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Comparison of Different Stimulation protocols used in IVF in a Low Resource Set Up

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Abstract

Objective: To evaluate and compare the effectiveness of GnRH agonist and GnRH antagonist protocols in in vitro fertilization treatment.

Methodology: This retrospective comparative study was performed in Reproductive Medicine and fertility Department CMH Dhaka, Bangladesh from July 2017 to February 2020. Among 239 patients 187 were in GnRH agonist protocol group and 52 patients were in GnRH antagonist protocol group. Protocols were selected as per clinician's preference and patient's requirement. Data was collected in a preformed data collection sheet and analyzed by using SPSS version 20.

Results: Pregnancy rate is higher in GnRH agonist protocol (43.47%) than that of GnRH antagonist protocol (29.4%). Ongoing pregnancy rate and Live birth rate (both 23.5%) in GnRH antagonist Protocol which is greater than long agonist protocol (on going pregnancy rate and birth rate is 20.2% and 18.11% respectively). There is no abortion and ectopic pregnancy in GnRH antagonist protocol group. Abortion rate is 18.1% and rate of ectopic pregnancy is 2.1% in long agonist protocol group. 4.2% patients developed severe OHSS in long agonist protocol group, which was nil in antagonist protocol group.

Conclusions: Regarding outcome Implantation rate is more in GnRH long agonist protocol. GnRH antagonist protocol has less chance of OHSS and better pregnancy outcome which is of great importance in low resource set up.

Key words: Controlled ovarian hyper stimulation, GnRH long agonist protocol, GnRH antagonist protocol.

Introduction

Controlled ovarian hyper stimulation (COH) is a fundamental Step of in vitro fertilization (IVF) that has been practice since its initial practice in 1970s[1]. Gonadotropin releasing hormone (GnRH) agonist protocol has been developed and employed in the setting of IVF-ET treatment ever since 1980s. The GnRH agonist protocol is designed to suppress the release of pituitary follicle stimulating hormone (FSH) and Luteinizing hormone (LH) by desensitizing the pituitary receptor[2, 3]. The GnRH antagonist have also been found effective for ovarian stimulation by directly binding to the GnRH receptors, and through which they block GnRH receptor activity in a competitive manner and induce an immediate, reversible and rapid suppression of gonadotropin release[4] As a result, the GnRH antagonist protocol has also been widely employed recently in the clinical setting of woman's with IVF-ET treatment [5]. Overall, both analogues are widely used in IVF to induce folliculogenesis via prevention of endogenous LH Surge and timed oocyte retrieval[6, 7]. Despite the fact the GnRH agonist protocol is accompanied by some disadvantage, it has become widely used in clinical IVF-ET treatment and its application is associated with an increase in the rate of pregnancy[8]. There is evidence that application of GnRH antagonist protocol decreases the duration of ovulatory stimulus and reduced the incidence of ovarian hyper stimulation syndrome[9]. While these observations are exciting and encouraging,

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controversial have also been reported[10, 11]. To further address this question, we conducted this study which may have a great significance in low resource set up to bring our maximum success date.

Methodology

This study was designed as retro prospective comparative study. All patient undergoing IVF treatment from July 2017 to February 2020 in Reproductive Medicine and fertility Department, CMH Dhaka were included in this study. Among 239 patients 187 were in GnRH-Agonist Protocol group and 52 were in GnRH antagonist protocol group. Agonist and antagonist protocols were chosen according to the clinician's choice and patient's requirements. All categories of patients including normo, hypo & hyper-responders were included in this study. Both conventional IVF & ICSI-IVF were done according to patients requirements. GnRH agonist was used as long protocol. In long protocol, leuprolide accrete (Lucrine^{R}) daily 0.5 mg was given on the 21st day of previous menstrual cycle and continued up to day of trigger. On second day of cycle after down-regulation of pituitary controlled ovarian hyper stimulation were started with inj Gonal F or inj Menogon 75 IU according to patients need. After 6 days of stimulation all were shifted to Menogon. In Antagonist regimes controlled ovarian hyper stimulation were started from 2nd day of menstruation and pituitary suppression was managed with Cetrorelix (Cetrotide .25). Flexible regime was preferred with Cetrorelix Starting on day of cycle when the leading follicle reached to 13-14 mm. Ovarian response was assessed by transvaginal ultrasonography (TV USG) in both cycles. When at least 3 or four follicle reached a mean diameter of 17 or 18 mm, 10000 IU of hCG or 250microrram Ovidrel was administered and after 36-38 hours TVS guided Oocyte retrieval was performed under total intravenous anesthesia. Conventional IVF, or IVF-ICSI or IVF-PESA, TESA-ICSI were done according to patients profile.

Embryo culture was done using G-Mops plus, G-IVF plus, G1-Plus, G2-Plus. Embryo were classified according to the number of blastomere, percentage of fragmentation and blastomere appearance as grade I,II,III IV. D_2 or D_3 embryos (gradeI and II) were transferred in fresh cycle or FET cycle. Each patient underwent only one cycle of fresh embryo transfer or frozen embrayo transfer. Among 187 patients of GnRH agonist protocol 138 completed embryo transfer cycle and 17 out of 52 patients of GnRH antagonist completed embryo transfer cycle. group Luteal phase support was given (Inj Gestone), Tab Microgest 100 mcg & Tab Duphaston 10 mg stared on day of oocyte pick up (OPU) in fresh transfer cycle or when endometrium well prepared in embryo transfer cycle (FET) and continued upto 18 days (until the serum B-HCG measurement). If pregnancy occurred progesterone was given until 12th week of gestation. The efficacy outcome measures included E_2 value on day of hCG, the number of oocyte retrieved, the pregnancy rate, ongoing pregnancy rate and birth rate. The outcome measures of the safety included the incidence of OHSS, abortion rate and the cycle cancellation rate.

Data were collected using a data sheet and then collected data were compiled and analyzed. Statistical analyses were performed using SPSS software (version 20.00).

Results

Patients of GnRH agonist and Antagonist were matched according to their age, BMI, basal hormonal level and AMH. I87 patients were in GnRH agonist protocol group and 52 patients were in GnRH antagonist protocol group. Patient's age of agonist group is 30.48±4.60 and mean age of antagonist is 33.58±5.48.BMI and basal hormone levels were almost similar. But AMH level is higher in Antagonist protocol group is higher (4.17 ± 3.4) than agonist

protocol group (2.9±2.4) as shown in Table 1

Table 1: Baseline characteristics

Parameters	GnRH agonist (n=187)	GnRH antagonist (n=52)
Age	30.48±4.60	33.58±5.48
BMI(kg/m2)	27.1±3.4	26.7±3.4
FSH	6.5±2.6	6.2±2.8
LH	5.3±3.3	5.8±3.5
AMH	2.9±2.4	4.1±3.4

BMI-body mass index, FSH-follicle stimulating hormone, LH-luteinizing hormone, AMH-anti mullerian hormone

Table 2: Efficacy outcome

Parameter	GnRH agonist	GnRH antagonist
E2 on Day of HCG	4663.19±4671	4984.34±4571
Retrieved oocyte number	8.44±7.2	8.23±7.3
Number of embryo	4.03±4.17	4.32±4.71

Table 2 shows there is lower E2 on day of HCG in agonist protocol (4663.19±4671) than antagonist protocol (4984±4571) no difference between retrieved oocyte number and number of developed embryo between agonist and antagonist protocol.

Table 3: Pregnancy outcome

Parameters	GnRH agonist Protocol	GnRH antagonist Protocol
Pregnancy rate%	60/138(43.47)	5/17(29.4)
Ongoing Pregnancy rate%	28/138(20.28)	4/17(23.5)
Abortion%	25/138(18.11)	0
Ectopic pregnancy%	3/138(2.1)	0
Birth rate %	25/138(18.11)	4/17(23.5)

Pregnancy rate was higher in long agonist protocol (43.47%) than that of GnRH antagonist protocol (29.4%). Ongoing pregnancy rate and Live birth rate (both 23.5%) in GnRH antagonist Protocol which was greater than long agonist protocol (on going pregnancy rate and live birth rate was 20.2% and 18.11% respectively). There is no abortion and ectopic pregnancy in GnRH antagonist protocol. Abortion rate was 18.1% and rate of ectopic pregnancy is 2.1% in long agonist protocol shown in table 3.

Table 4: Safety outcome

Parameters	GnRH agonist protocols	GnRH antagonist protocols
Severe OHSS %	8/187(4.2)	0
Cycle cancellation rate%	13/187(7.0)	8/52(15)
Total fertilization failure	14/187(7.48)	5/52(9.6)

Table 4 shows that Severe OHSS rate is nil in antagonist protocol. But cycle cancellation rate and total fertilization rate is more in antagonist protocol (15% and 9.6%)

Discussion:

Main goal of COH is to obtain a greater numbers of mature follicles by suppressing the premature LH surge. Compared to patients treated with GnRH antagonist protocol, patient treated with GnRH agonist protocol demonstrated a significantly higher number of oocyte retrieved and mature oocyte production[12, 13].High number of oocyte production with GnRh agonist long protocol suggested that protocol improved the number of embryos produced. Therefore GnRH long protocol also improve the cumulative pregnancy rate. A study conducted Rabinson at al. also favored the agonist protocol in patient with normal body mass index[14]. In our study we did not find any difference in oocyte retrieval and embryo production.

Fleming et al. first reported that IVF outcome started to increase with GnRH agonist usage However, most of these therapies failed because of detrimental

effect of premature progesterone rise and high E_2 levels(15,16) Basir et al. shown that high serum E_2 led to dis harmony between endometrial stoma and glands. As a result, implantation could be affected negatively [17]. Schachter et al. Shows that the E_2 value on day of HCG was slightly lower in GnRH antagonist group than GnRH agonist group probably due to that the antagonist repressed endogenous GnRH secretion in the follicle growth period[18]. In our study we found mild raise of E_2 level in day of HCG trigger. It may be due to most of patients of antagonist protocol were selected for PCOS patients. AMH 4.17±3.4 in antagonist protocol group compare to agonist protocol group (2.9±2.4) can approve this.

Takahashi and colleagues, the implantation rate and clinical pregnancy rate in antagonist protocol were significantly higher than that of agonist long protocol[19]. Meta-analysis shows clinical pregnancy rate was lower in GnRH antagonist group than in the GnRH agonist group but no statistically significant difference in the ongoing pregnancy rate and live birth rate in between two groups[20-24]. In our study we found pregnancy rate is higher in GnRH agonist group (43.47% versus 29.4%). But ongoing pregnancy rate and birth rate is better in GnRH antagonist group.

Lainas et al. shows that antagonist protocol in the prevention of moderate to severe ovarian hyper stimulation syndrome (OHSS), specially in woman with PCOS, because of its rapid suppression of gonadotropin[25]. Our study shows the similar result. In our study there is no OHSS in antagonist protocol group and 4.2% patients developed Severe OHSS in agonist protocol group. The study of Alama et al. Found administration of GnRH agonist following HCG administration to be important strategy to prevent OHSS[26].

Different studies show there is no significant difference in abortion rate and cycle cancellation rate in between two groups[20-24]. Cycle cancellation rate is higher (15.4%) in antagonist protocol group than agonist protocol group (7%) in our study. There was no abortion in antagonist protocol group and abortion rate was 18.11% was in agonist group in our study.

Conclusion:

During IVF treatment incidence of ovarian hyper stimulation syndrome (OHSS) was lower but cycle cancellation rate and Total fertilization failure was higher in GnRH protocol. Though Pregnancy rate was higher in GnRh agonist group on going pregnancy rate, birth rate is higher in GnRH antagonist group.

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