Usage of Cetrorelix Acetate in Assisted Reproductive Technologies

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Background and Objective of the Survey

Cetrorelix acetate is a gonadotropin-releasing hormone (GnRH) antagonist used in assisted reproductive technologies (ART), particularly in in vitro fertilization (IVF) cycles, to prevent premature ovulation and optimize the timing of oocyte retrieval.

In ART, controlled ovarian stimulation (COS) is initiated to stimulate the ovaries to produce multiple follicles containing mature oocytes. This is typically achieved using gonadotropins, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), administered via subcutaneous injections. However, in order to prevent premature ovulation (i.e., release of mature eggs before they can be retrieved), GnRH antagonists like cetrorelix acetate are introduced during the COS process.

Cetrorelix acetate acts by competitively blocking the GnRH receptors on the pituitary gland, thereby suppressing the secretion of LH. By inhibiting the surge in LH that triggers ovulation, cetrorelix acetate helps to maintain the optimal timing for oocyte retrieval during IVF cycles.

The timing of cetrorelix acetate administration is critical, and it is typically initiated once the leading follicle reaches a certain size (e.g., 12-14 mm) as determined by transvaginal ultrasound monitoring. Cetrorelix acetate is administered subcutaneously once daily until the trigger for final oocyte maturation (e.g., human chorionic gonadotropin, hCG) is administered to induce ovulation and allow for oocyte retrieval.

The objective of the survey is:

To study the usage of cetrorelix acetate in assisted reproductive technologies

Methodology of the Survey

A survey was conducted to study the usage of cetrorelix acetate in assisted reproductive technologies. A total of 50 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- The advantages of using GnRH-a in the final oocyte maturation
- Role of GnRH -a trigger to control OHSS
- GnRH -a trigger and all freezing embryos (Segmentation of cycle IVF)
- Luteal phase support following GnRH-a trigger
- American approach, Intensive LPS
- European approach (GnRH-a in combination with hCG supplement)
- Cetrorelix
- Pharmacology
- Pharmacodynamics
- Pharmacokinetics
- Clinical efficacy

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Gonadotropin-releasing hormone agonist (GnRH) is secreted from the mediobasal of the hypothalamus in the follicular phase of the menstrual cycle in a periodic pulse and is discharged into the pituitary portal system and bound to its receptors on gonadotroph cells in the anterior pituitary. Following, low and pulse release of follicular stimulating hormone (FSH) and luteinizing hormone (LH) happens which is necessary for the follicular growth and the ovarian secretion of estrogen. In the mid-cycle, in the presence of high levels of estrogen and low increased levels of progesterone, sudden surge of gonadotropins especially LH takes place which induces ovulation after 36-40 hrs.

Assisted reproductive technology (ART) consisting in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI) are based on the exact timing of ovulation, oocyte pick-up before ovulation and then insemination of oocyte. Due to biological activity of human chorionic gonadotropin (hCG) similar to LH, since the mid-1970s exogenous hCG has been used to trigger the final oocyte maturation. The release of oocyte occurs usually 36-40 hours after induction of ovulation similar to natural ovulation.

Stimulation of the gonadotropin surge for the final oocyte maturation in the midcycle was investigated in the 1970s and then by several research groups in the 1990s. As early as 1973, in Japan, Nakano et al. illustrated that ovulation in human could be induced by infusion of 600 µg GnRH synthetic for 6 hours and then followed by single dose 400 µg subcutaneously. However, some researchers have suggested that GnRH antagonist cycles may increase the hypophysis sensitivity in response to GnRH-a triggering.

In various studies using a dose or more GnRH agonist was proposed in the mid-cycle for gonadotropin surge stimulation. In this way it was observed that release of both gonadotropins, LH/FSH, was similar to natural condition; as well shorter duration of increasing LH avoids incidence of ovarian hyperstimulation syndrome (OHSS). In this review, based on existing studies on GnRH-a triggering, the advantages, problems, and also ways to reform its complications would be addressed.

The advantages of using GnRH-a in the final oocyte maturation[1]

In some studies, the use of GnRH-a in the final oocyte maturation has similar or better results compared to hCG trigger. Unlike hCG trigger, GnRH-a trigger stimulates FSH surge in addition to LH surge. FSH surge, in the mid-cycle, has a specific effect on oocyte maturation and leads to a further expansion of cumulus cells surrounding the oocyte and release of proteolytic enzymes involved in the process of ovulation. Lamb *et al* by adding a dose of FSH to the hCG trigger, showed better recovery of oocyte and higher fertilization rates in IVF compared with hCG trigger alone. Another advantage of this method is more maturity of the nucleus and the resumption of meiosis and eventually increasing the number of Metaphase II oocytes. In addition, increased levels of LH following injection of hCG is slower than that following GnRH-a trigger. Overall, GnRH-a trigger with effects of FSH along with the LH in the final follicular maturation, may result a more physiological maturity. Likely, more maturity of oocyte might be related to increase faster in LH surge compared with an increase of LH after 10.000 IU IM injection of hCG and also a concomitant increase of FSH.

GnRH-a decreases significantly the risk of OHSS and gradually is used in most clinics to induce final oocyte maturation in patients with the risk of OHSS. Although a few case of OHSS following GnRH-a trigger can be seen in the literature, in general using GnRH-a trigger, almost declines the risk of OHSS as a complication of ovarian stimulation by gonadotropins and its incidence is less common than hCG trigger. Also, by diminishing OHSS following GnRH-a trigger, health care costs would be decreased. It seems that in the patients who are at risk of OHSS, GnRH-a trigger instead of hCG trigger provides an opportunity to continue the cycle and fresh embryo transfer. In the past, this protocol was followed to freeze all embryos in many cases. Recent modifications of luteal phase after GnRH-a trigger make it possible to transfer embryo in the same cycle for many women at the risk of OHSS and provide a good outcome.

In addition, reduction of immature oocyte syndrome is as a result of GnRH-a trigger. Immature oocyte syndrome is defined as a situation that more than 25% of oocyte retrieval after ovarian stimulation in IVF/ICSI cycles are immature despite the right prescription of hCG for triggering and accurate time of oocyte collection. Following this syndrome, there will be lower pregnancy rates with causes less known. In a recent study of 27 women with a prior history of the immature oocyte syndrome resulting from hCG triggering, in their next cycle the mixture of GnRH-a (leuprolide acetate, 1 mg) and hCG (5.000-10.000 IU) were used to trigger resulting

to retrieve more metaphase II oocytes which was significantly higher compared to previous cycles. Consequently, the high quality embryos for transfer were obtained.

Role of GnRH -a trigger to control OHSS[1]

OHSS is the most serious complication and potentially fatal caused by controlled ovarian stimulation (COS) in ART. The biggest cause of OHSS is the presence of hCG, so that in early OHSS, the cause is exogenous hCG while delayed OHSS is often due to production of endogenous hCG following the pregnancy. HCG and LH activate the LH receptors, although the half-life of LH is less than 60 minutes, while hCG half-life is more than 24 hours. The long half-life and sustainable luteotrophic activity of hCG raise significantly vascular permeability stimulated by vascular endothelial growth factor (VEGF) as the major vascular mediator of OHSS. In order to decline the risk of OHSS, several strategies have been introduced, such as coasting technique, in vitro maturation (IVM), and finally GnRH-a triggering. In coasting technique, stopping the ovarian stimulation lead to dropping estrogen levels and induced atresia in the smaller follicles to reduce the incidence of OHSS. Unfortunately, this method has medium effect on the incidence of OHSS, and fewer oocytes often grew compared to those without coasting or even compared with GnRH-a trigger.

Another method to prevent OHSS is oocyte collection while most follicles are still small. This method, named IVM, can increase the number of immature oocytes. At present, researchers propose to use GnRH-a trigger instead of hCG trigger in patients of IVF/ICSI cycle with antagonist protocol and at high risk of OHSS, thus the possibility of achieving a greater number of mature oocytes from patients of high responder with low risk of OHSS is provided.

The most main clinical advantage of GnRH-a trigger is a potential to induce a rapid and reversible luteolysis and therefore decreasing the risk of OHSS progression. On the other hand, this is concomitant with severe luteal phase defect resulting from a short period of the induced LH and FSH peak. besides, it particularly inhibits the secretion of vasoactive products, especially VEGF, from the corpus luteum.

Recent studies have shown that gonadotropin and steroid levels during the luteal phase were significantly different in patients triggered by GnRH-a from hCG. Furthermore, the gene expression of enzymes involved in steroidogenesis, estrogen and progesterone, at the time of oocyte collection in patients with GnRH-a triggering to final oocyte maturation is less than

hCG triggering. In addition, a significant reduction of VEGF expression in patients receiving GnRH-a is obvious that can explain the cause of prevention of early OHSS. Although few cases of OHSS after GnRH-a trigger have been reported, it can be stated that trigger with GnRH-a without hCG approximately eliminates early OHSS.

In the largest RCT study performed up to now 266 women at the low risk of OHSS (≤14 follicles ≥11 mm) in a cycle of IVF/ICSI were divided into two groups on the trigger day; in the first group a bolus of 0.5 mg GnRH-a (buserelin) was administered while in another group 5.000 IU hCG was given. Women in the group triggered with GnRH-a had developed a mean of 8.1 follicles compared with 7.7 in hCG group. In the GnRH-a trigger group, following the trigger a bolus of 1.500 IU hCG in the oocyte retrieval day and another bolus of 1.500 IU hCG on oocyte retrieval +5 days to maintain the luteal phase were administered. In addition, the patients in two groups received the standard luteal phase support including oral estradiol and vaginal progesterone. In this study, although the ongoing pregnancy rate (OPR) did not differ between two groups, two cases of delayed moderate OHSS was reported in the first group.

In 2011 another study by koll *et al* was carried out on the effects of GnRH-a trigger in 15 women at low risk of OHSS with a history of previous IVF failure. The patients received one bolus of GnRH-a (triptorelin; decapeptiyle, Ferring) 0.2 mg for the final oocyte maturation and then to support the luteal phase, two boluses of 1.500 IU hCG were administrated, one day and four days after oocyte retrieval, respectively. These patients were not recieved any medication for luteal phase support. OPR was reported 47% and no cases of OHSS were found.

To determine whether GnRH-a trigger in women at high risk of OHSS is safe or not, a clinical trial consisted of 118 women was conducted. In this RCT, triggering was done in one group with hCG and in another group using GnRH-a. On average 14 oocytes were taken in above mentioned groups. OHSS was reported to be 3% in women with hCG trigger and no cases of OHSS were seen after GnRH-a trigger. Similar studies were performed by Tremellen and Radesic and lliodromiti *et al* in which a high level of OPR and low levels of abortion were reported in GnRH-a trigger group, resulting in both studies for delayed OHSS 1.4% and 0.72%, respectively.

Considering all studies, it can be concluded that GnRH-a trigger followed by a small bolus of hCG and embryo transfer in the same cycle prevents developing OHSS in high risk women (the average of 25 follicles or less with 11 mm in diameter). With this method in high responders (with an average of 17-18 oocytes), a significant decline can be seen in expected

OHSS. However, further studies determine the maximum number of oocytes and embryos to transfer in the same cycle will be necessary.

GnRH -a trigger and all freezing embryos (Segmentation of cycle IVF)[1]

Freezing all oocytes or embryos after GnRH-a trigger and transferring in the next cycle has recently been proposed that is called segmentation of IVF cycle. This procedure has been used with very good results in women who were exposed to risk of OHSS and also in women who needed fertility preservation. Moreover, another advantage is that the avoidance of embryo exposure to high concentrations of steroids following ovarian stimulation, which damages the endometrial receptivity and also are embryotoxic. Human studies have provided evidence of histologic changes in the endometrial tissue during implantation and in the development of the placenta following ovulation stimulation as well.

In some studies on normal responders who were at low risk of OHSS, OPR in the segmentation group was significantly higher than that when embryo transfer was done in the same cycle. Furthermore, a meta-analysis study support segmentation cycles to show that pregnancies resulting from frozen-thawed embryo transfer (FET) in IVF has better obstetric and perinatal outcomes than fresh embryo transfer. It is necessary to note that segmentation cycle requires very precise planning in the process of frozen-thawed embryo which is not available in all IVF centers. In addition, a number of researchers have reported a high rate of pregnancy loss, fetal abnormalities and epigenetic changes in FET cycles. At present, few studies have focused on the children resulting the FET cycles. For most patients and clinicians, embryo transfer in the same cycle leading to a healthy child is still the standard and preferred method of IVF.

Luteal phase support following GnRH-a trigger[1]

As noted earlier, a bolus of hCG first induces oocyte maturation, follicle luteinization and finally causing production of endogenous progesterone for implantation. Despite the removal of large quantities of granulosa cells in the oocyte retrieval, the corpus luteum under the influence of hCG is able to release efficient progesterone in order to stimulate uterus changes for embryo implantation. So, hCG trigger has provided a simple method in the clinic for fresh embryo transfer. This conventional method has been modified by another trigger, GnRH-a, which unlike hCG, does not affect the early luteal phase. On the other hand, the GnRH-a trigger

reduces LH levels through pituitary down-regulation, so that the amount of LH is inadequate for continuing the function of the corpus luteum. The reduction of the activity of the corpus luteum caused to decrease the progesterone levels in luteal phase which is very low for optimal embryo implantation. Therefore, the use of GnRH-a trigger without accurate luteal phase support causes a decrease in pregnancy rate. The preliminary results of the administration of GnRH-a trigger for final oocyte maturation revealed unsatisfactory results so that the high rate of pregnancy loss was associated with a significant reduction in OPR.

In 2006, the initial meta-analysis of three RCTs reported a significant decrease in pregnancy and raise in the pregnancy loss. But further investigations revealed that these disappointing results was due to the utilize of standard luteal phase support following GnRH-a trigger. As well, after COS, supraphysiologic levels of estrogen and progesterone directly inhibit LH secretion from the pituitary and has a negative feedback effect on the hypothalamic-pituitary axis.

During the luteal phase, LH performs a significant role not only in performance of corpus luteum but also in increasing the expression of growth factors and cytokines which implicated in the initial implantation. Following the failure of corpus luteum, serum levels of estrogen and progesterone significantly decrease which have adverse effects on endometrial receptivity in luteal phase. The mean of the luteal phase period without the use of supportive agents maybe very short after GnRH-a trigger for oocyte donors (about 4 days) in comparison with common hCG trigger (13 days) that shows a defection in corpus luteum function.

Beal *et al* suggested that in GnRH-a trigger cycles, post-monitoring following oocyte pick up is crucial and if insufficient response of LH was observed, booster dose of hCG must be used. The least effective LH serum levels is 12-15 IU/L about 12 hours after the trigger while the most desired result is obtained when the amount is 50 IU/L. Despite using intramuscular progesterone as supplementation in luteal phase support, the progesterone, like estradiol, had reduced levels. An important point is to adopt strategies to advance luteal phase steroid profile that raise endometrial receptivity in order to increase the rate of live birth to an acceptable level devoid of OHSS risk progression.

American approach, Intensive LPS[1]

Recently, the idea of luteal phase support using just steroids after GnRH-a triggering in patients with a raised risk of OHSS has been proposed. This concept was first introduced by Babyof et al in 2006 and again in 2008 by Enegman et al. In order to achieve the optimum level of luteal phase support, Engmann *et al* conducted a randomized clinical trial (RCT). They reported a high rate of OPR (53.3%) by monitoring of serum levels of steroids and intensive luteal phase support after GnRH-a trigger. In this way, the women were administered daily 50 mg IM progesterone beginning after oocyte collection to 10th week of pregnancy, and also since the next day of oocyte collection they received three 0.1 mg estradiol patches every other day.

At three different times (the day of embryo transfer, a week later oocyte collection and weekly after that) serum levels of estrogen and progesterone were evaluated. In order to keep serum estrogen levels over 200 pg/ml, either the dose of the patches, up to four patches (0.1 mg) in every day or by adding the oral micronized estrogen was done. Also serum level of progesterone was retained more than 20 ng/ml using IM progesterone dose up to a maximum 75 mg daily or by adding micronized vaginal progesterone.

The appropriate method of progesterone prescription in ovarian stimulation is still suspected It is possible that after GnRH-a trigger, IM method is preferred due to abnormal luteal phase and its necessity for sufficient protection and monitoring at this time. Available evidence is poor to support exogenous estrogen after the hCG trigger in IVF cycle, but it may be necessary due to dysfunctional corpus luteum after GnRH-a trigger. Transdermal estradiol patches is superior in comparison with oral estradiol because of the lack of liver passage. Since, endogenous hCG may not increase sufficiently during the luteal phase and early pregnancy, following GnRH-a trigger steroid supplementation should be continued in order to avoid early leuteolysis of corpus luteum.

Enegmann *et al* did a retrospective study in patients at OHSS risk with a maximum estrogen level peak less than 4.000 pg/ml. In order to obtain final oocyte mturation, patients received dual trigger (leuprolide acetate 1 mg +1000 IU hCG) in association with intensive luteal phase support (LPS). The results demonstrated higher implantation (41.9%, 22.1%, respectively) and live birth rates (58.8%, 36.8%, respectively) in dual trigger versus only GnRH-a trigger. In this study, it was observed if the intensive LPS was applied, with GnRH-a only, in patients with a maximum serum estradiol level of more 4.000 pg/ml, it could be an effective way to remain satisfactory levels of pregnancy. In patients with the highest serum estradiol levels less than

4000 pg/ml, dual trigger (GnRH-a and 1.000 IU hCG) may be appropriate to achieve the favorable rate of pregnancy by avoiding of OHSS. At present, the perfect type for luteal phase support after GnRH-a trigger is unknown, but some evidences indicate the importance of severe steroid support and serum monitoring through steroid dose regulation.

European approach (GnRH-a in combination with hCG supplement)[1]

In European protocol, Humaidan *et al* performed first a pilot RCT conducted on 45 patients (at low risk of OHSS) to evaluate a new method in which a single dose of hCG (1.500 IU) was given 12-35 hrs after GnRH-a trigger, followed by standard methods of LPS. Patients were divided into three groups. In first group GnRH-a trigger with hCG 12 hrs later, in second group GnRH-a rigger with hCG 35 hours later, and in the third group hCG trigger (10.000 IU) were performed. Although, adequate early luteal phase support was seen in GnRH-a trigger groups by adding 1500 IU hCG (12/35 h) after the trigger, but the mid-luteal phase progesterone levels in the second group was higher than the first group.

Meanwhile, a significant difference in clinical pregnancy rate (CPR) between 35-hr group and the hCG trigger group was not observed while the pregnancy rate was significantly lower in the group of 12-hr. So, they concluded that the perfect time of 1500 IU hCG after GnRH-a trigger seems to be 35 hours after the trigger. Complete separation of ovulation trigger from luteal phase support was mentioned another benefit of the 35-hour in this study. An RCT including 302 patients with normal gonadotropin levels divided into two groups, hCG trigger or GnRH-a trigger with a bolus of 1.500 IU hCG after 35 hours ,there was not a significant difference in birth rates between two groups (24% vs. 31%, respectively) and the incidence of OHSS rate (moderate and severe), was 2% after hCG trigger and no OHSS case in GnRH-a trigger was reported.

In this study, there was 7% difference between the two groups in the rate of delivery. Humaidan *et al* conducted an RCT in 390 patients for comparison between GnRH-a trigger and hCG trigger where the hCG dose was regulated regarding the ovarian response during the stimulation. This means that the patients with 14 or fewer follicles with size greater than 11 mm (low risk for OHSS) received two bolus of hCG, 1500 IU hCG on the day of oocyte retrieval +5 days in addition to 1500 IU on oocyte retrieval day. In patients with 15-25 follicles larger than 11 mm single bolus 1500 IU hCG 35 hours after the GnRH-a trigger was administered. All patients also received a standard level of luteal phase support. Patients with

more than 25 follicles were excluded from the study. The results showed no significant difference in the CPR between two groups, but the superiority was in favor of GnRH-a trigger. 3% incidence of OHSS was reported in patients with a high risk of OHSS in hCG trigger. However, the addition of hCG for luteal phase support after GnRH-a trigger in patients with high response significantly increased risk of delayed OHSS.

Suitable time for administration of low dose of hCG (12 vs. 35 hrs) after GnRH-a trigger is a subject of debate. Humaidan *et al* showed when the hCG was given 12 hours after GnRH-a trigger, the mid-luteal phase progesterone concentration and pregnancy outcome were poor. It seems that a period of resistance in early corpus luteum leads to impair the response of luteinizing granulosa cells against exogenous hCG stimulation. Dual trigger with GnRH-a and low dose of hCG have potential effect on oocyte maturation while low doses of hCG on the day of oocyte removal can affect the corpus luteum function and endometrial receptivity. Now, further studies are necessary.

Cetrorelix[2]

Cetrorelix is a basic peptide that does not contain acid components. The molecular weight is 1431.06 g/mol, calculated as the anhydrous free base. It is a structural analogue of native GnRH with antagonistic implication on the GnRH membrane receptor and without intrinsic effects on ovarian steroidogenesis. This synthetic decapeptide is made of single peptide compounds and has, in contrast with the native GnRH, substitutions of amino acids at positions 1, 2, 3, 6 and 10 (Figure 2). The D-amino acid compounds, in particular, result in an increased bioavailability because the enzymatic degradation is reduced in humans. Cetrorelix is available for subcutaneous injection as 0.25- or 3.0-mg sterile lyophilised powder for reconstitution with sterile water for injection (pH 5 – 8). The dilution volume is supplied in either 1.0 ml (0.25-mg vial, equivalent to cetrorelix acetate 0.26 – 0.27 mg) or 3.0 ml (3-mg vial, equivalent to cetrorelix acetate 3.12 – 3.24 mg).

Pharmacology[2]

The production and secretion of the gonadotropins LH and FSH is induced by the native GnRH peptide. The gonadotropins are released from the gonadotropic cells of the anterior pituitary. In the middle of the menstrual cycle, estradiol levels increase, after which native GnRH

liberation is enhanced due to a positive feedback, resulting in the so-called midcycle LH surge. Subsequently, the LH surge induces the ovulation of the dominant follicle in the ovary. Additionally, resumption of oocyte meiosis and luteinisation occurs. Cetrorelix competes with native GnRH for binding to membrane receptors on pituitary cells. When cetrorelix binds to the receptor, the receptor is blocked. Thus, the release of LH and FSH is controlled in a dose-dependent manner. At ~ 1 h (3.0-mg dose) or 2 h (0.25-mg dose) later, the onset of LH suppression occurs. The suppression is maintained by continuous cetrorelix application. LH suppression is more pronounced than FSH suppression. In contrast to treatment with GnRH agonists, there is no initial release of endogenous gonadotropins as the flare-up effect. This shows the immediate action of an antagonist. After discontinuation of treatment with cetrorelix, the effects on LH and FSH are completely reversible. This has been demonstrated in animals as well as in humans. Due to the delay of the LH surge, ovulation is also suppressed in females. This effect is dose dependent but FSH levels are not affected in the same way during COS. The duration of action is 4 days after a single 3.0-mg dose of cetrorelix, with a maximum of suppression of 70% on day 4. After application of a dose of 0.25 mg, the suppressive effect can be maintained by repetitive applications every 24 h.

Pharmacodynamics[2]

GnRH antagonist administration leads to a rapid suppression of pituitary gonadotropin release and reliably prevents premature LH surges in both single- and multiple-dose protocols. The LH suppressive effect of GnRH antagonists has been extensively studied in Phase I trials. After administration of a single dose of cetrorelix 0.25 mg for COS, LH drops down to a level of 90% within 3 h to a minimum of 0.1 – 0.2 mIU/ml and pulses with minimal amplitude can be observed during suppression. After administration of a 3.0-mg dose of cetrorelix on day 8 in a spontaneous cycle, endogenous LH levels significantly drop within 75 min and reach a nadir at 16 h, with a maximum decrease to 91% of pretreatment values. In contrast to a single dose of 0.25 mg GnRH antagonist, LH levels then remain low for at least 96 h in a stable manner. Duijkers et al. reported pharmacodynamics of a 0.25-mg dose of cetrorelix after administration on day 3 of the cycle in spontaneously cycling women; LH was suppressed by up to 75% with a nadir at 6 h after injection. In order to assess the suppressive effect on LH after the first cetrorelix injection (multiple-dose protocol for COS), the authors treated five women in a prospective, observational trial. LH values were at their lowest level 429 min after cetrorelix

application; the decrease in LH value was 73% (LHmax 1.83 mIU/ml and LHmin 0.49 mIU/ml). During the observational period of 32 h, 16 significant secretory peaks were detected and a mean secretion interpulse interval of 112 min was observed. Cetrorelix significantly suppressed pulsatile release of LH for 456 min, followed by a period of secretory pulses with decreased amplitude and pulse mass.

Pharmacokinetics[2]

The Tmax of the rapidly absorbed cetrorelix following subcutaneous injection are achieved ~ 1– 2 h after administration and the agent is transformed by peptidases. Following subcutaneous administration to healthy female subjects, the absolute mean bioavailability is 85%. After a single intravenous dose of 3.0 mg, the volume of distribution is 1.16 l/kg and in vitro protein binding to human plasma is 86%. The concentration of cetrorelix in the follicular fluid and plasma were similar on the day of OPU in patients undergoing COS. Plasma concentrations of cetrorelix were below, or in the range of, the lower limit of quantification on the day of OPU and embryo transfer after subcutaneous administration of cetrorelix 0.25 mg and 3.0 mg. Cetrorelix had no effects on hormone levels, aside from inhibition of LH surges during stimulation with HMG. In conclusion, there is no evidence for differences in pharmacokinetic parameters between healthy subjects and patients undergoing COS. However, enzyme (e.g., alanine aminotransferase, aspartate aminotransferase, gamma glutamyltranspeptidase, alkaline phosphatase) elevation up to three-times of the upper limit of normal occurred in 1 – 2% of patients treated with cetrorelix for COS, while pre-existing enzyme alteration was excluded. No pharmacokinetic studies have been performed in subjects with impaired renal or liver function and, in addition, not in the elderly or in children. Therefore, cetrorelix is contraindicated in severe renal impairment. Cetrorelix is rated Pregnancy Category X (positive evidence of serious foetal abnormalities in animals, humans or both; foetal risks clearly outweigh maternal benefit) and it is, therefore, contraindicated in pregnant women.

Metabolism[2]

Schwahn et al. studied the disposition and metabolism of a subcutaneously administrated dose of cetrorelix 0.1 mg/kg in rats and dogs. Rats excreted 24.3% of cetrorelix into the urine and 69.6% via the faeces. Excretion was nearly complete within 48 h and there was no enteral

reabsorption that was detectable. Dogs showed a Tmax of cetrorelix within 1.3 h. After application of a single dose of cetrorelix 0.25 mg intravenously, the plasma half-life (t½Plas) in humans is 12 h. After application of the same dose subcutaneously, the t½Plas in humans is 30 h. Differences in the t½Plas seem to be correlated with absorption processes at the location of application. Elimination half-life (t½) is 63 h after subcutaneous application of a single dose of 3.0 mg, but only 5 h after the application of a single dose of 0.25 mg; t½ is 21 h after application of cetrorelix 0.25 mg within a multiple-dose regimen. Linear plasma pharmacokinetics are observed after subcutaneous and daily application for 14 days. Following subcutaneous administration of cetrorelix 10 mg to human males and females, only unchanged cetrorelix was detected in the urine. Unchanged cetrorelix and small amounts of its metabolite, nona-, hepta-, hexa- and tetrapeptides, were found in bile samples within 24 h. There was between 2 and 4% of the initially administered dose that was found in the urine as unchanged cetrorelix, but 5 – 10% was eliminated as cetrorelix and the four metabolites, (1-9), (1-7), (1-6) and (1-4) peptides, in the bile. The (1-4) peptide is the predominant metabolite. This shows that only 7 – 14% of the initially administered dose could be recovered as unchanged cetrorelix and metabolites in the urine and bile up to 24 h. As the results of the studies of Schwahan et al. demonstrate, the remaining portion of the dose may have been recovered if bile and urine had been collected for a longer period of time. Cetrorelix was shown to be stable against Phase I and II metabolism in in vitro studies. Drug-to-drug interaction has not been investigated with cetrorelix

Clinical efficacy[2]

Infertility

To evaluate the clinical efficacy of cetrorelix in the treatment of infertility, Phase II dose-finding trials and Phase III clinical trials have been performed. In these studies, the clinical population consisted of Caucasians (95%) and African-Americans, Asians, Arabians and others (5%). Patients with polycystic ovary syndrome, low or no ovarian reserve and patients with endometriosis revised American Fertility Association (rAFS) stage III – IV were excluded.

Phase I and II studies

The extent of the LH suppression depends on the dosage and duration of cetrorelix administered. Two dose regimens for COS were investigated in Phase II studies. The administration of cetrorelix 0.25 mg within a multiple-dose regimen (Figure 1).

was established as the minimal effective daily dose. Patients were stimulated with gonadotropins, starting on day 2 or 3 of a normal menstrual cycle. Gonadotropin dosage was administered according to the individual response. Cetrorelix was initiated within the multiple-dose regimens on day 5 or 6 of COS as a dosage of 0.25 mg subcutaneously. The gonadotropins and cetrorelix were continued daily until the day of HCG administration (i.e., when the dominant follicle had reached a diameter of ≥ 18 mm, and estradiol concentration was > 300 pg/ml for each follicle having a diameter of > 15 mm). Alternatively, a single dose of cetrorelix 3.0 mg per treatment cycle can be administered (Figure 3) as the minimal effective dose to prevent premature LH surge with a protection period of 4 days. Within the single-dose regimen, administration of cetrorelix 3.0 mg was performed if the serum estradiol level was indicative of an appropriate stimulation response (400 pg/ml), usually on stimuation day 7. If HCG was not given within 4 days of the 3.0-mg dose of cetrorelix, then cetrorelix 0.25 mg was administered daily, beginning 96 h after the 3.0-mg injection up until and including the day of HCG administration (Figure 3). Two further nonrandomised dose-finding studies for the multiple and the single-dose cetrorelix regimens have assessed the minimal effective dose needed to prevent premature LH surge in COS for ARTs. Within the multiple-dose regimen, 69 patients were treated in three groups with different daily dosages (0.5, 0.25 and 0.1 mg; n = 7) of cetrorelix. Gonadotropin (HMG) administration started on cycle day 2 and cetrorelix was administered on stimulation day 6. No premature endogenous LH surge occurred in patients treated with cetrorelix 0.5 and 0.25 mg, but premature LH surge occurred in one of the seven patients who were treated with cetrorelix 0.1 mg. Therefore, cetrorelix 0.25 mg in a daily subcutaneous administration is the minimal effective dose needed to prevent premature LH surge. Olivennes et al. compared the administration of a single dose of cetrorelix 3.0 mg (n = 34) versus 2.0 mg (n = 32) in 66 patients undergoing COS for IVF. Patients received cetrorelix in this nonrandomised protocol on day 8 of the stimulation cycle. No difference was observed in the decrease of LH, but the LH secretion was suppressed for a shorter time in the 2.0-mg group and, in the same group, one LH surge was observed. No LH surge was observed in the 3.0-mg group. The groups did not differ concerning the IVF results. LH surge was prevented

in both groups for 3 days. Due to the LH surge in the 2.0-mg group, 3.0 mg is the minimal effective dose required to prevent premature LH surge within a single-dose regimen.

Phase III studies

Within five clinical Phase III studies, the efficacy of the cetrorelix 0.25-mg multiple-dose protocol and the 3.0-mg single-dose protocol was established for the treatment of infertility. To assess the safety and efficacy of the cetrorelix 0.25-mg multiple-dose protocol, 346 normally ovulating women were treated within a multi-centre, multinational, prospective uncontrolled Phase III study. A mean number of 25 ampoules of HMG were administered and 333 patients fulfilled the criteria for HCG administration (96% efficacy rate). Only 324 patients underwent OPU and in 2 of these cases no oocytes were retrieved. In total, 149 patients underwent IVF and 162 received ICSI treatment; 11 patients had both procedures. Clinical pregnancy rate per transfer was 24%. There were 12 abortions that were observed (17%). Two cases of severe OHSS (III) were reported (incidence of 0.6%), which is low compared with the incidence of 6.6% reported after the long-duration protocol. One case of hot flushes was reported to be related to cetrorelix administration. The incidence of premature LH surge was 0.9% and this was within the range to be expected after GnRH agonist administration. A further European Phase III prospective, controlled and randomised study compared cetrorelix and buserelin in the prevention of LH surge during COS for IVF/ICSI. In this study, 198 patients were randomised for treatment with cetrorelix and 95 patients to buserelin. In each group, 10 patients had to be excluded before stimulation started. Cetrorelix was administered within the 0.25-mg multiple-dose protocol and buserelin was administered daily intranasally. Patients in both groups were stimulated with HMG and cetrorelix was administered starting from day 6 of the HMG treatment period. In the cetrorelix group, 181 patients reached the day of HCG administration. There were 7 patients who were excluded because of poor ovarian response, risk for development of OHSS or premature LH rise (n = 1). The number of HMG ampoules administered was significantly lower and the duration of stimulation was significantly shorter in the cetrorelix group, affecting the comfort of the patients. LH concentrations were similar in both groups during suppression of the pituitary. The mean number of oocytes retrieved at OPU was significantly lower in the cetrorelix group but the fertilisation and the cleavage rates were similar in both groups (Table 1). The incidence of OHSS II – III was significantly higher in the buserelin group (6.5 versus 1.1%).

To assess the preventative effect on premature LH surge and IVF outcome, women were treated in a multi-centre, controlled and randomised prospective Phase III trial with either cetrorelix in the single-dose 3.0-mg regimen (n = 115) or with a depot preparation of triptorelin (n = 39) for IVF/ICSI. No LH surge occurred after cetrorelix administration, but the patients in the cetrorelix group had lower numbers of oocytes and embryos (Table 1). There was no statistically significant difference in the percentage of mature oocytes and fertilisation rates; the pregnancy rates also did not differ between both groups. Cetrorelix was well tolerated and the amount of gonadotropins administered was lower in the cetrorelix group.

Olivennes et al. reported two large multi-centre, multinational, prospective, uncontrolled Phase IIIb studies, one with the multiple-dose regimen and the other with the single-dose regimen: both with the use of either FSH or HMG as the gonadotropin for stimulation. More oocytes were retrieved and were available for insemination procedure when the patients were treated within the single-dose regimen (Table 1). However, the number of embryos obtained and transferred were comparable in both protocols. Pregnancy rates were similar in both regimens. Severe OHSS (III) occurred in < 1% of subjects in both studies. Local reactions (e.g., itching, local rash or oedema) were more frequently reported among the patients who were treated with the multiple-dose (12%) than the single-dose regimen (8%). The reason for this observation could be the higher frequency of injections in the multiple-dose regimen; 73% of patients in the single-dose regimen received only one injection. None of the local reactions were serious or led to discontinuation of the treatment. These two studies show that the single-dose cetrorelix protocol offers equal efficacy and safety to that of the multiple-dose regimen, whilst having the advantage of requiring only one injection (73%) in most patients.

Is a lower dose of cetrorelix acetate effective for prevention of LH surge during controlled ovarian hyperstimulation?[3]

Abstract

Purpose: This study was performed to evaluate whether a lower dose (0.2 mg) of cetrorelix would prevent premature LH surge in patients undergoing controlled ovarian hyperstimulation.

Methods: Controlled ovarian hyperstimulation was carried out in 45 patients, starting on menstrual cycle day 3 with recombinant FSH (r-FSH), and a cetrorelix of 0.2 mg was administered from day 5 evening of ovarian stimulation until the day before hCG injection.

Results: There was a statistically significant decrease in serum LH level one day after the first cetrorelix injection and on the day of hCG administration. Serum LH concentrations were maintained constantly low during the follicular phase with no premature LH surge occurring in any of the patients. Clinical pregnancy was achieved for 18 women (40%), with one of these experiencing intrauterine fetal death before 12 week' gestation.

Conclusion: This study demonstrates that a daily dose of cetrorelix 0.2 mg is able to prevent premature LH surge

References:

1. Alyasin A, Mehdinejadiani S, Ghasemi M. GnRH agonist trigger versus hCG trigger in GnRH antagonist in IVF/ICSI cycles: A review article. *Int J Reprod Biomed*. 2016;14(9):557-566.
2. Finas D, Hornung D, Diedrich K, Schultze-Mosgau A. Cetrorelix in the treatment of female infertility and endometriosis. Expert Opinion on Pharmacotherapy. 2006 Oct 1;7(15):2155-68.
3. Chen HJ, Lin YH, Hsieh BC, Seow KM, Hwang JL, Tzeng CR. Is a lower dose of cetrorelix acetate effective for prevention of LH surge during controlled ovarian hyperstimulation?. *J Assist Reprod Genet*. 2006;23(6):289-292.

Survey Form

1. In which phase of the menstrual cycle do you use Cetrorelix Acetate primarily?

A) Follicular phase

B) Luteal phase

C) Ovulatory phase

D) Menstrual phase

2. How frequently do you prescribe Cetrorelix Acetate in your ART practice?

A) Frequently (more than 75% of cases)

B) Occasionally (25-75% of cases)

C) Rarely (less than 25% of cases)

D) Never

3. In which ART procedure is Cetrorelix Acetate commonly used by you?

A) Intrauterine insemination (IUI)

B) In vitro fertilization (IVF)

C) Gamete intrafallopian transfer (GIFT)

D) Zygote intrafallopian transfer (ZIFT)

4. What percentage of your patients undergoing ART require the use of Cetrorelix Acetate to prevent premature ovulation?

A) < 25%

B) 25-50%

C) 50-75%

D) > 75%

5. What is the dosage regimen of Cetrorelix Acetate preferred by you during ovarian stimulation?

A) Once daily

B) Twice daily

C) Every other day

D) Once every 3 days

6. What is the typical duration of Cetrorelix Acetate administration during ovarian stimulation preferred by you?

A) 3 days

B) 5 days

C) 7 days

D) 10 days

7. In your experience, what percentage of patients exhibit adverse reactions to Cetrorelix Acetate administration?

A) < 5%

B) 5-10%

C) 10-20%

D) > 20%

8. What factors influence your decision to prescribe Cetrorelix Acetate in ART cycles?

A) Patient age

B) Ovarian reserve

C) Previous response to stimulation protocols

D) All of the above

9. What is your preferred method for triggering final oocyte maturation in patients receiving Cetrorelix Acetate?

A) Human chorionic gonadotropin (hCG) trigger

B) Gonadotropin-releasing hormone (GnRH) agonist trigger

C) Dual trigger (hCG + GnRH agonist)

10. How do you typically monitor patients after initiating Cetrorelix Acetate treatment?

A) Ultrasound monitoring

B) Hormonal assays (e.g., estradiol levels)

C) Clinical symptoms assessment

D) Combination of the above

11. According to you what is the primary goal of using Cetrorelix Acetate in ART cycles?

A) Enhancing sperm motility

B) Preventing premature ovulation

C) Promoting embryo implantation

D) Inducing ovulation

12. Which phase of the menstrual cycle is most critical for the administration of Cetrorelix Acetate as per your clinical experience?

A) Early follicular phase

B) Mid-follicular phase

C) Late follicular phase

D) Early luteal phase

13. How do you assess the effectiveness of Cetrorelix Acetate in preventing premature ovulation during an ART cycle?

A) Ultrasound monitoring of follicular development

B) Hormonal assays (e.g., LH levels)

C) Clinical symptoms assessment

D) Combination of the above

14. At what point do you usually begin administering Cetrorelix Acetate upon reaching the following lead follicle diameters:

A) 10-12 mm

B) 14-16 mm

C) 18-20 mm

D) 22-24 mm

15. In your opinion, what are the key advantages of using Cetrorelix Acetate in ART cycles compared to other methods of preventing premature ovulation?

A) Reduced risk of adverse effects

B) Improved patient compliance

C) Enhanced treatment outcomes

D) Other

Survey Findings

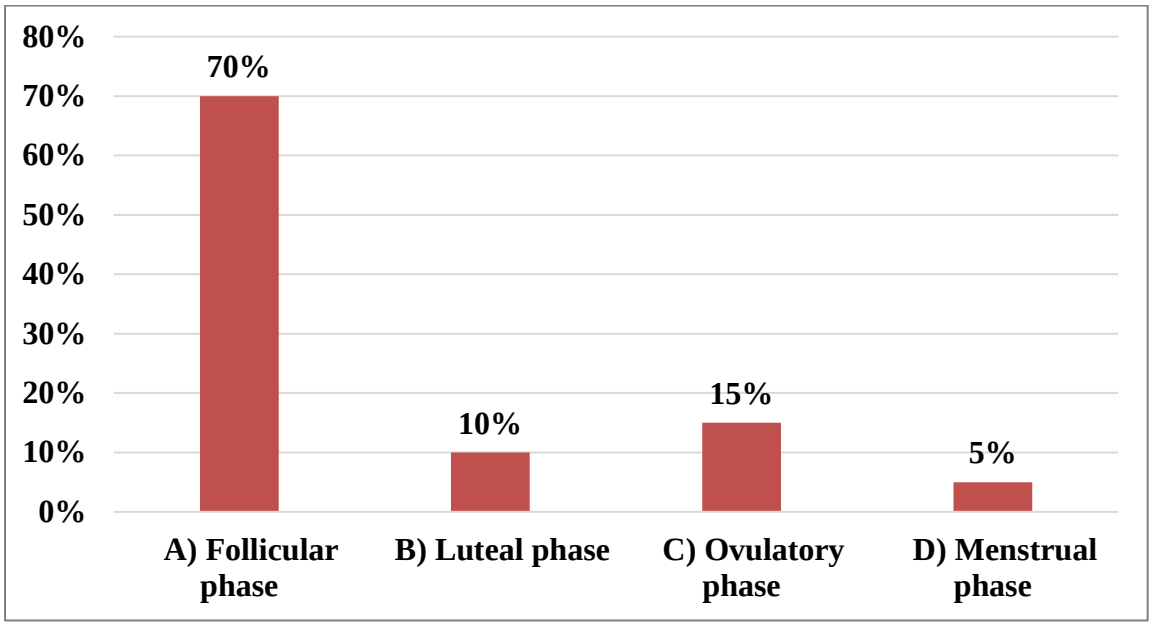
1. In which phase of the menstrual cycle do you use Cetrorelix Acetate primarily?

A) Follicular phase

B) Luteal phase

C) Ovulatory phase

D) Menstrual phase



Majority of doctors (70%) use Cetrorelix Acetate primarily in follicular phase of the menstrual cycle.

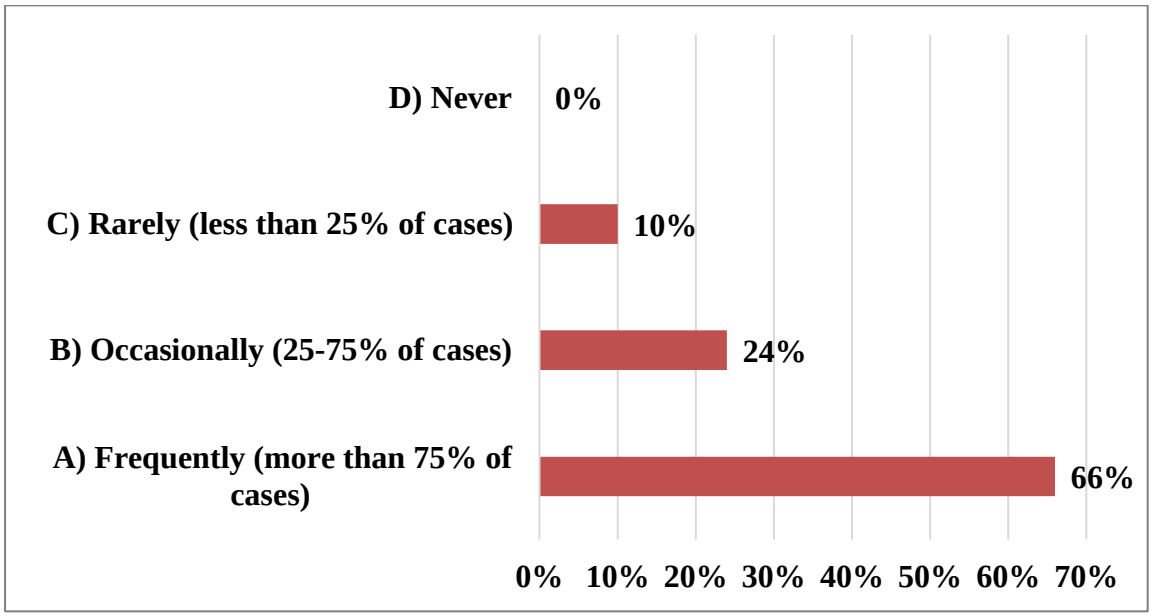
2. How frequently do you prescribe Cetrorelix Acetate in your ART practice?

A) Frequently (more than 75% of cases)

B) Occasionally (25-75% of cases)

C) Rarely (less than 25% of cases)

D) Never



According to 66% of doctors, they frequently (more than 75% of cases) prescribe Cetrorelix Acetate in their ART practice.

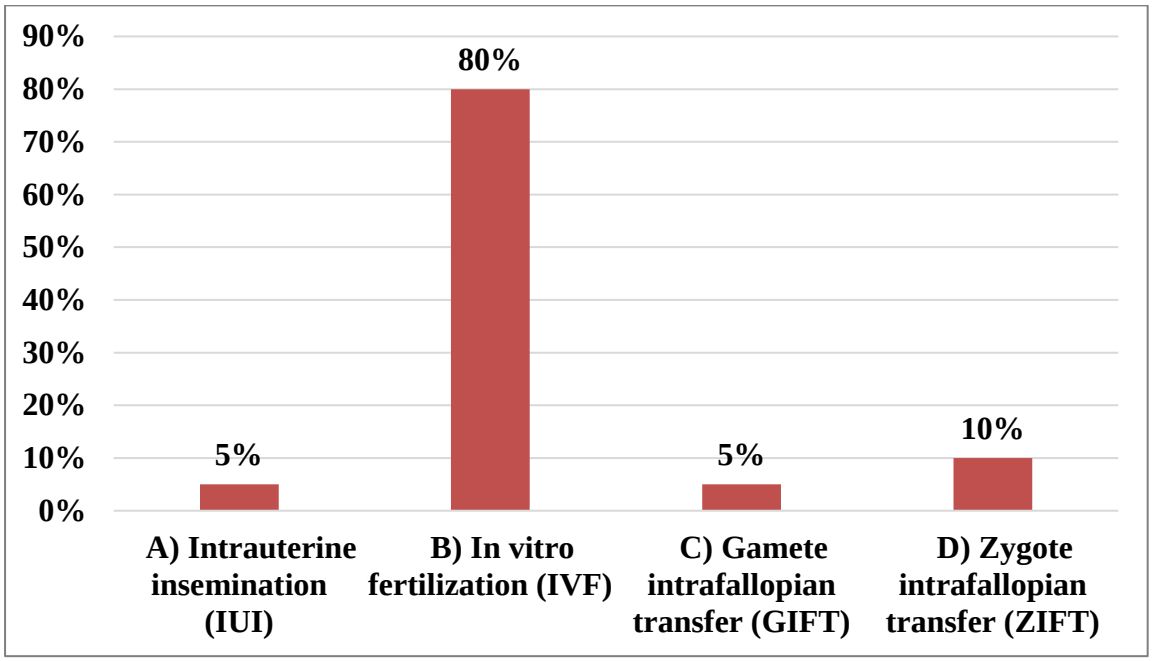
3. In which ART procedure is Cetrorelix Acetate commonly used by you?

A) Intrauterine insemination (IUI)

B) In vitro fertilization (IVF)

C) Gamete intrafallopian transfer (GIFT)

D) Zygote intrafallopian transfer (ZIFT)



Majority of doctors, 80%, commonly use Cetrorelix Acetate in vitro fertilization (IVF).

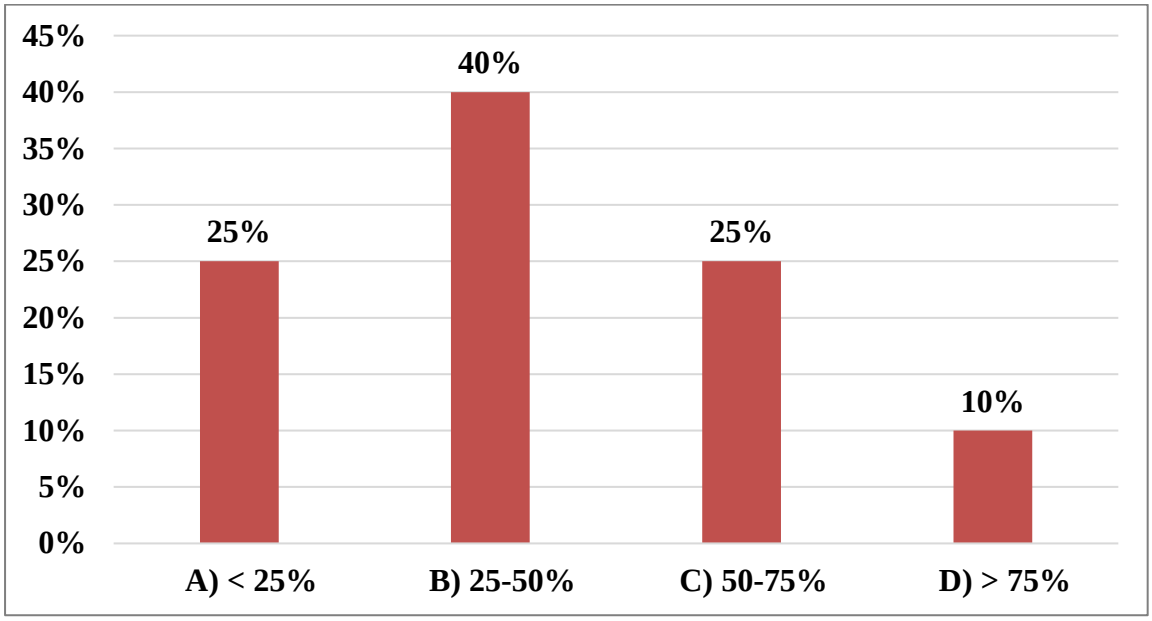
4. What percentage of your patients undergoing ART require the use of Cetrorelix Acetate to prevent premature ovulation?

A) < 25%

B) 25-50%

C) 50-75%

D) > 75%



As per 40% of doctors, 25-50% of their patients undergoing ART require the use of Cetrorelix Acetate to prevent premature ovulation.

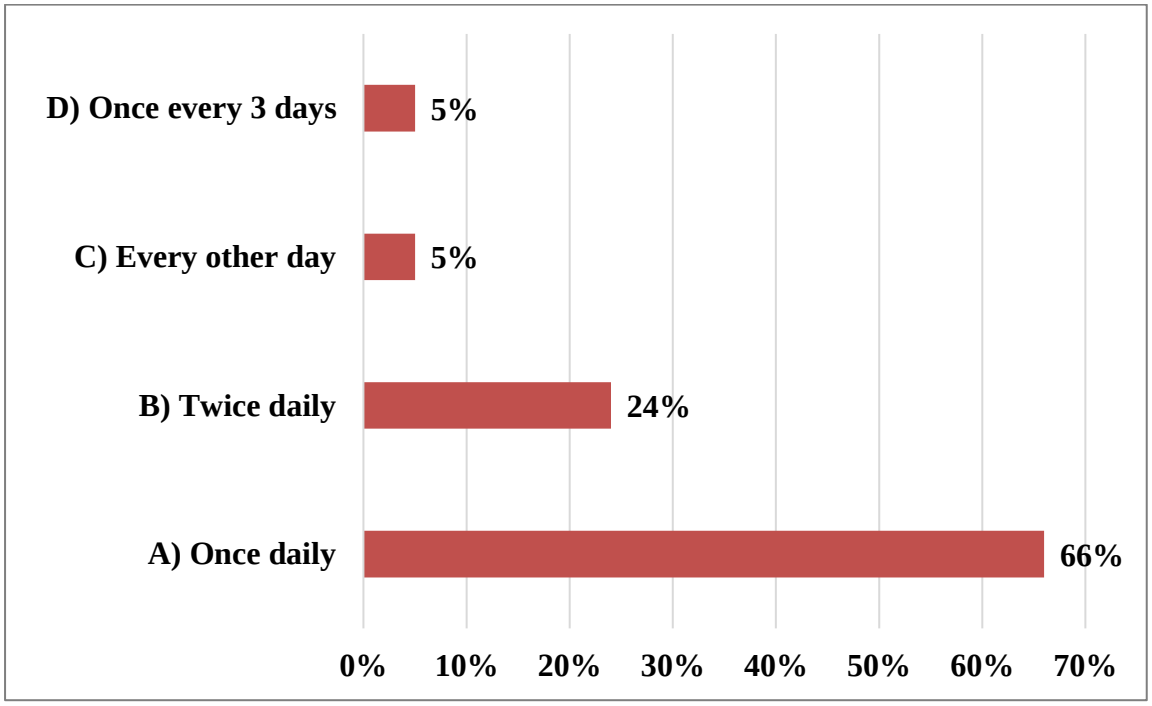
5. What is the dosage regimen of Cetrorelix Acetate preferred by you during ovarian stimulation?

A) Once daily

B) Twice daily

C) Every other day

D) Once every 3 days



66% of doctors prefer using Cetrorelix Acetate once daily during ovarian stimulation.

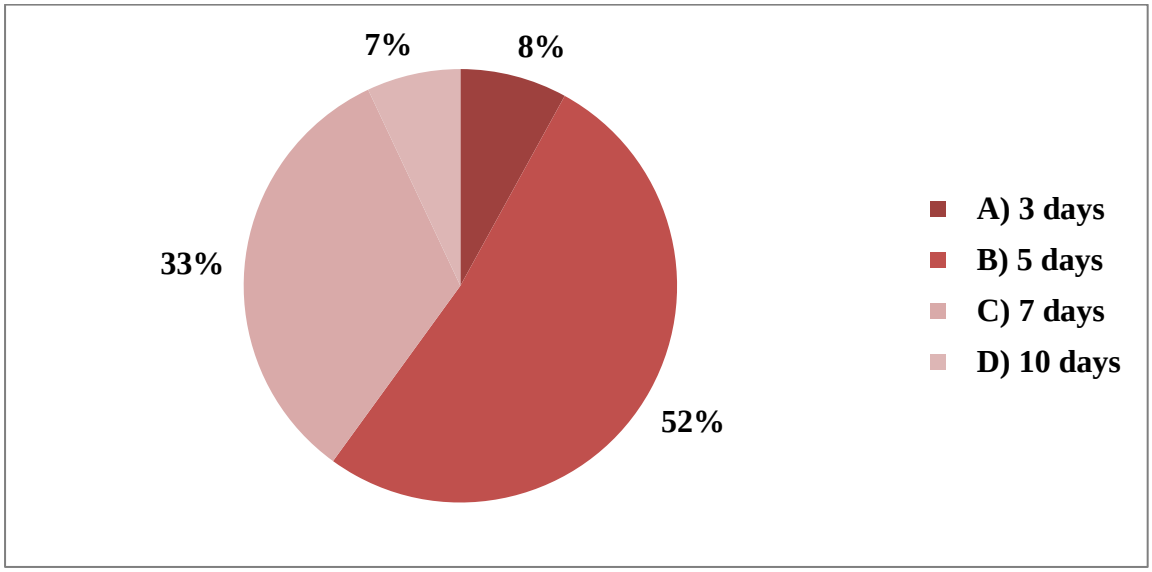
6. What is the typical duration of Cetrorelix Acetate administration during ovarian stimulation preferred by you?

A) 3 days

B) 5 days

C) 7 days

D) 10 days



52% of doctors prefer using Cetrorelix Acetate for the typical duration of 5 days during ovarian stimulation.

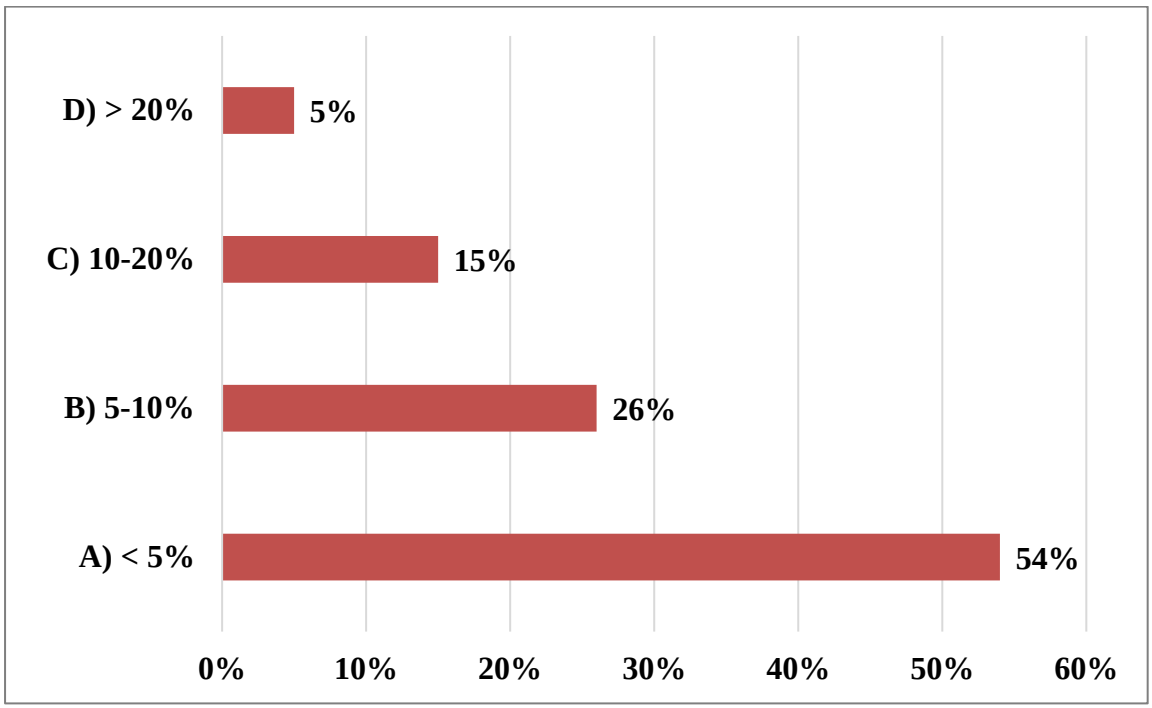
7. In your experience, what percentage of patients exhibit adverse reactions to Cetrorelix Acetate administration?

A) < 5%

B) 5-10%

C) 10-20%

D) > 20%



In the experience of 54% of doctors, < 5% of patients exhibit adverse reactions to Cetrorelix Acetate administration.

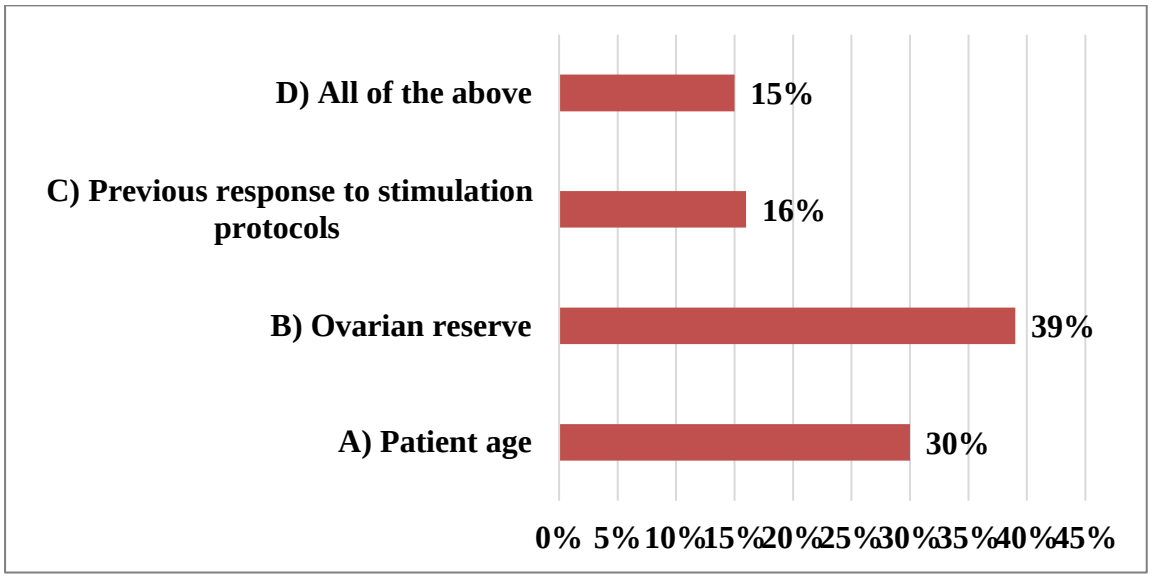
8. What factors influence your decision to prescribe Cetrorelix Acetate in ART cycles?

A) Patient age

B) Ovarian reserve

C) Previous response to stimulation protocols

D) All of the above



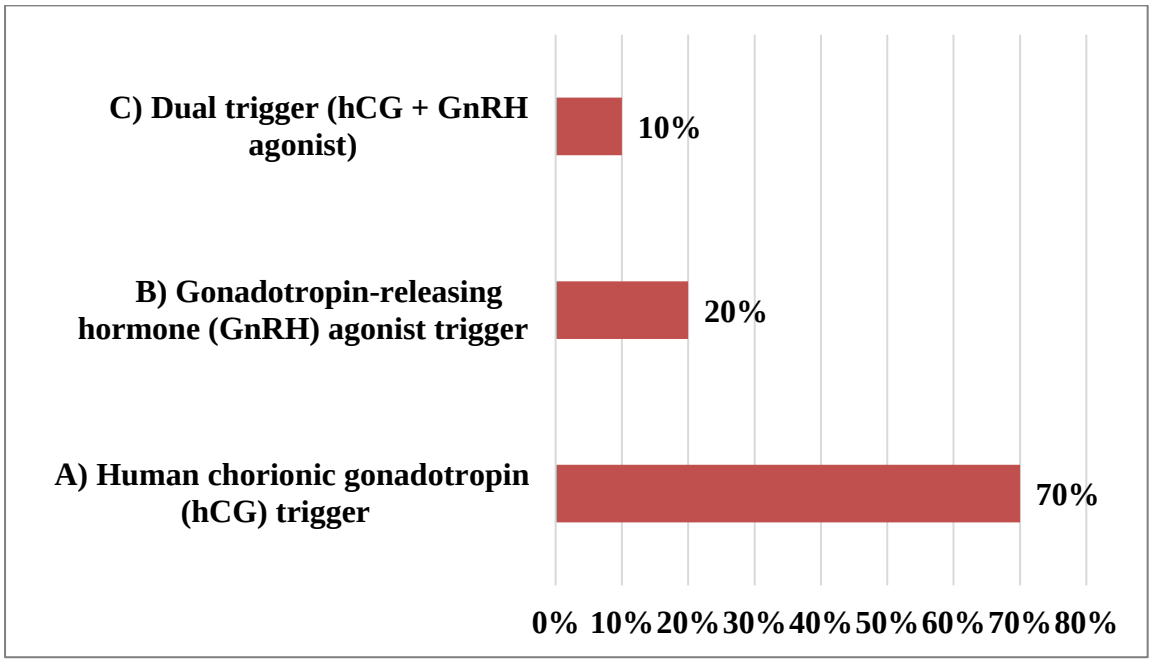
As per 39% of doctors, ovarian reserve influence their decision to prescribe Cetrorelix Acetate in ART cycles.

9. What is your preferred method for triggering final oocyte maturation in patients receiving Cetrorelix Acetate?

A) Human chorionic gonadotropin (hCG) trigger

B) Gonadotropin-releasing hormone (GnRH) agonist trigger

C) Dual trigger (hCG + GnRH agonist)



According to majority of doctors, their preferred method for triggering final oocyte maturation in patients receiving Cetrorelix Acetate is human chorionic gonadotropin (hCG) trigger.

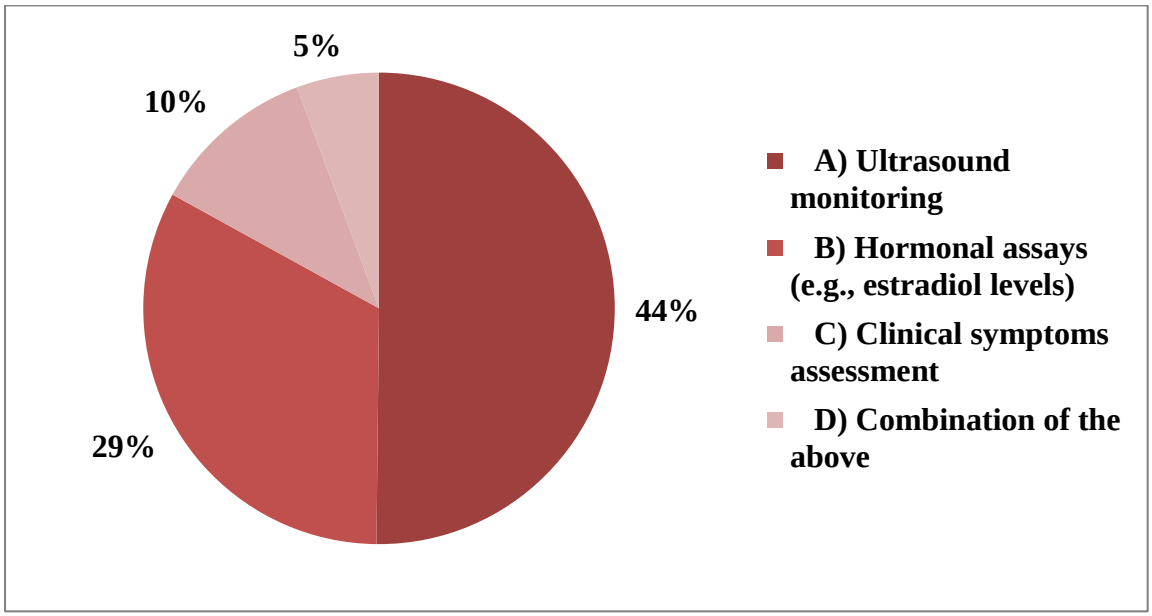
10. How do you typically monitor patients after initiating Cetrorelix Acetate treatment?

A) Ultrasound monitoring

B) Hormonal assays (e.g., estradiol levels)

C) Clinical symptoms assessment

D) Combination of the above



44% of doctors typically monitor patients after initiating Cetrorelix Acetate treatment using ultrasound monitoring.

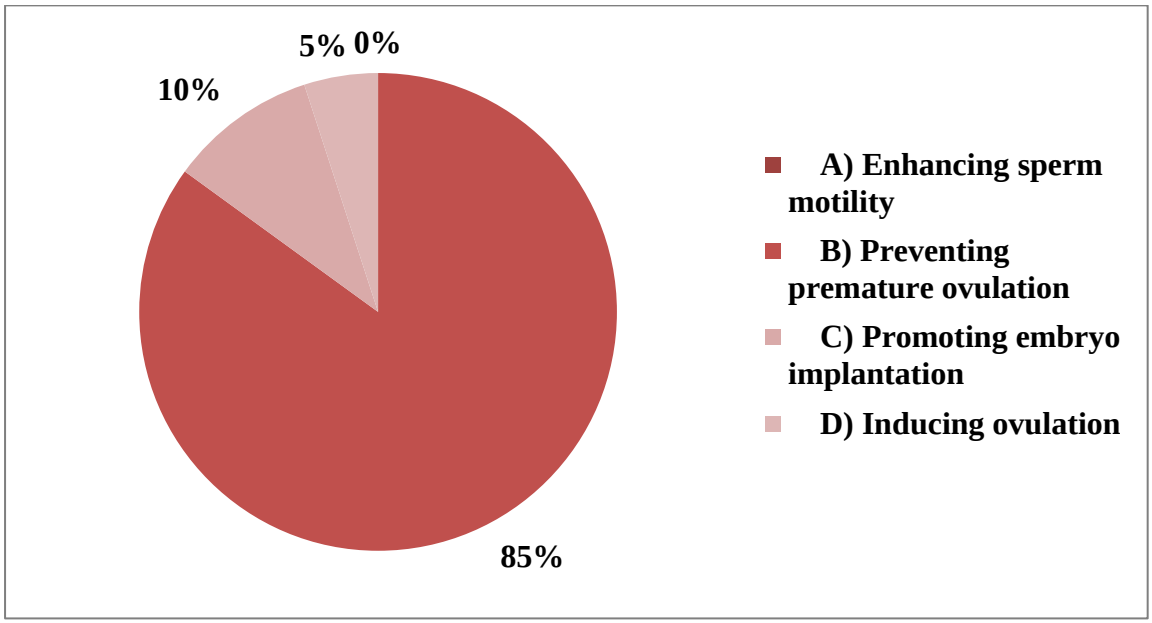
11. According to you what is the primary goal of using Cetrorelix Acetate in ART cycles?

A) Enhancing sperm motility

B) Preventing premature ovulation

C) Promoting embryo implantation

D) Inducing ovulation



According to majority of doctors, 85%, the primary goal of using Cetrorelix Acetate in ART cycles is preventing premature ovulation.

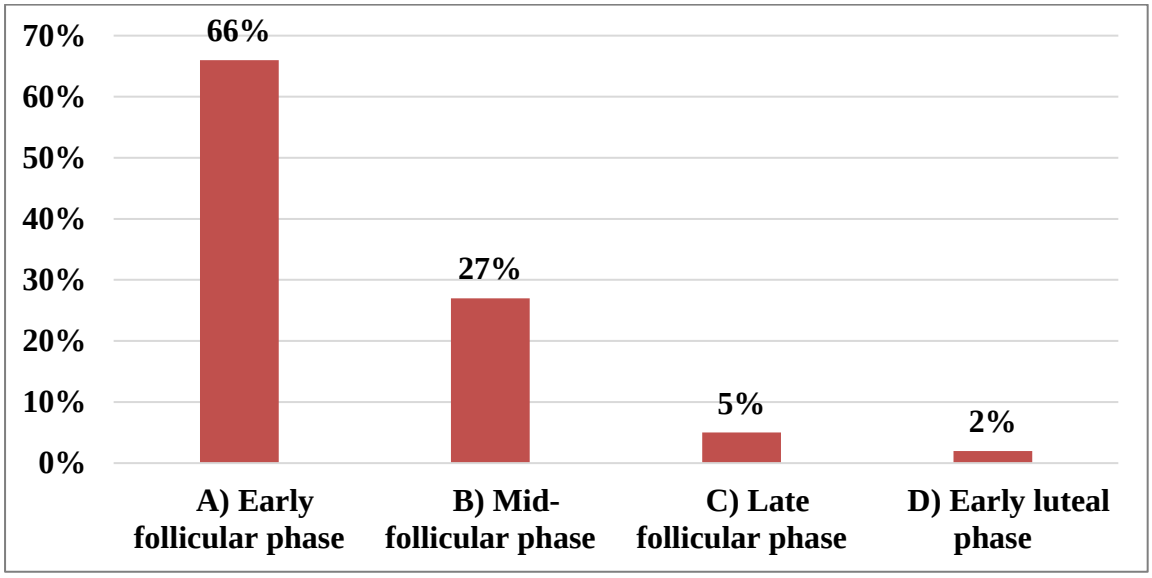
12. Which phase of the menstrual cycle is most critical for the administration of Cetrorelix Acetate as per your clinical experience?

A) Early follicular phase

B) Mid-follicular phase

C) Late follicular phase

D) Early luteal phase



As per the clinical experience of 66% of doctors, early follicular phase of the menstrual cycle is most critical for the administration of Cetrorelix Acetate.

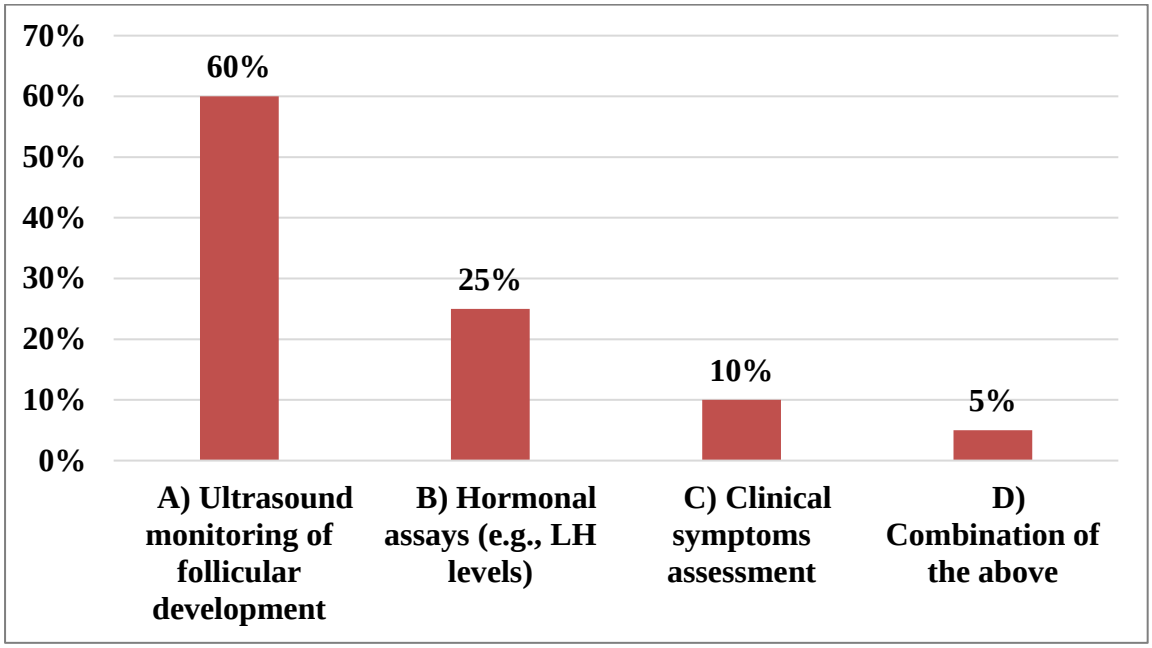
13. How do you assess the effectiveness of Cetrorelix Acetate in preventing premature ovulation during an ART cycle?

A) Ultrasound monitoring of follicular development

B) Hormonal assays (e.g., LH levels)

C) Clinical symptoms assessment

D) Combination of the above



60% of doctors assess the effectiveness of Cetrorelix Acetate in preventing premature ovulation during an ART cycle through ultrasound monitoring of follicular development.

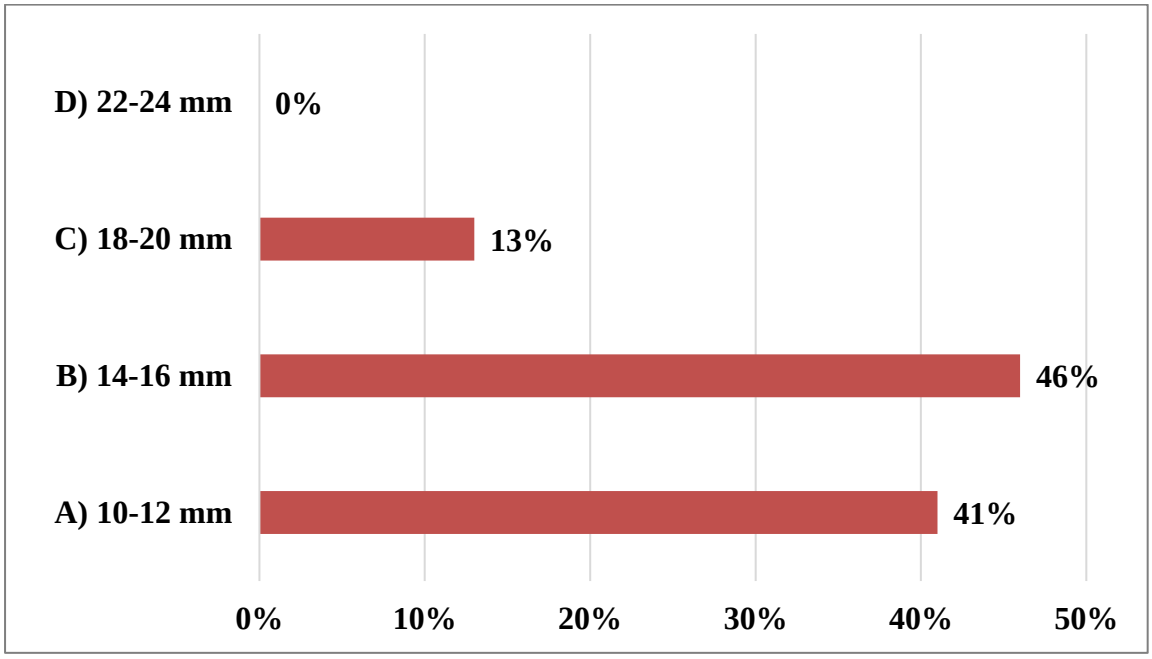
14. At what point do you usually begin administering Cetrorelix Acetate upon reaching the following lead follicle diameters:

A) 10-12 mm

B) 14-16 mm

C) 18-20 mm

D) 22-24 mm



46% of doctors begin administering Cetrorelix Acetate upon reaching the 14-16 mm lead follicle diameters.

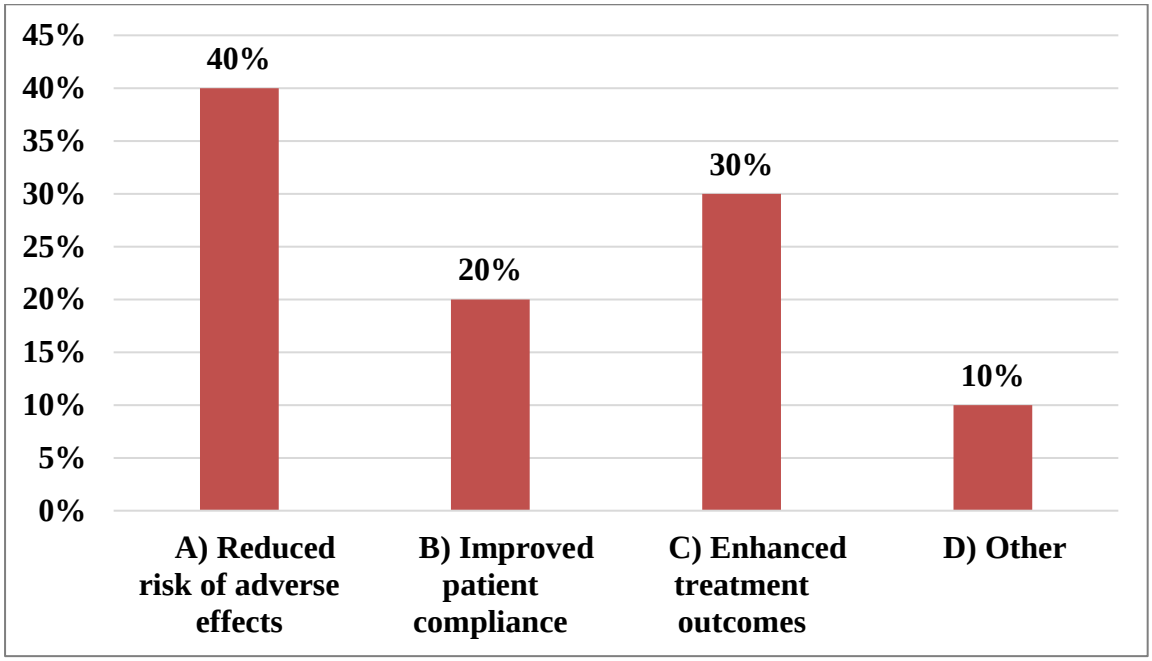
15. In your opinion, what are the key advantages of using Cetrorelix Acetate in ART cycles compared to other methods of preventing premature ovulation?

A) Reduced risk of adverse effects

B) Improved patient compliance

C) Enhanced treatment outcomes

D) Other



In the opinion of 40% of doctors, the key advantages of using Cetrorelix Acetate in ART cycles compared to other methods of preventing premature ovulation is reduced risk of adverse effects.

Summary

- Majority of doctors (70%) use Cetrorelix Acetate primarily in follicular phase of the menstrual cycle.
- According to 66% of doctors, they frequently (more than 75% of cases) prescribe Cetrorelix Acetate in their ART practice.
- Majority of doctors, 80%, commonly use Cetrorelix Acetate in vitro fertilization (IVF).
- As per 40% of doctors, 25-50% of their patients undergoing ART require the use of Cetrorelix Acetate to prevent premature ovulation.
- 66% of doctors prefer using Cetrorelix Acetate once daily during ovarian stimulation.
- 52% of doctors prefer using Cetrorelix Acetate for the typical duration of 5 days during ovarian stimulation.
- In the experience of 54% of doctors, < 5% of patients exhibit adverse reactions to Cetrorelix Acetate administration.
- As per 39% of doctors, ovarian reserve influence their decision to prescribe Cetrorelix Acetate in ART cycles.
- According to majority of doctors, their preferred method for triggering final oocyte maturation in patients receiving Cetrorelix Acetate is human chorionic gonadotropin (hCG) trigger.
- 44% of doctors typically monitor patients after initiating Cetrorelix Acetate treatment using ultrasound monitoring.
- According to majority of doctors, 85%, the primary goal of using Cetrorelix Acetate in ART cycles is preventing premature ovulation.
- As per the clinical experience of 66% of doctors, early follicular phase of the menstrual cycle is most critical for the administration of Cetrorelix Acetate.
- 60% of doctors assess the effectiveness of Cetrorelix Acetate in preventing premature ovulation during an ART cycle through ultrasound monitoring of follicular development.
- 46% of doctors begin administering Cetrorelix Acetate upon reaching the 14-16 mm lead follicle diameters.

- In the opinion of 40% of doctors, the key advantages of using Cetrorelix Acetate in ART cycles compared to other methods of preventing premature ovulation is reduced risk of adverse effects.

Consultant Opinion

Market Opportunities:

With a high frequency of prescription (66%) and common usage in in vitro fertilization (IVF) (80%), there is a significant market opportunity for pharmaceutical companies manufacturing Cetrorelix Acetate. Companies could focus on developing patient-friendly formulations or delivery methods to enhance the ease of use and compliance with Cetrorelix Acetate therapy in ART cycles.

Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the appropriate use of Cetrorelix Acetate in ART practice. Continuing medical education programs can help ensure that healthcare professionals stay updated on the latest evidence-based practices and guidelines for Cetrorelix Acetate administration.

Adverse Effect Management:

While most doctors (54%) report low incidence of adverse reactions to Cetrorelix Acetate, healthcare professionals should remain vigilant in monitoring patients for potential adverse effects. Regular follow-up visits and assessments, including ultrasound monitoring of follicular development, can help detect and manage adverse effects promptly, ensuring the safety and well-being of patients.

Withdrawal Management:

Clear guidelines should be established for the duration and dosage of Cetrorelix Acetate therapy in ART cycles to optimize outcomes and minimize the risk of premature ovulation. Healthcare professionals should tailor treatment plans based on individual patient factors, such as ovarian reserve and follicular development, to ensure the efficacy and safety of Cetrorelix Acetate administration.

Market Positioning:

Pharmaceutical companies can capitalize on the advantages of Cetrorelix Acetate, such as reduced risk of adverse effects and effectiveness in preventing premature ovulation, by emphasizing these benefits in their marketing strategies. Highlighting the safety profile and efficacy of Cetrorelix Acetate in ART cycles can help position it as a preferred option for preventing premature ovulation in patients undergoing IVF.

Personalized Treatment Decisions:

Healthcare professionals should consider individual patient factors, such as ovarian reserve, follicular development, and risk of premature ovulation, when deciding whether to prescribe Cetrorelix Acetate in ART cycles. Personalized treatment decisions can optimize outcomes and minimize the risk of adverse effects, ensuring the success of ART procedures.

Improving Patient Outcomes:

Patient education is essential to ensure optimal outcomes with Cetrorelix Acetate therapy in ART cycles. Patients should be informed about the purpose of Cetrorelix Acetate in preventing premature ovulation and the importance of adherence to prescribed regimens. Additionally, healthcare professionals should regularly assess patient response and adjust treatment plans as needed to achieve successful outcomes in ART cycles.

NOTES

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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