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GnRH Agonists: Are They Ready for Clinical Use as an Anti-adhesive Agent? A Review of the Literature

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Authors' contributions

This work was carried out in collaboration between all authors. Author VVP designed the study and wrote the first draft of the manuscript. Author GK managed the literature searches and contributed to the review of the article. Authors IK, KK and IA reviewed the article. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

GnRH agonists have been shown to intervene in the mechanism of adhesion formation in a variety of ways. Influence on the hormonal state, the inflammatory and coagulation processes contribute to the reduction of adhesion formation postoperatively. Most studies on this topic have been conducted in animal models and have indicated the possible clinical use of GnRH agonists for this purpose. The aim of this study is to investigate the literature review of the mechanisms and the possible advantages of GnRH agonists therapy in the prevention of postoperative adhesions.

Keywords: GnRH agonists; adhesions; anti-adhesive agents; literature review.

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1. INTRODUCTION

Adhesions are defined as abnormal fibrous connections joining tissue surfaces in abnormal locations [1]. They usually come from tissue damage, caused by surgical trauma, infection, ischemia, exposure to foreign materials etc. [2]. Adhesions are classified into two categories; primary or de novo adhesions are freshly formed, on locations where no pathogenic processes ever took place, whereas secondary or reformed adhesions recur at the same location despite previous adhesiolysis [3,4]. As far as gynecologic surgery is concerned, adhesions can be differentiated on the basis of location, into intra-abdominal or intrauterine.

In studies of patients with major gynecological procedures, adhesions have been reported to occur in 60 – 90% of cases [5,6,7,8]. Clinical experience indicates that both quantity and quality of adhesions differ greatly between individual patients and cannot be predicted when surgical characteristics alone are taken into consideration. In general, adhesion formation increases with the patient's age, the history of previous laparotomies and various individual factors such as nutritional status or disease states such as diabetes or concurrent infectious processes, which impair leukocyte and fibroblast function [7,9,10]. As far as surgical technique is concerned, peritoneal damage should be avoided by careful tissue handling, meticulous haemostasis, continuous irrigation, whereas unnecessary drying, ineffective use of foreign bodies, and suturing or clamping of tissue should also be avoided. The use of fine and biocompatible suture materials, atraumatic instruments and starch-free gloves is also recommended. Starched gloves are a significant risk factor for postoperative adhesions. It has also been shown that there is a significant effect of surgical experience on duration of surgery. With experience, duration of surgery progressively decreases, and postoperative adhesions also decrease in extent, tenacity, type and total score. According to the above, surgical training and the respect of some basic principles ("Halstedian principles") are important for adhesion prevention [11,12].

Among the complications of adhesion formation stands infertility [13,14,15]; by some estimates, 25% of the infertile patients have adhesive disease, secondary to either operations or infections [16]. Pelvic pain [17,18], intestinal obstruction [19] and reduced quality of life (6) are also consequences of adhesion formation. Adhesions are responsible for readmission to hospital, additional more complicated surgical procedures [20] and consequently, increased surgical costs [6,21]. According to a study conducted in Scotland, women undergoing an initial open surgery for gynecological conditions had a 5% likelihood of being rehospitalized because of adhesions over the next 10 years, whereas overall, adhesions may have contributed to rehospitalization in an additional 20% of patients [22].

Taking into consideration the high prevalence of adhesions and the increased postoperative morbidity, many surgeons have tried to develop a variety of surgical techniques and use several agents; however, at least 50% of patients still develop significant adhesions. Research in adhesion prevention has strongly focused on the following: 1) prevention of the formation of the pathologic bridging connective tissue through the application of barrier films and viscous intraperitoneal solutions at the conclusion of surgery to wounded surfaces. 2) application of protective polymer solution coatings at the beginning and during the surgery to all surfaces and 3) anti –inflammatory , antifibrotic agents.

In this study, an attempt to investigate the possible role of Gonadotropin – releasing hormone (GnRH) agonists in adhesion prevention has been made since combined pre-operative and post-operative treatment with GnRH agonists has been shown to decrease adhesion formation and reformation in both animal models and clinical trials.

2. GnRH AGONISTS

2.1 General Information

Gonadotropin – releasing hormone (GnRH) was discovered in 1971 and since then a number of agonists and antagonists were developed throughout 1970s and 1980s for the treatment of a variety of conditions and diseases [23,24]. The effects of these drugs are mediated by modulating the concentration of circulating hypothalamic – pituary – gonadal (HPG) hormones. Chronic administration of GnRH agonists leads to continuous stimulaton of the pituitary, which produces an inhibition of the hypophyseal – gonadal axis. The latter is postulated to be due to the "down regulation" of pituary receptors for GnRH, desensitization of the pituary gonadotrophs and a

suppression of circulating levels of LH, FSH and sex steroids within 2 – 4 weeks [25]. These actions of all GnRH agonists are completely reversible on discontinuation of treatment [26,27].

Indications for clinical use of GnRH agonists include prostate cancer, endometriosis, uterine leiomyomas, central precocious puberty and IVF techniques. At the same time, GnRH agonists are contemplated for clinical use in Alzheimer's disease, functional bowel disease, polycystic ovary syndrome, premenstrual syndrome and short stature [28].

Overall, GnRH agonists are considered to be safe and tolerable drugs. The initial stimulatory effect on serum concentrations of LH, FSH and sex steroids is the biggest concern, since this can exacerbate the condition and worsen the symptoms at first, until hormone levels drop to postmenopausal/castration levels. General side effects are similar to symptoms experienced during menopause, including nausea, amenorrhea, decreased libido, depression, hot flashes/sweats, insomnia, headaches, weight gain and impotence. Additionally, fertility can be affected while on therapy, but a full reversibility is referred within 24 weeks after discontinuation. The largest risk is the potential loss of bone mineral density, since the sharp decrease in serum estradiol influences bone health. In addition, GnRH agonists therapy is accompanied by a 30% increased risk of heart disease. Therefore, recent studies focus on "add – back" hormone replacement therapy, in order to minimize these negative effects [26,27,29,30,31].

2.2 Mechanisms of Adhesion Prevention with GnRH Agonists

GnRH agonists interfere with the mechanism of adhesion formation in different ways (Table 1).

In a few words, adhesion formation includes the production of a serosanguineous inflammatory exudate rich in plasma proteins such as fibrinogen following increased permeability of blood vessels in the traumatized tissue and the simultaneous activation of the coagulation cascade. Under optimal conditions, these minor peritoneal attachments are absorbed within a few days through normal tissue repair [32]. If they persist for more than 3 days, fibroblastic proliferation may take place, resulting in adhesion formation. By day 5 the organisation of collagen bundles begins and small vascular channels with endothelial cells appear [33]. Consolidation of these collagen bundles with vascularised granulation tissue constitutes an adhesion.

Table 1. GnRH agonist therapy: functions preventing adhesion formation

- Induction of hypoestrogenic state
- Influence on neoangiogenesis : altered expression of
  1. vascular endothelial growth factor
  2. basic fibroblastic growth factor
  3. platelet-derived growth factor
- Reduction of the growth hormone (GH) release stimulated by GH-releasing hormone
- Alterations in the vascular resistance index, pulsatility index, and vascular peak velocity.
- Reduction in the degree of inflammation in the peritoneal cavity
- Increase in fibrinolytic capacity :
  - reduction of
  1. Plasminogen activator inhibitor (PAI)
  2. Thrombin activatable fibrinolysis inhibitor (TAFI)

-alteration in the balance of the matrix metalloproteinase (MMP) and matrix metalloproteinase inhibitor (MMPI) system

- Reduction of the basal rate of coagulation processes:

reduction of

1. factor V (FV) and
2. factor VIII (FVIII)

Among the mechanisms with which GnRH agonists contribute to prevention of adhesion formation stands the induction of a hypoestrogenic state. Hypoestrogenic condition in rats was found to be associated with decreased adhesion formation. Additionally, estrogen – dependent growth factors and growth modulators have been reported to play an important role in adhesion formation [34]. The modification in the expression of the vascular endothelial growth factor, basic fibroblastic growth factor, and platelet-derived growth factor through the treatment with GnRH agonists influences neoangiogenesis [35]. At the same time changes in the vascular resistance index, pulsatility index, and vascular peak velocity are

observed [36]. The above lead to avoidance of bleeding and consequently to reduction of fibrin and matrix for invasion by fibroblasts [37]. Reduction of the growth hormone (GH) release stimulated by GH-releasing hormone contributes also to reduction of adhesion formation. Furthermore, treatment with GnRH-a seems to reduce the degree of inflammation in the peritoneal cavity [38] and subsequent exudation. The effectiveness of GnRH agonists therapy is also mediated by a relative increase in the fibrinolytic capacity and a4 reduction of the basal rate of coagulation processes. GnRH agonists cause simultaneously a reduction of Plasminogen activator inhibitor (PAI), thrombin activatable fibrinolysis inhibitor (TAFI) , factor V (FV) and factor VIII (FVIII) and an increase in protein C (PC) level without any influence on a2 – antiplasmin levels and plasminogen [39]. Finally, Gonadotropin-releasing hormone agonist therapy suppresses this adhesiogenic induction of matrix metalloproteinase (MMP) activity while concomitantly increasing matrix metalloproteinase inhibitor (MMPI) activity. The net effect of this alteration in the balance of the MMP and MMPI system is a suppression of adhesion formation and reformation [40]. A schematic of the mechanism of action of GnRH agonists in adhesion prevention is shown in Fig. 1.

2.3 GnRH Agonists Therapy in Adhesion Prevention: Results in Human and Animal Models

A number of studies (Table 2) have been conducted since early 90's in an attempt to investigate the potential use of GnRH agonists as a method preventing postoperative adhesion formation. In general, their methodology includes the preoperative administration of a GnRH agonist, with leuprolide acetate being the most commonly used agent, or of other potential anti – adhesive agents or of no other substances. After a mean period of 6 weeks, the subjects undergo a surgical procedure, which normally results in adhesion formation. A postoperative dose of a GnRH agonist may either be administered or not. The adhesion score is evaluated with a second surgical procedure and the efficacy of the GnRH agonist treatment is estimated.

It has been shown that a 6 – month therapy with GnRH agonists might reduce fibrin generation and adhesion formation through the reduction of plasma levels of Plasminogen activator inhibitor (PAI) [41]. In a rat model, it was found that reduced adhesion scores were achieved through GnRH agonist therapy in cases of induced endometriosis and adhesions. More specifically, preoperative GnRH-a therapy reduced adhesion scores in rats with surgically induced endometriosis (mean +/- SEM; GnRH-a 1.1 +/- 0.2 versus control 2.2 +/- 0.2) and adhesions (GnRH-a 0.3 +/- 0.1 versus control 0.6 +/- 0.1).

Table 2. Studies evaluating the role of GnRH agonists in the prevention of adhesion formation

Authors	Study results
Winkler U et al. [41]	A 6 – month therapy with GnRH agonists • reduces the basal rate of coagulatory processes. • reduces the frequency and extent of fibrin-generating and degrading processes . • might reduce adhesion formation.
Wright JA et al. [40]	• GnRH agonist therapy achieves decrease of postoperative adhesion formation . • Reduction in adhesion reformation after adhesiolysis requires combined pre – and post- operative GnRH agonist therapy.
Montanino-Oliva M. et al. [43]	Administrarion of GnRH agonist +/- medroxyprogesterone acetate 3 weeks preoperatively leads to prevention of postsurgical adhesions.
Sharpe – Timms KL et al. [40]	• Presurgical GnRH agonists therapy suppresses the plasminogen activator activity. • Combined pre- and post- surgical GnRH agonist treatment suppresses plasminogen activator and matrix metalloproteinase activity, increasing at the same time the activity of both plasminogen activator inhibitor and matrix metalloproteinase inhibitor. • GnRH agonists inhibit the proteolytic milieu and in this way, they reduce or prevent adhesion formation.

Table 2 continued in the next page……

Canbaz MA et al. [44]	GNRH-a was successful in reducing postoperative adhesion formation but was not superior to intraperitoneal RL
Roberts JE et al. [50]	Administration of a GnRH agonist does not seem to influence postoperative adhesion formation or wound healing
Yoldemir T et al. [45]	• Leuprolide acetate should be used before and after surgery in order to minimize inflammatory response. • The combination of a GnRH agonist and a progestin enhances the antiadhesive effect of oxidized regenerated cellulose.
Imai A et al. [46] **Schindler AE [47]**	Optimal adhesion prevention is achieved when pre – and post – operative therapy for a 2 – 3 month period is administered.
Marshburn PB et al. [48]	• Preoperative GnRH agonist is more effective than Interceed in preventing surgical adhesions in the rabbit uterine horn. • Optimal results are achieved through the combined use of GnRH and Interceed.
Coddington CC et al. [51]	GnRH agonist pretreatment did not decrease postoperative adhesions after abdominal myomectomy.
Tamay AG et al. [45]	• The administration of GnRH agonist therapy leads to lower extent and severity of adhesions scores (The extent of adhesion scores were 1.85 ± 0.86 and 0.42 ± 0.64, whereas the severity of adhesion scores were 1.71 ± 0.91and 0.50 ± 0.75 for control, and GnRH-a groups, respectively) . • GnRH agonists are superior to GnRH antagonists (non significant difference)
Di Nardo MA et al. [39]	GnRH agonist treatment intervenes in the pathophysiologic balancing mechanism during adhesion formation : • simultaneous reduction in the levels of PAI, TAFI, FV, and FVIII. • increase in PC level • lack of modifications in plasminogen and a2-antiplasmin levels

It was also suggested that combined preoperative and postoperative GnRH agonist therapy but not postoperative GnRH agonist therapy alone was responsible for a reduction in adhesion reformation after adhesiolysis. In the endometriosis model, adhesion scores after adhesiolysis were: for the combined pre – and post – operative GnRH-a therapy 1.1 +/- 0.3 and for the control group: 1.6 +/- 0.7). The results for the adhesion model were 0.3 +/- 0.2 and 1.0 +/- 0.5 respectively [42]. Another study showed that the intramuscular administration of 0.75 mg of leuprolide acetate three weeks before surgery resulted in the reduction of adhesion scores in comparison to the control group. More specifically, the adhesion scores were 4.7+/- 0.6 and 6.3 +/- 0.5 respectively, with the difference being significant (P<0.05) [43]. Sharpe – Timms et al. suggest that alterations in fibrinolysis and extracellular matrix remodelling are the possible mechanisms through which GnRH agonists induce reduction in adhesion formation. More specifically, postoperative adhesion scores were 1.1 +/- 0.3 and 2.6+/- 0.2 for the endometriosis model (autologous uterine tissue sutured to the mesentery) receiving GnRH agonist treatment and diluent respectively ($p<0.05$). The values for the adhesion model (uterine resection) were 0.3 +/- 0.2 and 1.4 +/- 0.3 respectively ($p<0.05$). [40]. Canbaz et al. [44] suggested that GnRH agonists were useful in reducing postoperative adhesion formation in rat models, with the GnRH-a group having significantly lower average adhesion scores compared with the control ($P<0.001$). The average adhesion score for the GnRH-a group and the group whose peritoneal cavity was instilled with Ringer's lactate solution before abdominal closure were not significantly different. A rat model was also used to reveal that the combination of leuprolide acetate (GnRH agonist) and medroxyprogesterone acetate improves the antiadhesive effect of oxidized regenerated cellulose. It was suggested that either of these pharmacologic agents should be used before and after the operation in order to minimize inflammatory response. Additionally, the group which received 0.75 mg leuprolide acetate intramuscularly 3 weeks before surgery

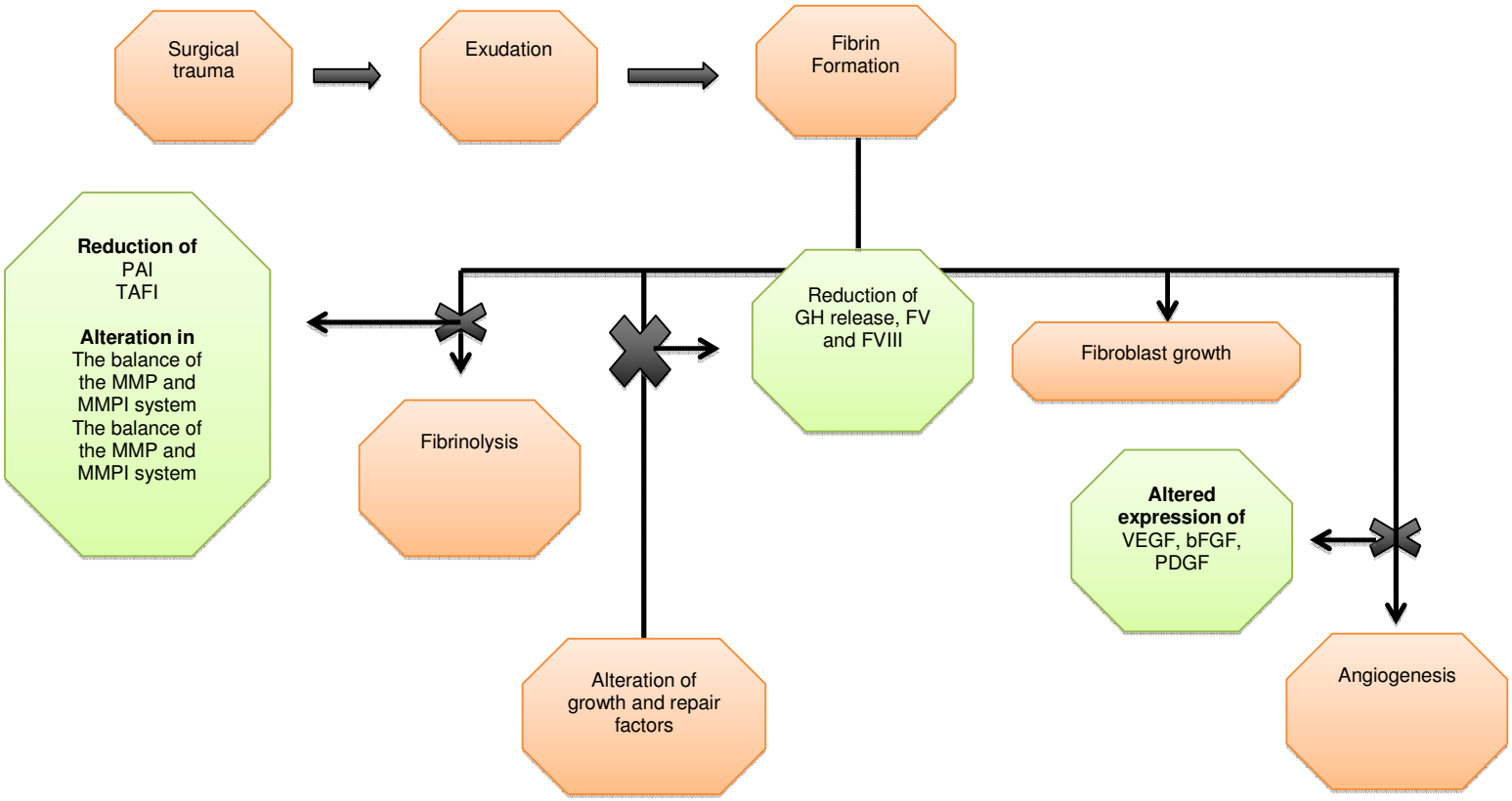

Fig. 1. Postoperative adhesions: Mechanism of formation and prevention with the use of GnRH agonists

Abbreviations: PAI: Plasminogen activator inhibitor, TAFI: Thrombin activator fibrinolysis inhibitor, MMP: Matrix Metalloproteinase, MMPI: Matrix Metalloproteinase Inhibitor System, GH: Growth Hormone, FV: Factor V, FVIII: Factor FVIII, VEGF: Vascular Endothelial Growth Factor, bFGF: Basic Fibroblastic Growth Factor, PDGF: Platelet Derived Growth Factor

had less severe adhesions than the control group (a < 0.0011) [45]. Imai et al. [46] in a prospective, randomised study showed that GnRH agonist therapy induces a shift to a more fibrinolytic activity mainly because of a decreased level of PAI (Plasminogen Activator Inhibitor) without changes in PA (Plasminogen Activator) level. GnRHa therapy (buserelin acetate, nasal 900 mg/day for 10 – 12 weeks preoperatively and for 4 weeks postoperatively) significantly reduced adhesion formation compared with control groups (adhesion scores; 0.2+/-0.4 vs. 2+/- 1, P < 0.0001). A similar study indicates that optimal adhesion prevention is achieved when pre – and post – operative therapy for a 2 – 3 months period is followed [47]. Preoperative leuprolide acetate (depot leuprolide acetate at a dose of 3.75 mg intramuscularly every 3 weeks for a 6-week treatment preoperatively) was found to be more affective than Interceed in the prevention of surgical adhesions in the rabbit uterine horn (p=0.002), whereas the combination of the two leads to optimal results due to reduction of microscopic tissue fibrosis [48].

When compared to control groups, GnRH agonists achieve better adhesion severity and extension scores. When GnRH agonists and antagonists come in comparison, the first ones are characterised by better adhesion extension and severity scores, which are not though significantly different. The above in combination with the higher cost of GnRH antagonists, makes them less appropriate for their use as anti-adhesive agents [49]. Through the investigation of the impact of gonadotropin-releasing hormone analogue (GnRH-a) on coagulation and fibrinolytic activities and its effectiveness on the prevention of pelvic adhesion after myomectomy it was shown that GnRH agonist treatment has important effects on the plasmatic levels of the fibrinolytic and coagulation parameters , thus leading to reduction of adhesion formation. The incidence, extent, and severity of adhesions were significantly lower in GnRH-a-treated patients compared with control group (P < 0.5) [39].

On the other hand, it was found that administration of a GnRH agonist does not seem to influence postoperative adhesion formation or wound healing in a rat model [50]. Coddington et al. [51] showed that patients who received placebo injections not only had fewer side effects (vasomotor symptoms) but also were characterised by a smaller adhesion area per centimeter of incision length into the uterus than the patients who received leuprolide acetate.

3. CONCLUSION

Adhesions is a common and potentially severe postoperative complication , which can have both short – term and long – term effects on a patient's life. The attempt to diminish the extent of this phenomenon has led to the application of new surgical techniques, barrier films and viscous intraperitoneal solutions, protective polymer solution coatings and to the administration of pharmacological agents. Among the pharmacological agents stand GnRH agonists, which have a variety of indications and their role is investigated in a number of diseases. Most of the studies conducted up to now have shown that a combined pre – and post – operative therapy with intramuscular GnRH agonists can lead to postoperative adhesion prevention. Their role in adhesion prevention should be further studied and a comparison to the newest anti-adhesive therapies should be conducted. Taking into account the already established indications of these drugs, their clinical use alone or in combination with other anti-adhesive agents should also be considered in an attempt to further ameliorate the results as anti-adhesive treatment.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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