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Use of Gonadotrophin Releasing Hormone Agonist Instead of Human Chorionic Gonadotrophin For Triggering Ovulation

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OBJECTIVE – To find out if nafarelin acetate and triptorelin which are potent GnRHa are as efficacious as HCG in triggering ovulation in stimulated cycles. **METHODS** – A prospective randomized comparative study was done. One hundred sixty-seven stimulated cycles in 66 infertile women undergoing intrauterine insemination were randomly assigned to receive either nafarelin or triptorelin, or HCG at the midcycle when the predetermined criteria were met. Various outcome measures were analyzed in 154 cycles which qualified for comparison. **Results and Conclusion** – It was found that the agonist preparations under study were equally effective as HCG in achieving comparable rates of ovulation. Conception rates were slightly lower though not statistically significanty so. Absence of ovarian hyperstimulation syndrome is an advantage. However, high incidence of short luteal phase can be a cause for concern.

Key Words : GnRH agonist, ovulation induction

Introduction

During the last two decades several cumulative improvements have taken place in the ovulation induction regimens[1]. In a natural menstrual cycle the midcycle surge of luteinizing hormone (LH) is responsible for the terminal events associated with ovulation. These changes include resumption of meiosis, luteinisation and follicular rupture. In the stimulated cycles in various ovarian stimulation protocols, human chorionic gonadotrophin (HCG) derived from urinary sources has been exclusively used to bring about these changes[2]. HCG has been performing the role of surrogate LH because of the structural similarity between the two hormones. While efforts are on to study HCG produced by genetically engineered recombinant technology[3,4] alternate method of stimulating pituitary gonadotrophs to liberate LH at the desired time appears to be an interesting option.

All women undergoing ovarian stimulation except WHO group I patients are expected to have adequate pituitary LH reserve. Mobilization of endogenous LH, which mimics the preovulatory surge, can be brought about through the initial flare up effect of any potent GnRH agonist (GnRHa). Work done earlier in some IVF cycles, when down regulation was not in vogue has shown that such a method is capable of inducing oocyte maturation, subsequent fertilization and viable pregnancy. At present almost all IVF cycles are down regulated with long protocol. Hence, the scope for use of GnRHa on short-term basis in place of HCG to trigger ovulation is applicable only to non-IVF cycles. With this back ground, the present study was undertaken to evaluate the efficacy of two different preparations of GnRHa in triggering ovulation in the cycles planned for intrauterine insemination (IUI).

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Material and Methods

This study included 66 infertile patients who met our inclusion criteria, viz., age less than 30 years, bilateral patent fallopian tubes as evidenced by HSG and laparoscopy, and husband's seminogram within normal limits. Normal levels of FSH and LH signifying adequate gonadotroph reserve were insisted upon. Cases of anovulation were not taken as exclusion criteria unless it was a case of polycystic ovarian syndrome (PCOS). Finding of any pelvic or uterine factors on hysterolaparoscopy was considered as criteria for exclusion. Thus we had a cohort of patients in their twenties who had either anovulatory or unexplained infertility awaiting induction of ovulation for IUI.The following was the standard protocol of stimulation.

Clomiphene citrate (CC) 100 mg daily was given from day 2 to day 6 of the cycle followed by injection of 75 IU of FSH from day 6 to day 9 of the cycle.The follicular maturation was assessed using the usual sonographic criteria as monitored by 5mHZ vaginal probe with Philips 2000 plus system. Once the dominant follicle was 18mm or more with endometrial thickness of 8mm or more, the cycles were randomly assigned to one of the following three regimes –

a) Injection HCG 10,000 IU given intramuscularly. (Group A)

b) Nafarelin acetate 400 µgm given as intranasal spray. (Group B)

c) Triptorelin 0.1 mg given intramuscularly. (Group C)

Sonographic evidence of ovulation was looked for after 24 and 48 hours of drug administration. IUI was performed on demonstration of ovulation. No luteal phase support was used since as per the study design, luteal phase length was a secondary outcome measure and exogenous support could mask the observable difference in this outcome. Pregnancy was diagnosed by a sensitive urine test (Velocit, Dr. Reddy's Laboratory) in case of amenorrhoea. For the patients who were pregnant, progestational support was instituted at this stage as per the center's protocol. Early pregnancy loss, if any in the first trimester was noted and this was included in the study. Luteal phase length was calculated in all nonconceptional cycles. A luteal phase of 12 days or less was taken as inadequate.

Results

Out of the 176 therapeutic cycles undertaken in 66 patients over a period of 6 months, 9 were dropped because of poor ovarian response. Among the remaining 167 cycles, 60 had been triggered with HCG (Group A), 55 with nafarelin (Group B) and 52 with triptorelin (Group C). As the cycles and not the patients were randomized, it is possible that the same patient could have received different triggering protocols in different cycles. Four cycles in group A, five in group B and four in group C had shown evidence of follicular rupture at sonography done after 24 hours. Since physiologically LH surge precedes ovulation by about 42 hours, evidence of ovulation at 24 hours suggests that the endogenous LH surge had already been initiated by the natural process before administration of HCG or GnRHa. The drug might have only played a supportive role if any. Hence these 13 cycles were excluded from the study though IUI was duly performed. Thus 56 cycles from Group A, 50 cycles from group B and 48 from group C were available for comparison (Table I).

Following outcome measures have been compared between the three groups in Table II –

a) number of ovulatory cycles,

b) cases of ovarian hyperstimulation syndrome (OHSS),

c) number of conceptions,

d) number of early pregnancy losses,

e) number of ovulatory but nonconceptional cycles,

f) inadequate luteal phase length in nonconceptional cycles.

Discussion

The GnRH agonists have been playing a significant role in the assisted conception scenario whenever down regulation is required. With the arrival of antagonists providing new clinical opportunities, the flare effect of agonists may soon be considered a liability[5]. The same flare effect however, can be used to advantage when the cycle has not been down regulated. The dynamics of FSH and LH secretion after any short acting GnRH is acute LH release reaching it's maximum after about 4 hours, with a small but synchronous FSH peak[6]. The duration of LH peak is dependent on initial dose, but repeated administration does not prolong the duration[7]. However, the peak value of the surge is not dose dependent beyond a threshold[8]. The importance of repeating the dose in this background is only to cover for very occasional cases of trigger escape at the first dose. We have not repeated the dose in the current study. The randomization was done on the basis of the cycles instead of the patients so that the constitution of the groups becomes more comparable. This kind of randomization can expose the same patient to all the treatment protocols so that results are comparable. Such a study design does have the power and advantages of a cross over study. The ovulation rates are comparable between both the GnRHa groups indicating the efficacy of both the intranasal and intramuscular preparation of GnRHa in triggering ovulation. Other workers have reported similar ovulation rates achieved with other injectable preparations[9]. The pregnancy rates in the ovulatory cycles and subsequent early pregnancy wastages between the three groups are also comparable ($p > 0.05$). As regards ovarian hyperstimunation (OHSS), there were two cases of grade II in the whole series both occurring in group A. Our incidence is lower than that in other series because of difference in stimulation protocols[10]. This finding of significantly lower incidence of OHSS has been reported by other workers even when high risk cases have been assigned to GnRH analogue group in the study design[11]. Reduced risks of OHSS is possibly due to lower levels of serum estradiol detected in the luteal phase whenever GnRH analogues are used in place of HCG[12].

Another important concern when using an agonist to trigger ovulation is the high incidence of short luteal phase. Our findings of 21% and 19% in groups B and C respectively are slightly higher than the reported incidence of 16% to 18% by other authors[8,11]. The differences between group A and B and between group A and C are statistically highly significant ($p < 0.001$),

Table I. Cycles compared

Therapeutic cycles started	176		
Cycle excluded due to poor response	9		
Cycles used for random assignment	167		
Study groups	**A**	**B**	**C**
Cycles assigned to the group	60	55	52
Cycle excluded because of early ovulation	4	5	4
Cycles available for comparison	56	50	48

Table II. Outcome measures

EVENTS	GROUP A (n=56)		GROUP B (n=50)		GROUP C (n=48)	
	Number	Percentage	Number	Percentage	Number	Percentage
Ovulatory cycles	52/56	92.8	46/50	92	44/48	91.7
Ovarian hyperstimulation	2/26	3.6	-	-	-	-
Conceptions	9/52	17.3	8/46	17.4	7/44	15.9
Early pregnancy losses	1/9	11.1	1/8	12.5	1/7	14.2
Nonconceptional cycles	43/52	82.7	38/46	82.6	37/49	84.1
Short luteal phase[a]	3/43	7.0	8/38	21.0	7	19.0

[a] Differences between group A and B, and between A and C are statistically significant
X^2 (Fisher exact) = 32.03, df = 2, $p<0.001$

though they may not have ultimately affected the ovulation and conception rates. Several factors may be involved in causing short luteal phase. These include a defective LH surge or a spray malfunction in group B. It is also possible that the duration of LH surge achieved with GnRH analogue is not adequate. In a natural cycle LH rises for 14 hours, plateaus for 14 hours and declines for 20 hours[13]. Whereas in GnRHa triggered cycles the whole event is confined to 24 hours. Increasing the dose might alter the duration but the purpose of cost reduction, which is also an advantage, cannot be retained. The cost of our dose schedule for analogue is almost 30% of that of the HCG schedule.

As protocols for ovulation induction are being continuously refined new drugs will be marketed. After dominating the scene for decades urinary HCG is being challenged by recombinant HCG for performing the role of surrogate LH[14]. At the same time use of GnRH agonist to trigger endogenous LH to achieve the same aim is an interesting option. Our study suggests that the ovulation and conception rates are comparable with those of HCG regime. The advantage of avoiding OHSS is definitely worth noting, but the potential shortcomings of a short luteal phase cannot be ignored.

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