Antagonist use in intrauterine insemination (IUI) cycles

İntrauterin inseminasyon sikluslarında antagonist kullanımı

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Abstract

Intrauterine insemination is the first method of treatment for many causes of infertility, mainly unexplained infertility,male subfertility, and ovulatory dysfunction.Despite its popularity, the effectiveness of IUI treatment is not consistent,and the role of IUI treatment in practice protocols has not been clarified.The success of IUI depends on a number of parameters linked both to the pathology underlying the infertility and to the treatment.The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. One of the challenges to optimize the COS/IUI outcomes is to prevent the occurrence of the premature LH rise and consequent luteinization.24% of IUI cycles suffer from premature LH surge.The potential beneficial effect of a GnRH antagonist on pregnancy rates in IUI cycles, while preventing prematureLH surge, has not been adequately assessed.Administration of a GnRH antagonist almost completely abolishes premature luteinization but does not substantially improve the pregnancy rate.Co-treatment with GnRH antagonists can be restricted to the time in the cycle where there is a risk of a premature increase in LH.

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Key words: Premature LH surge, Intrauterine insemination (IUI), GnRH antagonist

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Özet

İntrauterin inseminasyon (IUI) başta açıklanamayan infertilite, erkek subfertilitesi ve ovulatuvar disfonksiyon olmak üzere birçok infertilite nedeninde ilk kullanılan tedavi seçeneğidir. Popülerliğine rağmen intrauterin inseminasyonun etkinliği kanıtlanmamıştır ve protokollerdeki yeri netleştirilmemiştir. IUI'nun başarısı altta yatan infertilite patolojisi ve tedavi ile ilişkili bazı parametrelerle ilişkilendirilmiştir. Reprodüktif siklustaki midsiklus LH salınımı merak uyandırıcı bir endokrinolojik olaydır. KOH/IUI sikluslarının optimum olabilmesi için aşılması gereken zorluklardan biri de erken LH artışının ve takip eden lüteinizasyonun önlenmesidir. IUI sikluslarının %24'ünde erken LH artışı gözlenir. Prematür LH salınımını azaltan GnRH antagoistlerinin IUI sikluslarındaki gebelik oranları üzerine etkisi yeteri kadar araştırılmamıştır. GnRH antagonisti uygulaması erken lüteinizasyonu engellerken gebelik oranını arttırmamaktadır. GnRH uygulamaları siklus içinde erken LH artışı riskinin en fazla olduğu zaman dilimi ile kısıtlanabilir.

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Anahtar kelimeler: Erken LH artışı, intrauterin inseminasyon (IUI), GnRH antagositleri

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Intrauterine insemination (IUI) is the first line technique for many conditions of infertility such as unexplained infertility, mild male factor infertility and minimal or mild endometriosis. It is accepted as a stop-gap treatment while waiting for, or instead of, in vitro fertilization (IVF).The first paper entitled "intrauterine insemination (IUI)" was published in 1962 (1). Since then, IUI has evolved through innovations such as sperm preparation, monitoring for pre-ovulatory timing and induction of ovulation with human chorionic gonadotrophin (hCG). Despite the fact that it has not been classified as an assisted reproductive technique (ART) (2, 3), it is widely used, often as an empirical treatment, for a broad range of profertility indications. The European IVF Monitoring Programme in 2004 reported 98 388 IUI cycles from 19 countries leading to 12 081 births (12.3% per cycle), of which 87% were singleton and 13% were multiple births (4). Several studies have demonstrated that IUI with controlled ovarian stimulation (COS) is superior to IUI alone (5-14).

The success rate of IUI with ovulation induction varies widely, with pregnancy rates ranging between 8 and 18% per cycle (7, 8, 15-17). These discrepancies in pregnancy rates found among the various published studies are due to the selection of patients, duration of infertility, aetiology of infertility, sperm preparation, total number of motile sperm inseminated, number of inseminations, monitoring of the cycle, timing of IUI and protocols of ovarian stimulation.

The midcycle LH surge in the reproductive cycle is an intriguing endocrinological phenomenon. The exact time at which ovulation occurs after LH surge begins cannot be known earlier. It varies from 24 to 56 hours. Oocyte-fertilization capacity and sperm lifetime are <1 day and 1.4 days, respectively. Insemination needs to be performed close to ovulation time, and accurate synchronization is compulsory. The LH surge can occur in various follicular sizes, and individual follicular maturation adds to the risk of trial failure. Urinary LH recording may present false-negative results when peak LH concentrations are low (<40 IU/L). One of the challenges to optimizing the COS/IUI outcomes is to prevent the occurrence of the premature LH rise and consequent luteinization which, as is well known, is a possible complication of stimulated cycles (18-21). It has been calculated that 24% of IUI cycles suffer from premature LH surge (20) and this can result in IUI

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procedure cancellation. Obviously, this represents economic and psychological stress for the patients. Increasing E2 levels may induce an LH surge, with disastrous effects for follicular progress and growth. If a fertility facility and a clinician are available, IUI can be timed according to LH levels. Otherwise, LH rise leads to cycle cancelation. This is especially important if premature luteinization takes place on Friday and a weekend insemination is impossible. For that reason, some authors have administered a GnRH antagonist that rapidly inhibits LH rise. The exact details of the mechanism in many species, including humans, are still not known, while it is known that central signalling by hypothalamic GnRH is permissive (22). Complete blockade of the GnRH receptor terminates the periovulatory LH surge, although alterations in the magnitude of GnRH secretion are not crucial for timing and size of the LH surge (23). The LH surge is an absolute requirement for luteinization, final maturation of the oocyte and follicle rupture. It is obvious, too, that the organ containing the mature, ready to ovulate, follicle(s) should send out the crucial signals. Indeed, most data indicate that the timing of the occurrence of the LH surge is governed by signals from the ovaries (22). The main signal is presumably the progressive rise in estradiol secretion from the dominant follicle. The positive feedback of estradiol comes from progressive pituitary sensitization to GnRH in combination with a progressive and time dependent increase in estradiol levels. Several mechanisms underlie this phenomenon: first, estrogen enhances pituitary sensitivity to GnRH; second, non-esteroidal ovarian compounds such as activin increase in concentration, whereas gonadotrophin surge inhibiting factor decreases (24); and third, subtle rises in progesterone concentration may augment LH secretory sensitivity to GnRH (25). A premature LH surge can be defined as a premature rise in LH (>10 IU/l) accompanied by a concomitant rise in progesterone (>1μg/l-3.2nM/l)(26).Premature LH surge in the natural cycle seems very rare (27), but may be more frequent in older women since their maximum follicle diameter at the time of ovulation is substantially smaller (27, 28). Premature LH surges also occur in 25-30% of stimulated IUI cycles (26, 29) and theoretically may interfere with timing of the IUI or result in cancellation and more treatment failures.

GnRH agonists have been the standard of care for more than a decade in reducing the incidence of premature LH surge by reversibly blocking pituitary gonadotrophin secretion in IUI stimulated cycles (15, 30-32). Nevertheless, these drugs are nowadays completely abandoned in IUI cycles because of the excessive follicular simultaneous selection they cause (with consequent higher incidence of multiple pregnancy and OHSS) and because of the long pretreatment period required. As an alternative to GnRH agonists, GnRH antagonists have been proposed to prevent the premature LH surge during IVF cycles (33, 34) and COS/IUI treatments (28, 35-38). These drugs do not produce a flare-up effect reducing synchronous follicular pool recruitment. Moreover, the potential advantage of a GnRH antagonist is that pituitary gonadotrophin secretion is suppressed immediately after the start of therapy. GnRH antagonists are easy to incorporate in a IUI scheme by adding it either in a fixed (day 6) protocol or in a flexible protocol. Antagonists, on either a fixed or a flexible protocol, have been proven successful in suppressing LH rise in superovulated cycles. In addition, GnRH antagonists can be safely administered in IUI cycles without compromising the luteal phase (35). In this study, lower midluteal E2 was observed in the antagonist group than in the control group, but this had no effect on progesterone concentration and pregnancy rates. Controversial evidence exists about the adverse effects of GnRH antagonists on the endometrium and oocyte quality. Some studies show that the administration of GnRH antagonist does not impose adverse effects on the endometrium (39), while others show that endometrial maturation may be accelerated by three days through genetic changes (40). In FSH-stimulated cycles, rapidly rising estradiol levels induce premature LH surge in immature follicles, but in milder stimulated cycles the process of natural LH surge allows better follicle maturation and a higher chance of pregnancy. So, the administration of GnRH antagonist could be useful in these patients. Furthermore, because LH surge could last up to two days in some women, it is better to trigger ovulation by HCG after onset of the surge, thereby increasing the chance of pregnancy (41). Therefore, co-treatment with GnRH antagonists can be restricted to the time in the cycle where there is a risk of a premature increase in LH. Probably, premature luteinization is not the cause but one of the consequences of the poor quality of growing follicle (Fig. 1) (26). In seven RCTs, the aver-

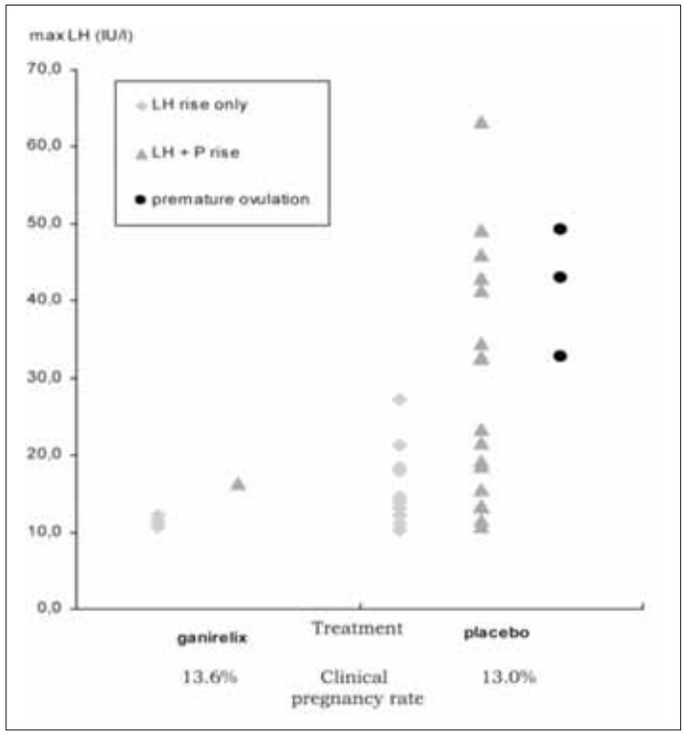

Figure 1. Premature LH surge during mild FSH stimulation with and without antagonist (203 cycles) (26). Max LH (IU/l) is shown in subjects treated with either ganirelix or placebo and having premature LH rises only, premature LH and progesterone and premature ovulation

age ongoing pregnancy rate was only 5.3% greater with GnRH antagonist treatment (95% CI: 1.5, 9.2). This means that it would take 20 cycles of GnRH antagonist administration to have one pregnancy more than without GnRH antagonist treatment (Fig. 2). From the randomized controlled trials of this meta-analysis, it is clear that allowing for follicle growth and avoiding premature LH rise, increased pregnancy rates are observed with GnRH antagonist administration. A parallel trend for multiple pregnancy rates in the GnRH antagonist group was observed, although this did not reach statistical significance. This meta-analysis of early data might enhance further research in this direction (42). There is also another study showed that OC pretreatment afforded flexibility in scheduling, while a reduced dose of ganirelix avoided excessive suppression of LH. The excellent results in this pilot study for IUI suggest this regimen could be further evaluated for scheduling IUI and IVF cycles (43).

Recent studies have already reported higher mean follicular diameter and no difference in pregnancy rates, whereas others reported a difference in pregnancy rates after GnRH antagonist administration. However, the incremental cost of antagonist administration and the possibility of not improving pregnancy outcome must be considered. This might add to the reluctance to adopt this technique as a standard method of treatment in IUI superovulated cycles. The small size of studies performed until now and the different schemes for antagonist administration might further reinforce this reluctance. The potential beneficial effect of GnRH antagonist on pregnancy rates in IUI cycles, while preventing premature LH surge, has not been adequately assessed. For the GnRH antagonist administration group, higher pregnancy rates are observed when all RCTs that reach statistical significance are synthesized (Fig. 3A). For both regimens (ganirelix and cetrorelix), a trend for higher pregnancy rates was observed. When examining for multiple pregnancy rates, a trend for difference is observed between the two groups, favoring antagonist administration (Fig. 3B, 3C). The results of the clinical pregnancy rates in this meta-analysis are consistent with the studies done by Allegra et al. and Gomez-Palomares et al. (30, 37). On the other hand, when an evaluation of the clinical significance of antagonist coadministration was performed, 4 (95% CI 3-6) patients were needed to treat to prevent an additional LH rise and 19 (95% CI 10-81) patients to achieve an additional pregnancy. In trying to interpret these results, the use of an antagonist superovulated IUI scheme may be justified when an LH rise is expected, e.g., previous cycle LH rise, avoidance of insemination during weekend, or big follicles required. The use of such a scheme over the currently used scheme cannot be justified to increase pregnancy rates. This meta-analysis consists of six trials with 1,069 subjects. Data are pooled for all infertility groups, and no results can be drawn specifically for each group. From this meta-analysis, increased duration of therapy is observed, although this did not reach statistical difference. None of the studies included in the meta-analysis mentioned side effects from this increased duration of therapy. It is not evident whether this increased duration was responsible for the positive effect on pregnancy rates. Certain issues need to be addressed by future clinical research. Further research is needed to identify which group of patients will benefit from adding GnRH antagonist to an IUI scheme. Older patients with short follicular phase and reduced ovarian reserve might benefit. Also for women with reduced ovarian reserve, premature luteinization occurs more frequently. This is due to defective production of gonadotropin surge attenuating factor (GnSAF). On the other hand, a prolongation of follicular phase might allow for an increased number of mature follicles, which may enhance the possibility of pregnancy. In addition, patients with a previous cancelled cycle because of premature luteinization are candidates for this treatment. It is controversial whether this protocol can be used for a weekend- free IUI. During the weekend, small fertility clinics do not have a clinician available to perform the IUI. If the patient chooses such a small clinic for her treatment, she is at risk of having the added cost of antagonist. In the case that she undergoes three or more cycles, that increased cost may be significant. Cost-effectiveness analysis must be conducted in each center that uses this protocol. In most European countries, the cost of treatment cycles is covered by government funds. In addition, trained fertility nurses

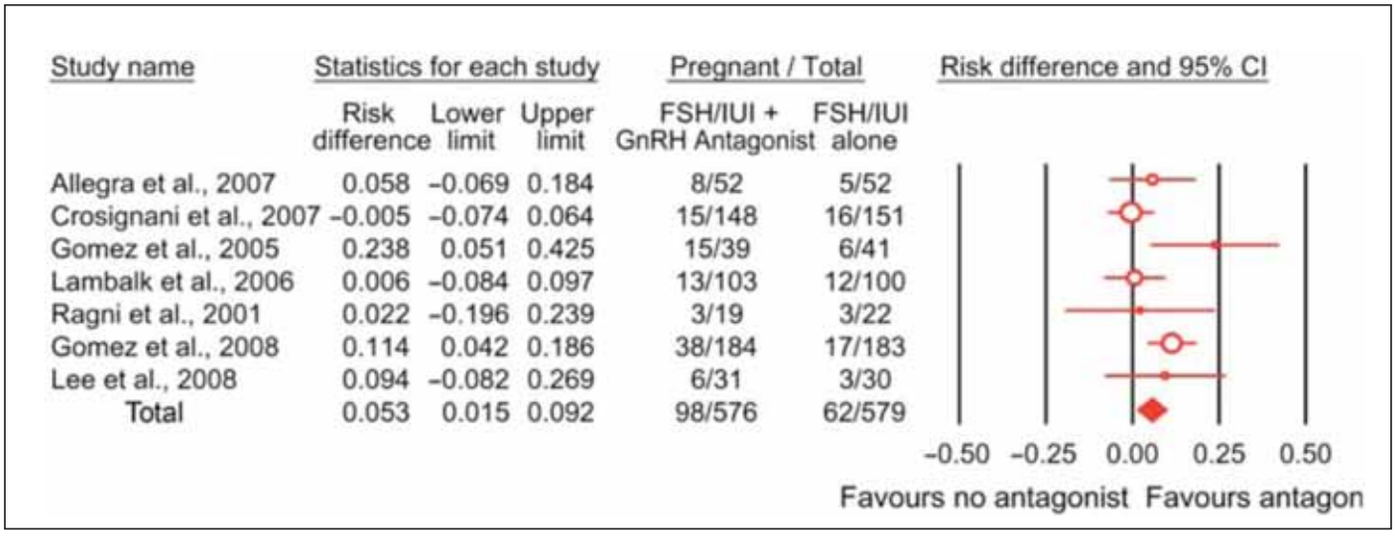

Figure 2. Ongoing pregnancy rate per couple with one cycle of FSH/IUI with and without GnRH antagonist treatment

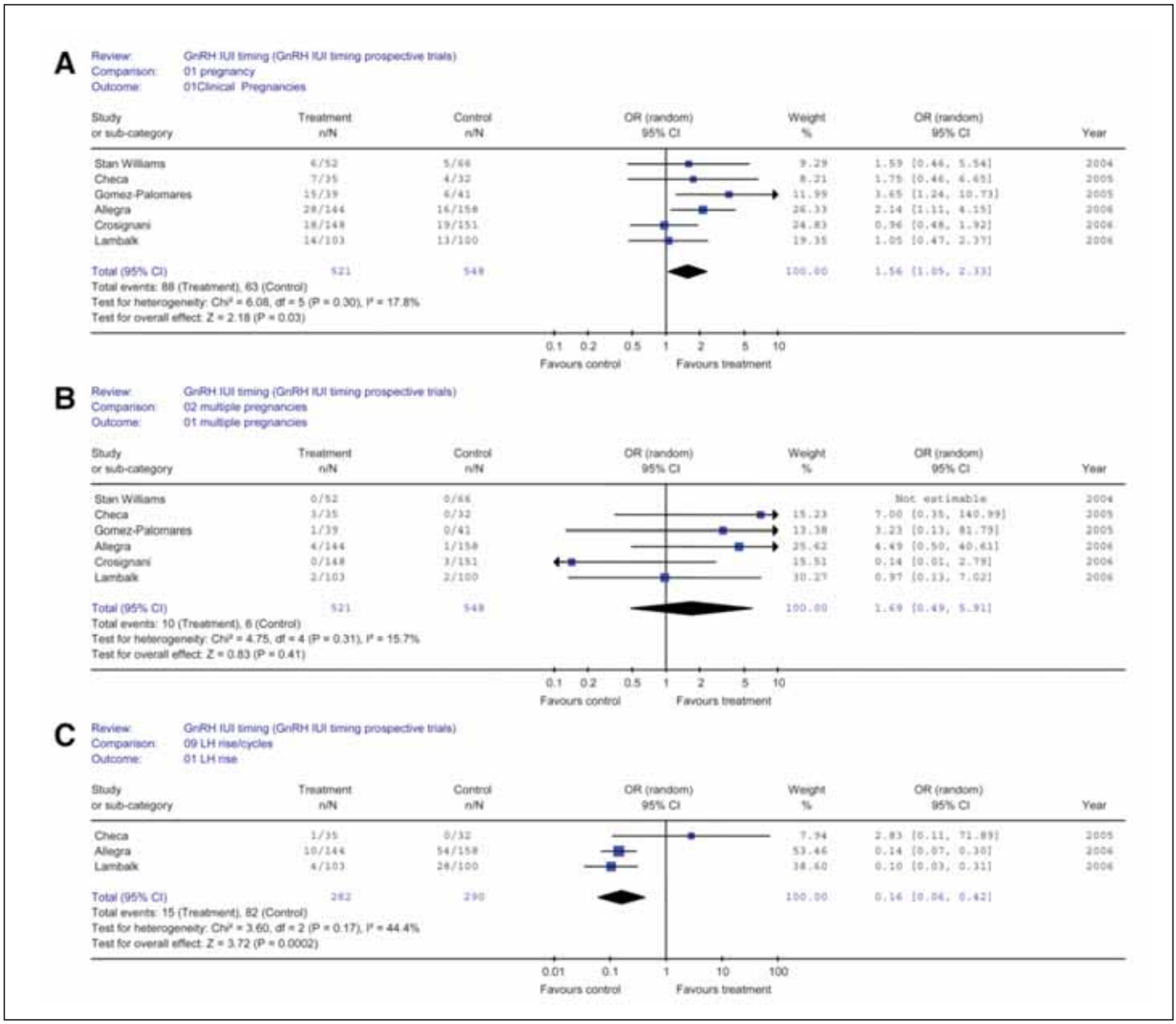

Figure 3. (A) Overall results of GnRH antagonist administration vs. control for intrauterine insemination (IUI) timing after a gonadotropin regimen and the odds for pregnancy. (B) Overall results of GnRH antagonist administration vs. control for IUI timing after a gonadotropin regimen and the odds for multiple pregnancy rates. (C) Subgroup analyses for LH rise after GnRH antagonist administration vs. control for IUI timing in a gonadotropin regimen. In all panels, each study is shown as an odds ratio estimate, with whiskers corresponding to 95% confidence intervals, and studies are ordered by year of publication. (Kosmas. GnRH antagonists for IUI timing: a meta-analysis. Fertil Steril 2008)

can perform the IUI. It is obvious that it is not an issue of an available clinician but rather of an available team and the willingness to provide extensive care. Follicle-stimulating hormone for ovulation induction in IUI has to be used as a second-line treatment (24). When this scheme is chosen, the addition at the end of GnRH antagonist and the cycle prolongation might increase pregnancy rates. Thus, prolongation of follicular phase and further follicular maturation may be important for pregnancy rates. In conclusion, more studies are needed on improving pregnancy rates in IUI superovulated cycles. It seems that antagonist schemes can help in this effort.

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