine leiomyomas and as a bridge to other treatment strategies	–	–
SOGC 2015[68,69] **/2019**[70]	Effective medical treatments for women with abnormal uterine bleeding (I) Effective medical treatments for women with bulk symptoms associated with fibroids (I)	No role for medical therapy as a stand-alone treatment for fibroids in the infertile population (III)	Effective at correcting anemia and should be considered preoperatively in anemic patients (I-A) Have been shown to decrease fibroid size, improve anemia, and reduce the probability of perioperative blood transfusions (I-A)
RANZCOG 2001[71] **/2018**[72]	Effectively reduces uterine and fibroid size, but sole use limited to 6 months (A) 3-month treatment followed by combined addback therapy result in fibroid shrinkage as an alternative for patients contraindicated to or not wishing to undergo surgery; fibroid will return to pretherapy size upon treatment cessation (B)	Medical management of fibroids delays efforts to conceive and is not recommended for the management of infertility associated with fibroids	Treatment for 2–4 months prior to surgery recommended for patients with a large uterus (>18 weeks size) or preoperative anemia (B)
CNGOF 2012[73]	–	–	Preoperative management for uterine fibroids associated with anemia or when the size of the fibroid must be reduced before endoscopic or transvaginal surgery (grade A[b])

Note: [a]Guidelines focusing on AUB.[b]Recommendation statement specifically mentions leuprorelin and triptorelin.

Abbreviations: ART, assisted reproductive technology; ACOG, American College of Obstetricians and Gynecologists; AUB, abnormal uterine bleeding; AUB-L, abnormal uterine bleeding associated with leiomyoma; CNGOF, French National College of Gynaecologists and Obstetricians; CSOG, Chinese Society of Obstetrics and Gynecology; GnRH, gonadotropin-releasing hormone; NICE, National Institute for Health and Care Excellence; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada.

28.6%).[76] Goserelin also brings about rapid shrinkage of fibroid and uterine sizes. In a study where 6-month goserelin was investigated as an alternative to surgery, a fibroid reduction of >30% was achieved in 18 of 21 patients, with greatest reductions in fibroid and uterine sizes observed during the first 2 months of treatment.[77] In patients with uterine sizes >600 cm^3, a randomized study reported a significantly greater mean reduction in uterine size with goserelin 10.8 mg (54% reduction; n=22) than with goserelin 3.6 mg (43% reduction; n=23) after 3-month treatment.[78] The rapid

restoration of hemoglobin levels and reduction of fibroid and uterus sizes by goserelin are both conducive features for facilitating surgical therapy. A recent multicenter, prospective study reported that in 53 patients with symptomatic uterine fibroids, preoperative treatment with a single dose of goserelin 10.8 mg significantly raised hemoglobin levels (+26.6%) and reduced fibroid (-35.14%) and uterine (-27.03%) sizes, and the patients reported significantly improved symptom control and health-related quality of life.[79]

Fibroid regrowth and uterus enlargement have been observed after cessation of goserelin treatment.[77] As such, the possibility of longer goserelin treatment together with add-back therapy was investigated. Maheux et al reported on the use of 12-month goserelin in 8 patients, with conjugated estrogens and medroxyprogesterone acetate added after the first 3 months.[80] The mean fibroid size decreased by 49.3% during the first 3 month and remained largely unchanged during the subsequent 9 months; no significant change in bone mass was detected during the study period.[80] On the other hand, in a randomized trial by Caird et al, similar decreases in BMD were observed in patients receiving 12-month goserelin with or without medroxyprogesterone acetate (n=12 per group), whereby the spine BMD were still 4.5% and 5.3% below baseline, respectively, when followed-up 1 year after treatment cessation.[81]

Goserelin administered before hysterectomy for uterine fibroids confers clear advantages. Both randomized and non-randomized studies showed that 2–6-month goserelin treatment raised the preoperative hemoglobin levels, reduced intraoperative blood loss and the need for transfusion, and made the surgical operation technically easier.[82–84] However, the benefit of goserelin administered before hysteroscopic myomectomy is less well established, where benefits reported in a single-arm study in the 1990s were not consistently observed in two small RCTs in the 2010s.[85–87] The discrepant results are likely attributable to differences in study design (single-arm vs RCT), small sample sizes in the RCTs (18–32 patients per treatment arm), and the possibility that improvements in hysteroscopic equipment and surgical techniques over time have reduced the incremental benefit of preoperative goserelin. Future well-designed RCTs with larger sample sizes are needed to clarify the benefit of preoperative goserelin before hysteroscopic myomectomy.

Goserelin in Special Cases of Leiomyomatosis

In rare cases, smooth-muscle tumors histologically similar to uterine fibroids show unusual growth patterns; these neoplastic lesions are classified into three types, namely, leiomyomatosis peritonealis disseminata (LPD), intravenous leiomyomatosis (IVL), and benign metastasizing leiomyoma (BML).[88,89] Because of the presence of estrogen and progesterone receptors (ER/PR) in the smooth-muscle cells of these lesions and the lesion regression observed with reduced serum estradiol levels, GnRH agonists are an appropriate treatment option that can be considered, especially when surgical lesion excision is not feasible or when the patient is unwilling to undergo surgical castration.[88] For LPD particularly, the complete excision of the multiple disseminated lesions is challenging and the numbers of lesions and previous surgeries may be associated with an elevated risk of postoperative recurrence,[89] making GnRH agonist treatment an important tool for the management of LPD.[88]

The use of goserelin has been documented in a number of cases of smooth-muscle tumors of unusual growth patterns. In a case of LPD, the patient had undergone four surgeries for uterine fibroids over the previous 8 years before presenting with LPD.[89] The patient refused surgery and did not respond to treatment with tamoxifen or ulipristal acetate, but achieved an asymptomatic state with substantial nodule shrinkage with 16 months of goserelin treatment.[89] Although there has also been a case report of LPD with disease progression despite goserelin treatment,[90] this should not negate the value of goserelin as a potential treatment option for LPD.

In a case of IVL where complete tumor excision was not feasible, the patient received surgical removal of the intracardial portion of the tumor followed by goserelin treatment, which led to a significant shrinkage of the residual tumor mass in the inferior caval vein at 6 months follow-up.[91]

In patients with BML, successful use of goserelin to achieve a stable disease or tumor shrinkage has been documented in case reports of postoperative recurrence[92] or residual tumors after partial excision,[93,94] including complex cases such as BML with both pulmonary and nervous system involvement[93] or BML with concurrent IVL.[94] Short-term use of goserelin before surgical castration,[90,95] as well as prolonged goserelin treatment without surgical therapy,[90,96] have also been reported in some case reports or case series of BML.

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Abnormal Uterine Bleeding

The term "abnormal uterine bleeding" (AUB) describes uterine bleeding with any departure from a normal menstrual cycle pattern in regularity, frequency, duration, or heaviness of flow.[97] The International Federation of Gynecology and Obstetrics (FIGO) system of PALM-COEIN classifies AUB according to structural/anatomical (PALM: polyp; adenomyosis; leiomyoma; malignancy and atypical hyperplasia) and functional (COEIN: coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; not otherwise classified) causes.[98] Among AUB of different causes, the utility of GnRH agonists in AUB-A and AUB-L has been demonstrated in "Adenomyosis" and "Uterine Fibroids". Suggestions on the use of GnRH agonists in AUB-M are also emerging, consistent with the increasing recognition of GnRH agonists for treating endometrial cancer (EC) ("Endometrial Cancer"). For women with idiopathic AUB, AUB due to a benign uterine pathology, or AUB-C, GnRH agonists can be considered with iron supplementation to correct of preoperative anemia and to reduce surgical morbidity and mortality, even now with low quality of evidence.[54,55] GnRH agonists will effectively reduce menstrual bleeding and may be used if other medical or surgical treatments have failed or are contraindicated.[99]

Research that established the use of goserelin as a preoperative endometrial thinning agent in AUB predates the PALM-COEIN classification system and may include patients with AUB of undistinguished causes or a mix of patients with AUB-P, AUB-A and AUB-L, while patients with AUB-M were often excluded. In a prospective, randomized study of 60 patients (including 22 with polyps, submucosal fibroids or septal uterus), the endomyometrial strips removed during endometrial resection weighed about two-thirds less in patients receiving goserelin 4–6 weeks preoperatively compared to those without preoperative treatment; the preoperative goserelin treatment also significantly shortened the duration of surgery.[100] When assessed at 3 months and 1 year after endometrial resection, patients who had received preoperative goserelin showed a trend of better bleeding control in terms of blood loss-assessment chart scores and the proportions with amenorrhea or scanty bleeding, an effect enhanced by the addition of a post-operative dose of goserelin.[100,101] A multi-national prospective, randomized, double-blind study reported that 3 years after endometrial ablation, the group with 8-week preoperative goserelin treatment still showed a higher amenorrhea rate than the sham control group that approached statistical significance (21% vs 14%; odds ratio 1.8, P=0.0571).[102] The goserelin group also had higher incidences of subsequent hysterectomy and repeated ablations, but the between-group differences were not statistically significant.[102]

The use of goserelin in other types of AUB has been reported in a small number of patients. A study evaluating 6-month goserelin treatment in 23 patients with anovulatory uterine bleeding and severe iron-deficiency anemia reported effective control of bleeding and improvement in hematological parameters; additionally, regression of endometrial hyperplasia was noted in 11 of the patients.[103] In a report of 3 cases of AUB with anticoagulant therapy, one patient received goserelin 10.8 mg with add-back norethindrone acetate, and another received goserelin 10.8 mg after failing LNG-IUS and depomedroxyprogesterone acetate (DMPA) treatments; both achieved effective bleeding control and remained amenorrheic at 2-year follow-up.[104]

Fertility and ART

Globally, the 12-month period and lifetime prevalences of infertility are estimated at 12.6% and 17.5%, respectively.[105] Pituitary downregulation with GnRH agonists is one of the routine methods used in ART protocols such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to prevent premature LH surges during controlled ovarian stimulation, and confers the benefits of fewer cycle cancellations and more oocytes retrieved, with the latter being an important prognostic factor for successful pregnancy.[106] The short (GnRH agonist commenced simultaneously with stimulation) and the long (GnRH agonist commenced ≥2 weeks before starting stimulation) protocols are the most commonly used, standard GnRH agonist protocols. Additionally, the ultralong protocol (GnRH agonist treatment for 3–6 months before ART) has been investigated and practiced in patients with endometriosis- or adenomyosis-associated infertility with the hope of improving the fertility outcomes.

The advantage of the goserelin long protocol was first demonstrated in a prospective, randomized study published in 1992, where goserelin administered 2–3 weeks before starting human menopausal gonadotropin (HMG) stimulation was compared with clomiphene citrate administered for 5 days before starting HMG stimulation in unselected patients

undergoing IVF.[107] Compared with clomiphene citrate (n=151), goserelin (n=152) yielded significantly better outcomes in terms of a lower cancellation rate (2.6% vs 20.5%), more oocytes retrieved (mean number 14.2 vs 6.1), a higher pregnancy rate/cycle (36.8% vs 24.5%), and a higher live birth rate/cycle (25.7% vs 18.5%).[107] Although significantly more ampoules of HMG (44.9 vs 9.9) and longer stimulation durations (mean 11.2 days vs 8.7 days) were needed with goserelin, the impact of these is likely outweighed by the benefit of reduced cycle cancellations and the ultimate increase in pregnancy rate per cycle.[107] In a recent retrospective study of 154 women undergoing IVF/ICSI, a long protocol using goserelin (n=24) was associated with significantly lower total gonadotropin usage and shorter stimulation duration compared with triptorelin (n=94) and leuprorelin (n=36), as well as numerically higher clinical pregnancy (57.9% vs 41.7% and 39.4%) and live birth rates (52.6% vs 32.5% and 33.3%).[108]

Compared with shorter-acting GnRH agonists, single-dose goserelin offers greater convenience and guaranteed adherence, in addition to comparable efficacy. Two randomized studies dated a decade apart compared single-dose goserelin with daily buserelin[109] and daily leuprolide acetate.[110] In both studies, the time needed to achieve down-regulation, the duration of follicular stimulation, and the numbers of oocytes retrieved were comparable between groups. Both studies reported more ampoules of follicular stimulation with goserelin. The study with a larger sample size pinned the significantly higher ampoules (goserelin vs daily buserelin) down to the patient subgroups receiving GnRH agonists in the follicular phase and aged >40 years.[110]

For patients with endometriosis-associated infertility, the ultralong protocol of 3–6-month GnRH agonist treatment before ART has once been considered beneficial, based on a Cochrane review published in 2006 (3 RCTs included).[111] However, an updated Cochrane review[112] incorporating more recent, statistically better powered studies[113] (8 RCTs included) revealed no advantage of the ultralong GnRH agonist protocol in patients with endometriosis, leading to a corresponding update in the ESHRE guidelines (Table 1). For goserelin, a small, single-arm study reported that after 6-month goserelin treatment, a high pregnancy rate of 57.1% (8 patients) were achieved at the first ART attempt.[114] In a subsequent prospective comparative study, 110 patients were randomized to surgery alone or surgery followed by 5–6-month goserelin treatment, before undergoing up to 3 cycles of ART programs.[115] The patients were categorized into four subgroups by endometriosis stage and type of ART, and higher pregnancy rates were observed with goserelin treatment in three of the subgroups (stage II disease with intrauterine insemination [IUI]: 86% vs 58%; stage III/IV disease with IUI: 100% vs 70%, P=0.055; stage III/IV disease with IVF/ICSI: 82% vs 40%, P<0.05).[115] The general pregnancy rate at the study center then was only approximately 35% for IVF/ICSI,[115] lower even than those reported for the surgery-alone group in the study, which raised the question of potential selection bias for patients with better prognosis.[113]

For patients with adenomyosis-associated infertility, the use of GnRH agonists for 2–6 months is considered beneficial pretreatment before fresh or frozen embryo transfer (SOCG and COGA guidelines, Table 2). A case series of 4 women with adenomyosis and multiple prior IVF failures reported successful pregnancy with 6–8 weeks of GnRH agonists pretreatment.[116] A retrospective study reported that for women with adenomyosis, those with 2–3 months of GnRH agonist pretreatment before fresh embryo transfer (n=87) had significantly more oocytes retrieved than those without GnRH agonist pretreatment (n=116), and those undergoing GnRH agonist pretreatment and frozen embryo transfer (n=38) had the highest number of oocytes received and clinical pregnancy rate (39.5%) among the three groups.[117] Another retrospective study with propensity score matching similarly reported more favorable results for fresh embryo transfer cycles with ≥3-month GnRH agonist pretreatment versus without (clinical pregnancy rate 83.3% vs 47.0%, P=0.016), whereas such benefit was not observed for frozen embryo transfer cycles with either 1-month, 2-month, or ≥3-month of GnRH pretreatment.[118] Goserelin was among the GnRH agonists used in all these three studies, although the exact numbers of patients using goserelin were not reported.

Use of Goserelin in Female Cancers

The use of GnRH agonists for preservation of ovarian function and fertility in female patients receiving chemotherapy has been extensively studied and well established in breast cancer.[119–121] Some researchers have since advocated for the use of GnRH agonists in all cancer patients receiving chemotherapy who wish to preserve fertility,[122,123] although the evidence in cancer types such as ovarian, endometrial, and cervical cancers is still limited.[124] Apart from protecting

ovarian function, GnRH agonists like goserelin may confer other objective benefits in the treatment of gynecologic cancers, especially where ER/PR are likely implicated in the cancer pathology.

Breast Cancer

Breast cancer is a leading cause of cancer morbidity and mortality in all female cancers worldwide.[125] Compared to postmenopausal patients, premenopausal patients with breast cancer are more likely to have hormone receptor (HR) positive tumors and prognostic risk factors such as lymph node positivity.[126,127] The use of GnRH agonists to achieve ovarian function suppression (OFS) has been a well-established adjuvant treatment modality for premenopausal patients with HR-positive breast cancer.[128] GnRH agonists can also be used during adjuvant chemotherapy to protect ovarian function in premenopausal patients regardless of HR status.[128]

Goserelin was first demonstrated as an equally efficacious and well tolerated alternative to adjuvant chemotherapy of cyclophosphamide, methotrexate and fluorouracil (CMF) in an international RCT of premenopausal women with ER-positive, node-positive early breast cancer (n=1,640).[129] The ZIPP trial then established comparable efficacy of adjuvant goserelin treatment to that of tamoxifen in premenopausal women with early breast cancer; compared with patients receiving neither adjuvant therapy (n=476), those receiving 2-year goserelin (n=469) had a significantly lower risk (−13.9 percentage points) for recurrence, new tumor or death at a median follow-up of 12 years.[130] The Stockholm part of the ZIPP trial (STO-5) further reported on the 20-year benefit of 2-year adjuvant therapy in ER-positive patients, whereby compared to no adjuvant treatment (n=145), goserelin (n=155) significantly reduced the risk of distant recurrence (hazard ratio=0.49), with the benefit particularly pronounced (hazard ratio=0.24) in genomic high-risk patients (n=158).[131] STO-5 also reflected goserelin's effect of ovarian function protection: among the node-positive patients receiving CMF, 36% of those on concurrent goserelin had menses resumption one year after treatment completion, markedly higher than in those receiving concurrent tamoxifen (13%), tamoxifen plus goserelin (7%), or neither (10%).[132] Consistently, two recent prospective studies reported that compared to chemotherapy alone, the addition of goserelin was associated with a higher probability of ovarian reserve recovery[133] and a significantly lower risk of premature ovarian insufficiency (odds ratio 0.23 for GnRH agonists [goserelin or leuprorelin] vs control)[134] one year after treatment completion. The benefit of goserelin on ovarian function protection was further reinforced by a systematic review published in 2025 that included 29 prospective studies, in which adding goserelin to chemotherapy led to higher rates of menstrual recovery and pregnancy compared with chemotherapy alone.[135]

Endometrial Cancer

Worldwide the age-standardized incidence rate of EC is estimated at 9.57 per 100,000 women in 2017.[136] The traditional Bokhman system classifies EC into two types: type 1 EC is hormone-dependent in early stages and constitutes a substantial proportion (85%) of all EC cases; type 2 EC and late-stage type 1 EC do not express ER/PR.[137] It is estimated that 15% of EC cases occur in premenopausal patients,[138] who would potentially have the need for fertility preservation. GnRH agonists, through the classical pituitary suppressive effects, can form part of the fertility preserving therapy for young patients with early EC and its pre-cancer, atypical endometrial hyperplasia, as reflected in several guidelines (Table 4). [54,55,139–142] Research into the heterogeneity of EC has led to more fine-tuned molecular classification systems, such as the TCGA and the ProMisE (modified based on TCGA) systems.[143] Among the four molecular subtypes of EC under the ProMisE system, the p53 wild-type/copy-number-low (p53 wt) subtype typically includes ER/PR-positive tumors that are potentially responsive to hormone therapy.[143] Besides ER/PR expression-predicted responsiveness, GnRH agonists have been explored for direct anti-tumor potential in treating advanced or recurrent EC, since GnRH receptors are expressed in most EC as part of an autocrine system implicated in cell proliferation and apoptosis.[137]

For fertility-sparing treatment of patients with early-stage EC, the use of goserelin has been investigated for combined medical therapy and for medical therapy after conservative surgery. In a prospective cohort study, 32 patients aged ≤42 years with grade 1 endometrial adenocarcinoma were treated with goserelin plus LNG-IUS; the rates of complete and partial responses were 63% (n=20) and 9% (n=3), respectively, after 6 months of treatment, and all patients achieved complete responses with continued treatment up to 9–12 months.[145] The recurrence rate within 6–12 months after complete response was 6% (n=2).[145] In a retrospective case series study, 18 patients aged ≤41 years (endometrial intra-

Table 4 Guideline Recommendations on the Use of GnRH Agonists in Uterine Cancer

Guideline	Endometrial Cancer	Other Uterine Cancers
NCCN 2024[144]	–	Among "other recommended regimens" for low-grade ESS, adenosarcoma without SO, and ER/PR-positive uterine sarcomas (category 2B)
CNGOF 2023a,[54]	For patients with AUB-M associated with atypical endometrial hyperplasia, GnRH agonists associated with other progestogen treatment or conservative surgery (endometrial ablation) may have benefits (no formal recommendation)	–
CSOG 2022a,[55]	For young patients with AUB-M and desiring fertility preservation, GnRH agonists can be used	–
CSCO 2023[139]	GnRH agonist plus LNG-IUS and GnRH agonist plus letrozole are among the recommended regimens for fertility-preserving treatment (II), especially for patients not suited for progesterone treatment, eg, those with obesity, hepatic dysfunction, thrombophilia, or failure/recurrence after progesterone treatment	–
ESMO 2022[140]	Hormone therapy could be considered as front-line systemic therapy for recurrent/metastatic low-grade carcinomas endometrioid histology [III, A], but GnRH agonists are **not** named among the recommended hormone therapies	–
CACA 2022[141]	GnRH agonists are among the commonly used hormone treatments for certain type I endometrial cancer For fertility-preserving treatment of young patients • If the preferred treatment of 6-month high-dose oral progesterone leads to some but not a complete response, the addition of GnRH agonists can be considered Hysteroscopic electric resection with pre-/post-operative LNG-IUS plus GnRH agonist can be considered	–
ESGO/ESTRO/ESP 2020[142]	For fertility preservation in early-stage endometrial carcinoma, levonorgestrel intrauterine device in combination with oral progestins with GnRH analogs is a treatment that can be considered (IV, B)	–

Note: [a]Guidelines focusing on AUB.

AUB, abnormal uterine bleeding; AUB-M, abnormal uterine bleeding associated with endometrial malignancy and atypical hyperplasia; CACA, Chinese Anti-Cancer Association; CNGOF, French National College of Gynaecologists and Obstetricians; CSCO, Chinese Society of Clinical Oncology; CSOG, Chinese Society of Obstetrics and Gynecology; ER, estrogen receptor; ESGO, European Society of Gynaecological Oncology; ESMO, European Society for Medical Oncology; ESP, European Society of Pathology; ESS, endometrial stromal sarcoma; ESTRO, European Society for Therapeutic Radiology and Oncology; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor; SO, sarcomatous overgrowth.

epithelial neoplasia n=9, grade 1 endometrial carcinoma n=7, combined histology n=1, grade 2 endometrial carcinoma n=1) received 3-month goserelin treatment after an endometrial resection.[146] With a median follow-up of 40.7 months, a complete response rate of 66.7% (n=12) was reported, with the remaining 6 patients achieving stable diseases.[146] The relapse rate was 25% (n=3). Among the 12 patients who attempted to conceive, 8 patients obtained a total of 14 pregnancies that resulted in 11 live births.[146]

In patients with advanced or recurrent EC, direct evidence for the efficacy of goserelin is currently scarce. A study published in 1996 reported "a significant and durable antitumor effect" in 32 patients with recurrent EC who received GnRH agonist treatments, but only 1 of the patients used goserelin.[147] A study published in 2002 specifically evaluated the efficacy of goserelin in 40 patients with recurrent EC.[148] The median age of the patients was 71, and the prior treatments included radiation therapy, progestational therapy, and chemotherapy.[148] With an overall response rate of 11% (including two [5%] complete responses and three [7%] partial responses) and a median progression-free survival of 1.9 months, the study concluded that the efficacy of goserelin as a single-agent treatment is limited for treating recurrent EC.[148] When goserelin is used in combination with the aromatase inhibitor letrozole, Dong et al reported a case where

the combination proved a helpful salvage treatment in a patient with inoperable EC and multiple comorbidities, controlling the recurring vaginal bleeding and achieving notable improvements on MRI after 6-month treatment.[149]

Beyond the scope of EC treatment, GnRH agonists like goserelin may be useful for treating uterine sarcoma, another type of uterine cancer, as reflected in the NCCN 2024 guidelines for uterine neoplasms (Table 4).[144] Most low-grade endometrial stromal sarcoma (LG-ESS) express ER/PR, making them potential targets for hormone therapy. Alkasi et al reported a case of recurrent LG-ESS where the patient, after initial surgical treatment and repeated surgery for solitary metastases, achieved long-term (9-year follow-up) disease-free survival upon receiving goserelin for 2 years followed by anastrozole treatment.[150]

Ovarian Cancer

The world average incidence and mortality rates of ovarian cancer are estimated at 6.6 and 4.2 per 100,000, respectively.[151] Epithelial ovarian cancers (EOC) make up ~90% of all ovarian cancers and are classified into five histological subtypes. The remaining ~10% of ovarian cancers are non-epithelial in origin, including germ cell tumors, sex cord-stromal tumors, and borderline tumors. Old age is considered a risk factor for ovarian cancer, with mean patient ages above 55 years for most subtypes.[151] Majority of the patients are diagnosed at an advanced stage, and disease recurrence and progressive resistance to platinum-based chemotherapy remain major challenges in the treatment of ovarian cancer. Furthermore, apart from high-grade serous carcinoma, the other subtypes of EOCs as well as most non-epithelial ovarian cancers tend not to respond to chemotherapy well and currently lack efficacious treatment options. The utility of GnRH agonists has been recognized or investigated in several aspects of ovarian cancer management, including as a hormone maintenance therapy for non-high grade subtypes of EOC and platinum-resistant recurrent EOC,[152] for treating non-epithelial ovarian cancer,[153] and for protecting ovarian function. Notably, the 2024 revision of the NCCN guidelines has added goserelin as an option for the treatment of stage IC-IV low-grade serous carcinoma and grade 1 endometroid carcinoma, either as maintenance treatment after systemic chemotherapy (preferred) or as an alternative primary systemic therapy.[154]

The use of goserelin in patients with advanced and/or recurrent ovarian cancer has been investigated in several studies of limited sample sizes in the 1990s–2000s. In a Phase 2 study, 26 patients with recurrent advanced EOC (including 17 with platinum-resistant diseases) received tamoxifen plus goserelin.[155] The resultant clinical benefit rate of 50% (one complete response, two partial responses, 10 stable diseases ≥6 months) and median overall survival of 13.6 months represent considerable efficacy in this study population, which were characterized by highly aggressive disease, poor prognosis, and heavy pretreatment. Notably, four patients (including 3 with platinum-resistant disease) continued the treatment beyond 2 years without disease recurrence.[155] Another study on the tamoxifen plus goserelin combination reported a median OS of 8 months in 25 patients with recurrent, chemotherapy resistant ovarian cancer, with one patient noted for being progression-free at 8 years follow-up.[156] In patients with stage III/IV ovarian cancer, one study explored the use of goserelin as first-line adjuvant therapy after maximal debulking surgery: compared to chemotherapy alone (n=20), the addition of goserelin (n=19) conferred a significantly higher rate of complete remission (57.89% vs 15%) and numerically better survival results.[157] This study also noted that the levels of FSH were significantly lower in patients surviving at least 5 years and in those with complete remission.[157]

Limited but intriguing data have been reported on the efficacy of hormonal therapy in non-epithelial ovarian cancer, particularly in granulosa cell tumors (GCT, the most common subtype of sex cord-stromal tumors [SCST]).[158] Direct evidence on the use of goserelin in GCT is currently limited to 6 cases including 2 partial responses, 1 stable disease, and 3 progressive diseases for best overall response.[158,159]

Although a minority in ovarian cancer, young patients diagnosed with early-stage disease present a special need for fertility preserving therapies, as the standard fertility-sparing surgery of unilateral salpingo-oophorectomy would leave patients with only one ovary and thus more prone to the ovarian toxicity of post-operation platinum-based chemotherapy. The effect of GnRH agonists for preserving ovarian function in such patients was prospectively evaluated by Xie et al (n=158)[160] Although not randomized, the control group receiving conventional chemotherapy and the group receiving GnRH agonist co-treatment had generally balanced representations of histological subtypes (EOC: 60% vs 49%; germ cell tumors: 30% vs 40%; SCST: 10% vs 10%). In the GnRH agonist group, 25 of 77 patients received goserelin, injected 7–14 days before chemotherapy, every 28 days until 2 weeks post chemotherapy. One year after chemotherapy, effective protection of ovarian function was observed

in the GnRH agonist group, with significantly more favorable results versus the control group in terms of serum marker levels (AMH, FSH, and FSH/LH ratio), menstrual resumption, and quality of life.[160]

Cervical Cancer

Cervical cancer ranks fourth in both incidence and mortality among female worldwide.[161] Since cervical cancer is more prevalent among younger women aged 20–39 years,[162] fertility preservation is increasingly recognized as an important issue related to quality of life, especially in the management of patients with early-stage diseases, for whom the effectiveness of anticancer treatment is usually good. Fertility-sparing surgery can be offered to patients with early-stage cervical cancer, with survival benefits comparable to that of radical hysterectomy; however, patients treated with fertility-sparing surgery may still face the issue of an increased risk of pregnancy complications.[163]

The ESGO/ESTRO/ESP 2023 joint guidelines for cervical cancer mentions that treatment of premature ovarian failure should be recommended if the anticancer treatment to be received by the patient might damage gonadal hormone function.[164] Consistently, in a recent review of fertility-sparing treatment options for patients with cervical cancer, Terzic et al named ovarian suppression with GnRH agonists among the options to be considered when surgical and non-surgical fertility-sparing treatment options are not accessible or not feasible, such as when the patient has to forego an ovarian tissue retrieval surgery in order to receive urgent anticancer treatment.[163] Evidence specific to the use of goserelin as a fertility-sparing treatment for cervical cancer remains to be established.

Use of Goserelin in Precocious Puberty

Central precocious puberty (CPP), also known as gonadotropin dependent precocious puberty, is the early onset of puberty caused by premature activation of the hypothalamic-pituitary-gonadal axis. The aim of CPP treatment includes to suppress puberty progression, to normalize the rates of height growth and bone age advance, and to preserve patients' adult height potential. GnRH agonists can halt puberty progression by suppressing the premature secretion of sex hormones and have been used for CPP management since the 1980s.[165]

In children with CPP, goserelin brings about rapid initial growth deceleration, an effect reported in a retrospective cohort as significantly greater than that of leuprolide over the first 6 months of treatment (change in height standard deviation score [SDS] -0.2 [n=17] vs 0.003 [n=23], P=0.025).[166] Goserelin 3.6 mg and 10.8 mg both can effectively suppress pubertal development and decelerate height growth and bone age advance over 1–2 years of treatment,[165,167] although a retrospective study reported that to achieve adequate suppression, a larger proportion of patients required more frequent injections with goserelin 10.8 mg (71% [20/28] at 6–10-week intervals) than with goserelin 3.6 mg (44% [15/34] at 3-week intervals).[167] A cohort study observed that in patients receiving goserelin 10.8 mg, those with prior goserelin exposure experienced significant increases in peak LH and FSH between weeks 8 and 12, showing a significantly higher week-12 median peak FSH level compared to patients on *de novo* goserelin treatment (1.6 IU/L [n=15] vs 1.0 IU/L [n=24]); this waning of gonadotropin suppression towards the end of the treatment cycle likely underlies the need for more frequent injection.[168] Increases in BMI during goserelin treatment have been reported,[166,167,169] especially for goserelin 10.8 mg.[167] In a retrospective study of 46 girls with CPP or early puberty, mean BMI SDS increased significantly from 0.93 to 1.2 during treatment with goserelin 10.8 mg (median treatment duration: 2.9 years), but the mean BMI SDS returned to before-treatment level for the 11 girls who reached final heights (1.18 before treatment; 1.41 at the end of treatment; 1.16 at final height); notably, 9 of the 11 girls attained final heights within or above their target range.[169]

Safety and Tolerability

Goserelin is generally safe and well tolerated, especially if used with add-back therapy to attenuate the symptoms of the induced menopause-like state, such as hot flashes, night sweats, mood swings and vaginal dryness. The impact of prolonged goserelin treatment on BMD is the safety issue receiving most attention. Add-back hormonal replacement therapy (HRT) can help reduce the bone loss during long-term goserelin treatment. In young women with endometriosis or female cancers, the use of goserelin is generally associated with bone loss to some extent; add-back therapy can be used to counter this effect for patients with endometriosis but usually not for cancer patients. For treating adolescent

endometriosis with secondary dysmenorrhea or acyclic and/or cyclic pelvic pain, GnRH agonists can be used with caution, with age limits of 16 or 17 years old and with add-back therapy required;[170–173] some also consider it necessary to monitor BMD in adolescent patients at the end of 9–12 months of GnRH agonist treatment and at least every two years if the treatment is prolonged.[171] In patients aged >40 years with uterine myomas, significant bone loss (-4.4%–-7.6%) was observed after 12-month goserelin treatment, which was reversed slightly 6 months after treatment.[174] In a prospective randomized study, patients with chronic cyclical pelvic pain received goserelin 10.8 mg for 18 months with HRT initiated either immediately or with a 6-month delay.[175] Both groups showed similar BMD decreases at 18 months (-1.167%–-4.617% vs -2.990%–-4.730%), which were partially reversed 12 months after treatment cessation (-0.783%–-3.865% vs -2.992%–-3.290%).[175] In patients with breast cancer, 2-year OFS with goserelin without HRT led to a significant reduction in BMD (-5%), which partially recovered (by 1.5%) 1 year after treatment cessation.[176] In another prospective partially-randomized study of endometriosis, BMD reduction occurred during long-term goserelin use and was not fully recovered by up to 6 years after treatment, and use of HRT did not affect this process.[177] The lack of benefit of HRT on BMD recovery observed in that study may be attributable to bias introduced by the partially randomized design, in which patients could choose whether to receive HRT and only those without a preference were randomized.[177] More well-designed clinical research is warranted to reconcile these seemingly contradictory findings regarding long-term BMD recovery after goserelin treatment.

Conclusion

Goserelin has proved to be a reliable and versatile drug in an ever-expanding range of gynecological conditions. In benign gynecological conditions, goserelin provides rapid symptom relief, reduction of lesion and uterine sizes, facilitation of surgical therapy, and improved fertility outcomes. Its utility also extends to rare variants of benign gynecological conditions. In female cancers, goserelin plays an established role as adjuvant therapy in premenopausal patients with ER-positive breast cancer. Emerging evidence supports its use in fertility-sparing treatment of early-stage endometrial cancer and in the management of recurrent and/or advanced ovarian cancer, while its potential in cervical cancer and advanced or recurrent endometrial cancer awaits further investigation. Across oncology and benign indications, goserelin also provides ovarian function protection for patients at risk of ovarian toxicity from chemotherapy. Prolonged use of goserelin leads to BMD losses, which can be managed using add-back therapies, are partially reversible after treatment cessation, and are often outweighed by the benefits of goserelin treatment including improvements in patients' quality of life. Collectively, the expanding body of evidence underscores goserelin's continued relevance as a flexible and valuable agent in contemporary gynecologic practice.

Data Sharing Statement

No additional data available.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have no conflict of interest to declare.

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