Clinical outcome of Stimulation Protocols in Assisted Reproductive Technology

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ABSTRACT

Background: Assisted Reproductive Technology (ART) is a complex and costly procedure where individualized ovarian stimulation protocols play a pivotal role in determining outcomes. Appropriate selection of stimulation protocols based on patient characteristics can improve treatment success. Evaluating these protocols through standard key performance indicators (KPIs) provides insight into clinical efficacy and patient benefit.

Objective: To compare and evaluate the clinical outcome of stimulation protocols of ART.

Methods: This Quasi-experimental study was conducted in the Department of Reproductive Endocrinology and Infertility at CMH Dhaka from September 2022 to August 2023. A total of 70 patients undergoing IVF were included, with 32 (45.7%) managed using gonadotropin releasing hormone (GnRH) agonist protocol and 38 (54.3%) with GnRH antagonist protocol. Clinical outcomes assessed included cycle cancellation rate prior to oocyte pick-up (OPU), ovarian hyperstimulation syndrome (OHSS) incidence, empty follicle syndrome (EFS), oocyte retrieval rate, proportion of metaphase II (MII) oocytes at ICS and OPU-related complications.

Results: Cycle cancellation rates were 3.1% for the agonist group and 7.9% for the antagonist group. Oocyte retrieval rates exceeded 60% among about half of the patients in both protocols. EFS was observed in 5.3% of antagonist cases but none in the agonist group. A significantly higher proportion of MII oocytes (>70%) was seen in the antagonist protocol ($p<0.05$). OHSS occurred in 7.9% of antagonist and 3.1% of agonist cycles. OPU complications occurred in 2.6% of antagonist cases and none in the agonist group.

Conclusion: Both agonist and antagonist protocols demonstrated comparable clinical outcomes. The findings suggest that either protocol can be effectively used in ART, with selection tailored to individual patient profiles.

Keywords: ART, GnRH agonist protocol, GnRH antagonist protocol.

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INTRODUCTION

Assisted Reproductive Technology (ART) has emerged as a cornerstone in the management of infertility but remains a complex and resource-intensive process. This integrates a sequence of clinical and laboratory steps. These includes controlled ovarian stimulation, oocyte pick-up (OPU), fertilization, embryo culture and either embryo transfer (ET) or cryopreservation, ultimately leading to implantation and live birth if successful.[1] Due to its multifaceted nature, ART demands seamless coordination between clinicians and embryologists, and success is highly dependent on the selection and execution of appropriate stimulation protocols.

One of the significant challenges in ART cycles is managing patients with high ovarian reserve, who are prone to hyper-responsiveness to gonadotropin stimulation. This excessive response may result in iatrogenic complications such as ovarian hyperstimulation syndrome (OHSS), ovarian torsion and related discomfort.[2] To address this, various mitigation strategies have been developed. Among them, replacing the conventional human chorionic gonadotropin (hCG) trigger with a gonadotropin releasing hormone (GnRH) agonist for final oocyte maturation and administering GnRH antagonists or cabergoline post-OPU have shown effectiveness in reducing the incidence of OHSS.[3,4]

Despite the success of these strategies in lowering severe OHSS rates, mild to moderate forms persist, often causing abdominal pain and bloating.[5] The adoption of patient-friendly protocols, particularly GnRH antagonist protocol has gained f a s c i n a t i o n due to their lower hormonal load, reduced costs, decreased need for intensive monitoring and enhanced safety profile.[6-9] The cornerstone of successful ART lies in personalized ovarian stimulation which aligns the protocol with individual patient characteristics to improve outcomes while minimizing risks.

Given the economic constraints and resource limitations, especially in government or military healthcare settings, performing ART becomes even more challenging. Furthermore, societal expectations and institutional accountability amplify the pressure on providers to optimize outcomes with limited means. A patient-centered ovarian stimulation strategy is the foundation of successful ART. By tailoring stimulation protocols to individual patient profiles, clinicians can improve clinical outcomes while reducing complications, costs and treatment burden. Evaluating the efficacy of various stimulation protocols using standard key performance indicators (KPIs) not only enhances patient care but also supports evidence-based practice and rational use of limited resources.

This study was therefore undertaken to assess the clinical outcomes of different stimulation protocols in in vitro fertilization (IVF), aiming to guide optimal protocol selection and responsible utilization of resource-limited settings.

MATERIALS AND METHODS

This Quasi-experimental study was conducted in the Department of Reproductive Endocrinology and Infertility, Combined Military Hospital (CMH), Dhaka, Bangladesh from September 2022 to August 2023, following ethical clearance from the ethical committee of CMH Dhaka.

The sample size calculated by using the formula n = z2pq/d2 was 96. But during the study period 70 patients met the inclusion and exclusion criteria. So 70 women aged 21– 40 years undergoing IVF for medical indications or fertility preservation were enrolled after providing written informed consent. Exclusion

criteria included uncorrected endocrine disorders, major systemic illnesses or refusal to participate. Participants were allocated to either GnRH agonist or antagonist stimulation protocols based on clinical indications. Data were collected through hospital record sheets, laboratory and radiology reports using a structured data collection sheet. Clinical outcomes—such as cycle cancellation rate, OHSS rate, empty follicle syndrome, oocyte retrieval rate, proportion of MII oocytes at ICSI, and OPU complications—were assessed during the stimulation phase, at oocyte retrieval (typically within 10–14 days of starting stimulation) and 7 days after OPU.

Continuous variables (e.g., age, BMI, number of oocytes retrieved) were expressed as mean ± standard deviation, and categorical variables (e.g., protocol type, occurrence of OHSS, cancellation status) as frequencies and percentages. Data analysis was performed using SPSS version 23.0. The chi-square test was applied to compare categorical variables and the independent samples t-test was used for continuous variables. A p-value of <0.05 was considered statistically significant. Homogeneity testing was not applied, as it was not required for the descriptive and comparative objectives of this study.

RESULTS

TABLE-I: Socio-demographic characteristics of the patients (n=70)

Socio-demographic characteristics	Number of patients	Percentage
Religion		
Islam	67	95.7
Hindu	3	4.3
Husband occupation		
Service holder	64	91.4
Businessman	5	7.1
Teacher	1	1.4
Wife occupation		
Housewife	51	72.9
Service holder	16	22.9
Businessman	3	4.3

Table-1 showed sociodemographic characteristics which revealed that 95.7% couples were Muslim. 91.4% of the husbands were service holders and 72.9% wives were housewives.

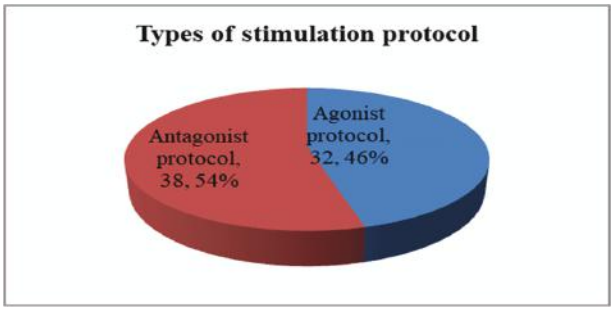

Figure-1: Types of stimulation protocols

Figure-1 showing 38.54% patients underwent IVF with agonist protocol while 32.46% had antagonist protocol

TABLE-II: Relation between age and BMI of the respondents with stimulation protocol (n=70)

Age and BMI	Type of stimulation protocol		p value
	Agonist protocol (32)	Antagonist protocol (38)	
	Mean±SD	Mean±SD	
Age of husband (years)	34.6±4.5	36.1±6.0	0.236^{ns}
Age of wife (years)	28.9±3.9	30.4±4.5	0.155^{ns}
BMI of wife (kg/m^2)	24.3±3.3	24.9±3.7	0.482^{ns}

Table-2 revealed that there was no significant difference in mean age of husband and wife and BMI of the wives in two stimulation protocols (p>0.05).

TABLE-III: Relation between type and duration of subfertility of the respondents with stimulation protocols (n=70)

Subfertility history	Type of stimulation protocol		Total	p value
	Agonist protocol (32)	gonist protocol (38)		
Type of subfertility	n(%)	n(%)		
Primary	21 (65.6)	31 (81.6)	52	0.12^{ns}
Secondary	11 (34.4)	7 (18.4)	18	
Duration of subfertility				
≤5	8 (25.0)	7 (18.4)	15	
6-10	15 (46.9)	15 (39.5)	30	0.55^{ns}
11-15	9 (28.1)	15 (39.5)	24	
>15	0 (00)	1(2.6)	01	

Table III revealed most patients were suffering from primary subfertility in both protocols (65.6% in agonist and 81.6% in antagonist protocol). Duration of subfertility was 6-10 years in most of the patients (46.9 % in agonist protocol and 39.5% in antagonist protocol).

TABLE-IV: Relation between indication of IVF of the respondents with stimulation protocol (n=70)

Indication of IVF	Type of stimulation protocol		Total	p value
	Agonist protocol (32)	Antagonist protocol (38)		
Female factor (61.42%)	n (%)	n (%)		
Tubal damage or blockage	10 (31.3)	4 (10.5)	14	0.125^{ns}
POCS	4 (12.5)	13 (34.2)	17	0.011^{s}
DOR (AMH <1.1 ng/ml)	2 (6.3)	8 (21.0)	10	0.026^{s}
Pelvic endometriosis	1 (3.1)	1 (2.6)	02	0.709^{ns}
Male factor (38.57%)	15 (46.9)	12 (31.6)	27	0.190^{ns}

Table IV revealed female factor was present in 61.42% cases and male factor was present in 38.57% cases. Among female factors significant higher number of cases with PCOS and DOR were treated by antagonist protocol. Most patients with tubal factor were treated with agonist protocol.

Cases of pelvic endometriosis was treated by both protocols equally.
Most patients with male factor were treated by agonist protocol.
Male factor included azoospermia, severe oligozoospermia, asthenozoospermia and severe OAT.

TABLE-V: Relation between clinical outcome with stimulation protocol (n=70)

Variables	Type of stimulation protocol		Total	p value
	Agonist protocol (32) n(%)	Antagonist protocol (38) n(%)		
Cycle cancellation before OPU	1 (3.1)	3 (7.9)	04	0.37^{ns}
Oocyte recovery rate (>60%)	16 (50)	18(47.4)	34	0.82^{ns}
Empty follicle syndrome	00	02(5.3)	02	0.29^{ns}
Complication rate after OPU	00	01 (2.6)	01	0.54^{ns}
Early onset OHSS	01 (3.1)	03(7.9)	04	0.375^{ns}

Table V revealed that clinical outcomes including cycle cancellation before OPU, oocyte recovery rate (>60%), empty follicle syndrome, complication rate after OPU and early onset OHSS showed no statistically significant differences between the agonist and antagonist protocol groups. Although the antagonist group had slightly higher rates in all these parameters, the differences were not significant (p>0.05), indicating comparable safety and effectiveness of both protocols in these aspects.

TABLE-VI: Relation between No. and proportion of MII oocyte at ICSI with stimulation protocols (n=70)

Variables	Type of stimulation protocol		p value
	Agonist protocol (ICSI=19)	Antagonist protocol (ICSI=17)	
No of MII oocyte			
>10	04 (21.1)	03(17.6)	0.79 ^{ns}
≤ 10	15 (78.9)	14 (82.4)	
Proportion of MII oocyte			
>70%	09(47.4)	15(88.2)	
≤70	10 (52.6)	02(11.8)	0.009^{s}

Table VI revealed among patients undergoing ICSI, the number of MII oocytes retrieved was similar between the two groups, with no statistically significant difference (p=0.79). However, the proportion of MII oocytes >70% was significantly higher in the antagonist protocol group (88.2%) compared to the agonist group (47.4%) (p=0.009), indicating better oocyte maturation with the antagonist protocol.

DISCUSSION

This Quasi-experimental study was conducted in the Department of Reproductive Endocrinology and Infertility, CMH Dhaka, to evaluate the clinical outcomes of different ovarian stimulation protocols — (agonist and antagonist) used in assisted reproductive technology (ART). All IVF procedures were

carried out for medical indications only, with no fertility preservation cases. The common indications included tubal blockage, polycystic ovary syndrome (PCOS), low ovarian reserve, pelvic endometriosis, and severe male factor infertility, consistent with previous findings by Dunselman et al.[10]

Cycle cancellation before oocyte pick-up (OPU) is a critical performance indicator in ART. In our study, the cancellation rate was higher in the antagonist group, primarily due to poor ovarian response, exceeding the benchmark value of 6% suggested by the Maribor Consensus.[11]

Oocyte recovery rate (ORR) was >60% in 50% of patients undergoing the agonist protocol and 47.4% in the antagonist group, where triggering was done at an average follicular size of ~20 mm. This is similar to the findings of Bosdou et al.[12] who reported a mean ORR of 62.5%.

Empty follicle syndrome (EFS) was found in 5.3% of patients in the antagonist group but was absent in the agonist group. While our data differ slightly, it is worth noting that EFS is generally considered a rare, isolated event rather than a distinct clinical syndrome, as outlined by van Heusden et al.[13]

A total of 36 patients underwent intracytoplasmic sperm injection (ICSI), among whom the proportion of metaphase II (MII) oocytes was evaluated. In the antagonist group, 88.2% of cycles achieved >70% MII oocytes, aligning with the Maribor Consensus competence value of 74%.[11] However, in the agonist group, only 47.4% achieved this level, indicating a statistically significant difference favoring the antagonist protocol in terms of oocyte maturity.

Regarding procedural complications, only 2.6% of patients in the antagonist group experienced minor complications such as post-OPU per vaginal bleeding and haematuria, whereas no complications were observed in the agonist group. Our complication rate was higher than the 0.4% reported by Levi-Setti et al.[15] possibly due to procedural technique.

Early-onset ovarian hyperstimulation syndrome (OHSS) was more frequent in the antagonist group (7.9%) than in the agonist group (3.1%). These findings contradict those of Al-Inany et al.16 who reported a lower OHSS incidence (2.14%) with antagonist protocols compared to 6.43% in agonist cycles. The discrepancy may be attributed to the higher prevalence of PCOS patients in our antagonist group, many of whom received hCG triggers, a known risk factor for OHSS.

Overall, while both stimulation protocols showed comparable safety and clinical effectiveness, the antagonist protocol demonstrated superior performance in terms of oocyte maturity but also carried a slightly increased risk of minor complications and early-onset OHSS in specific subgroups.

In our country study on evaluation of clinical outcome of stimulation protocols of ART as per standard KPI is very scarce, so this study will add in this field. Our study has also few limitations, like- limited number of patients were included. This could lead to bias as the results cannot be generalized to the wider population. Duration of study was also very short and only two stimulation protocols were studied. There was no case of fertility preservation.

CONCLUSION

Both GnRH agonist and antagonist protocols yielded comparable ovarian responses and clinical outcomes in terms of oocyte recovery rate, oocyte maturity, incidence of OHSS, and post-OPU complications. Although the cycle cancellation rate due to poor ovarian response was slightly higher with the antagonist

protocol, it demonstrated a significantly greater proportion of mature (MII) oocytes. Given its simplicity, shorter duration, and cost-effectiveness, the GnRH antagonist protocol may be considered a more patient-friendly option in routine clinical practice.

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