Oocyte and Embryo Qualities in Different Stimulation Protocols in IVF/ICSI Cycles: A Retrospective Study

Original Article

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ABSTRACT

Background: Worldwide, ovarian stimulation for Intracytoplasmic Sperm Injection (ICSI) uses GnRH analogues, agonists, and antagonists. They control pituitary activity to prevent LH surges and optimize oocyte retrieval. The consequences of advances on oocyte quality and embryo development are uncertain. GnRH agonists desensitize pituitary GnRH receptors gradually, while antagonists immediately decrease gonadotropin release. Oocyte and embryo quality and development, as well as mother age, hormonal condition, and infertility duration, have been examined to affect ICSI success.

Objectives: To examine the effects of the multiple-dose GnRH antagonist protocol on egg, embryo, and embryo development in IVF/ICSI cycles compared to the long protocol.

Patients and Methods: Two hundred and thirty two patients were included in this retrospective study. It was conducted in Division of Assisted Reproduction, Department of Obstetrics and Gynecology, South Valley University, Tanta University, and private centers. It included patients in the period from July 2017 to December 2022. Patients' data, stimulation protocols, oocytes and embryo qualities were assessed and pregnancy rates. Patients were allocated according to stimulation protocol into agonist and antagonist groups. Data were gathered and analyzed.

Results: Basal demographic data of both groups was comparable. Gonadotropins dose in both groups were 3899.26 ± 1363.99 IU/ml in antagonist group versus 3737.69 ± 932.26 IU/ml in agonist group (*p*=0.287). Oocytes numbers, and quality of oocytes were better in agonist protocol but the differences were not significant. Stimulation duration was negatively correlated. Embryo quality was comparable in both groups (*p*=0.681).

Conclusion: The GnRH agonist regimen had increased mature oocytes with good quality oocytes but differences not reaching clinical significance. Fertilization rates and embryo parameters were similar, however stimulation duration significantly affected oocyte and embryo quality.

Key Words: Anti-Mullerian hormone, GnRH agonist, GnRH antagonist, embry, oocytes.

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INTRODUCTION

Gonadotropin releasing hormone (GnRH) analogues, which can be either agonists or antagonists, are widely used all over the world for the purpose of ovarian stimulation in intracytoplasmic sperm injection (ICSI). The major objective of these analogues is to limit the action of the pituitary gland, which has the effect of inhibiting the early production of luteinizing hormone (LH). As a result, the time of the oocyte retrieval may be more precisely controlled. There is still a lack of clarity on the influence that these technologies have on the quality of oocytes and the development of embryos^[1], despite the fact that there have been breakthroughs in the technology that are used for ovarian stimulation and with the knowledge that is available about reproductive outcomes. Following the initial rise in gonadotropin production from the pituitary gland, the production of gonadotropins from the pituitary gland gradually decreases as a result of the continuous administration of GnRH agonists. When GnRH agonists are administered to the pituitary gland, they cause the receptors to become desensitised. GnRH antagonists, on the other hand, are able to diminish gonadotropin in a quick and immediate manner by competitively antagonising GnRH receptors^[2].

An examination was conducted on a number of factors that contribute to the effectiveness of intracytoplasmic sperm injection (ICSI). These factors included the age of the mother, the levels of hormones, the length of time the patient had been infertile, and the receptiveness of the endometrium^[1]. The amount and quality of oocytes, as well as the grading and development of embryos, were additional aspects that were investigated in this study^[3]. The primary aims of this retrospective cohort study were to investigate the impact of GnRH agonist and GnRH antagonist treatments on oocyte quality and embryo development, as well as the reproductive outcomes of the study participants^[4].

In the context of in *vitro* fertilisation (IVF) treatment, it is of the utmost importance to have a thorough understanding of the influence that ovarian stimulation strategies have on the quality of the embryo. A great number of clinical research have been conducted over the course of the past twenty years to explore the differences in operations that are carried out by GnRH agonists and GnRH antagonists. Although the majority of the study focused on the clinical consequences of these therapies, there is still a lack of understanding about the precise influence that GnRH analogues have on the quality of oocytes and embryos, as well as the development of embryos^[5,6].

The aim of this study was to evaluate the impact of a multiple dose regimen of GnRH antagonists in comparison to the extended regimen of GnRH agonists on the quality and development of oocytes and embryos in IVF/ICSI cycles.

PATIENTS AND METHODS

The study utilized a retrospective cohort design and collected data from patients who participated in the IVF/ ICSI program at the Division of Assisted Reproduction, Department of Obstetrics and Gynaecology, South Valley University, Tanta University, and private facilities. An evaluation was carried out to determine the suitability of bicycles that occurred between July 2017 and December 2022 for potential inclusion.

Eligibility

Patients were included based on their compliance with the specified inclusion and exclusion criteria. The criteria for inclusion were as follows: (a) individuals aged between 20 and 35 years, (b) body mass index within the range of 18 to 29.9, (c) normal levels of hormones including TSH, Testosterone, and Prolactin (e) normal condition of the endometrial cavity, and (f) transfer of blastocysts on the fifth day. The exclusion criteria encompassed the following: (a) endometriosis grade III or IV, (b) azospermic male, (c) concurrent medical diseases such as Diabetes mellitus, adrenal or thyroid abnormalities, and (d) prior ovarian surgery. The study eliminated cycles that were cancelled (no oocyte retrieval was done) and cycles that used preimplantation genetic diagnosis (PGD).

Patients were aalocated into 2 groups:

• During the ovarian stimulation process, the antagonist group was administered a GnRH antagonist by the physician.

• The GnRH agonist procedure was utilised at the agonist-group level.

Interventions

Protocols of stimulation

- Flexible GnRH antagonist protocol was applied using Cetrorelex Acetate (Cetrotide; Merck-Serono, Geneva) in a dose 0.25 mg per day was used in antagonist group when dominant follicle reach 14 mm till the day of triggering of ovulation.
- The agonist employed in the agonist protocol was Triptorelin (Decapeptyl, Ferring pharmaceutical, Switzerland) at a daily dosage of 0.1 mg, commencing from the midluteal phase of the preceding cycle before the treatment cycle.
- Gonal F (Follitropin alpha, Merck-sorono, Geneva) was utilized as a means of stimulating using recombinant FSH. The dosage of folliclestimulating hormone (FSH) was modified based on the patient's age, body mass index (BMI), and ovarian reserve in both groups. Ovarian response was assessed in patients every other day.
- Ovulation was stimulated by administering 5,000-10,000 IU of HCG (Choriomon; IBSA) once a dominant follicle reached a diameter of at least 18 mm. In cases of Polycystic Ovary Syndrome (PCOS) when the antagonist protocol was employed, a trigger called agonist (Decapeptyl 0.1mg) was administered subcutaneously in the form of two ampoules. This was done to reduce the occurrence of ovarian hyperstimulation syndrome.
- The process of extracting oocytes was carried out with the assistance of transvaginal ultrasound guidance, within a time frame of 36-38 hours after applying the trigger.
- Embryo transfer was done on day 5 where 2 blastocysts were transferred under ultrasound guidance.
- Luteal support was initiated with Prontogest vaginal ovules 400 mg (IBSA), administered intravaginally twice daily for a duration of 14 days starting from the day of ovum pick up.

Oocyte quality assessment

Prior to the injection of sperm, comprehensive assessments were carried out in order to take into account the morphology and maturity of the oocyte. For the purpose of this evaluation, particular morphological criteria were utilized. Standard oocytes were distinguished by the presence of a cytoplasm that was uniform and homogeneous, a polar body that was round or oval in shape and had a smooth surface, a zona pellucida that was normal, and a perivitelline space that was usual. The presence of vacuoles, refractile particles with a granular appearance, and aggregation of endoplasmic reticulum inside the cytoplasm were the identifying characteristics cytoplasmic dysmorphisms. of Extracytoplasmic dysmorphisms included abnormalities in the form of the oocyte, thickness and/or darkening of the zona pellucida, expansion of the perivitelline space, fragmentation, enlargement, and/or degeneration of the polar body, and irregularities in the shape of the oocyte. Both inside and outside of the cytoplasm, there were several dysmorphisms that were seen.

The existence of a polar body was used as a criterion for determining the maturity of the oocyte. At the metaphase II (MII) stage, oocytes were considered to be mature. On the other hand, immature oocytes were classed as those that lacked a polar body, possessed a germinal vesicle (GV), or were at the MI stage. In order to get the maturation index, the number of MII oocytes was divided by the total number of oocytes that were extracted.

For the purpose of estimating the pregnancy rate, the proportion of pregnant women among all of the women who were included in the same treatment regimen group was determined.

Blastocyst quality assessment

A cavity that is filled with fluid, an inner cell mass (ICM), and a trophectoderm (TE) are the components that make up a blastocyst. We utilized the Gardner method, which operates on a scale ranging from 1 to 6, with 5 signifying the most advanced growth. This system evaluates the quality of the cavity as well as its expansion. Letters (A, B, and C) were used to classify the quality of the Inner Cell Mass (ICM) and Trophectoderm (TE), with A being the greatest quality and B, C, and C respectively signifying good, fair, and poor quality. Information of an alphanumeric nature, such as 4AA or 2AC, was used to represent the overall quality. The percentage of embryos that were good and those that were bad was used to characterize the quality of the embryos.

Data collected

The comprehensive clinical dataset comprises a multitude of factors pivotal to the assessment and treatment of female fertility. These include but are not limited to the woman's age, body mass index (BMI), levels of day 3 follicle-stimulating hormone (FSH), antimullerian hormone (AMH), and thyroid stimulating hormone (TSH), as well as the indication necessitating intracytoplasmic sperm injection (ICSI). Through the utilization of ultrasound technology, thorough evaluations are conducted, encompassing the count of follicles within the antrum, the condition of the endometrial cavity, detection of any uterine abnormalities or pathologies, and identification of pelvic lesions.

Central to the treatment protocol are considerations such as determining appropriate gonadotropin dosage, duration of stimulation, attainment of mature follicles (typically 18 mm or larger), and monitoring the thickness of the endometrial lining. Parameters of utmost importance throughout the process include the count of retrieved oocytes, assessment of oocyte quality, maturation index, as well as evaluation of both quantity and quality of developing embryos, culminating in the determination of the number of embryos to be transferred.

Subsequent calculations involve the determination of fertilization rates, implantation rates, and clinical pregnancy rates, providing essential metrics to gauge the efficacy of the intervention.

Ethical issues

Despite its retrospective nature, this study received approval from the local ethics committee of South Valley University. Data privacy was upheld throughout the duration of the study.

Statistical methods

The demographic and clinical data underwent examination using descriptive statistics. The data was managed and analysed using the Statistical Package for Social Sciences (SPSS) software, especially version 26. Qualitative variables were assessed by calculating frequencies and percentages, and comparisons were conducted using the Chi-square test. The ordinal variables were assessed based on their median and range. Statistical significance was established by using a *P value* of 0.05 or less.

RESULTS

A total of 275 cycles were examined. Thirteen cases were excluded and 262 cases were allocated to either agonist or antagonist group. Exclusion of cancelled cases and PGD cases as shown in (Figure 1).

No significant disparities were detected between the two cohorts concerning their baseline characteristics. This includes the average age of patients, their body mass index (BMI), and the duration of infertility. Additionally, the type and etiology of infertility were consistent across both groups. Notably, (Table 1) illustrates that there were no notable discrepancies in anti-mullerian hormone (AMH) levels.

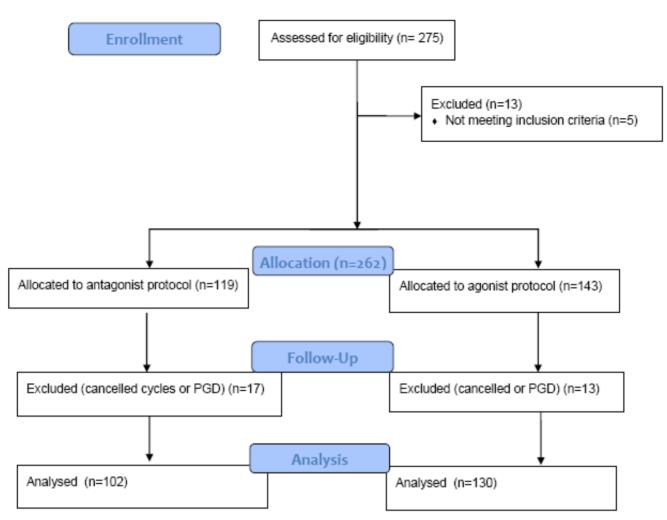


Fig. 1: flow chart of patients in this study

Table 1: Baseline characteristics of the patients

	GnRH Antagonist (N = 102)	GnRH Agonist (N = 130)	P. Value
Age (years)	29.21 ± 3.98	28.91 ± 3.97	0.569
BMI (Kg/m ²)	25.59 ± 2.81	25.63 ± 2.65	0.923
Type of infertility (n,%)			
Primary infertility	70 (69.3%)	90 (69.2%)	1
Secondary infertility	31 (30.7%)	40 (30.8%)	1
Duration of Infertility (years)	5.56 ± 2.81	5.98 ± 3.18	0.298
AMH (ng/mL)	3.41(2.24)	2.23(0.51)	0.11
Cause of infertility (n,%)			
Ovarian factor	44 (43.6%)	1 (0.8%)	
Male Factor	22 (21.8%)	51 (39.2%)	
Tubal Factor	10 (9.9%)	21 (16.2%)	
• Unexplained	16 (15.8%)	39 (30.0%)	
Uterine Factor	0 (0.0%)	5 (3.8%)	
Combined factors	9 (8.9%)	13 (10.0%)	

BMI: body mass index

(Table 2) delineated the specifics of ovarian stimulation. Notably, there were no statistically significant differences between the groups regarding the dosage of gonadotropins (p=0.287) or the duration of infertility (p=0.239). While

the oocyte count was marginally lower in the antagonist group at 13.19 ± 4.42 compared to 14.69 ± 7.21 in the agonist group (*p*=0.05), both cohorts displayed similar oocyte maturity and quality, as indicated by (Figures 2,3).

	GnRH Antagonist (N = 102)	GnRH Agonist (N = 130)	P. Value
Gonadotropins dose (IU/ml)	3899.26 ± 1363.99	3737.69 ± 932.26	0.287
Duration of stimulation	12.10 ± 1.71	11.85 ± 1.45	0.239
Number of Oocytes/cycle	13.19 ± 4.42	14.69 ± 7.21	0.05
Maturity of oocytes (n,%)			
• Mature	1295 (86.5 %)	1559 (90.9 %)	0.289
• Immature	201 (14.4 %)	156 (9.1 %)	0.208
Morphology of oocytes (n,%)			
• Normal	1218 (81.4%)	1419 (82.7%)	0.798
• Abnormal	77 (5.1%)	140 (8.2%)	0.354

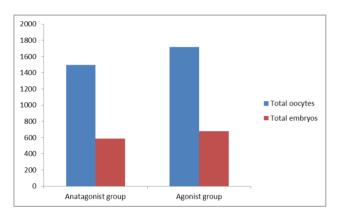


Fig. 2: Total number of oocytes & embryos in all cycles

Despite the absence of statistically significant discrepancies, it's pertinent to acknowledge that the GnRH agonist group did exhibit slightly higher values in certain fertilization parameters. However, there were no

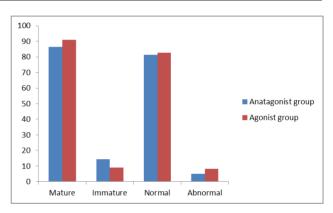


Fig. 3: Quality of retrieved oocytes

discernible differences in embryo characteristics, including quantity, quality, and average fertilization rate, between the two groups. (Table 3) highlights the parity in the utilization of various media across the cohorts.

	GnRH Antagonist (N = 102)	GnRH Agonist (N = 130)	P. Value
Fertilization	7.46 ± 3.29	7.04 ± 2.74	0.294
Number of Embryos/cycle	5.77 ± 2.63	5.24 ± 2.32	0.104
Quality of embryos (n, %)			
Good quality	498 (85.0%)	565 (83.0%)	
Poor quality	88 (15.0%)	116 (17.0%)	0.681
Media used in ICSI cycles (n,%)			
Autologous FF	32 (31.7%)	44 (33.8%)	0.597
Embryo Glue	30 (29.7%)	44 (33.8%)	
Global Total	39 (38.6%)	42 (32.3%)	

The (Table 4) presented the rates of pregnancy. There were no notable disparities between the two groups in terms of chemical, clinical, and continuing pregnancy rates (p=0.177, 0.062, 0.175) correspondingly.

The study revealed a significant negative correlation between the duration of stimulation and both oocyte and

embryo quality. The incidence rate ratio (IRR) was 0.94 (95% CI: -0.09, -0.04, p < 0.00001) for oocyte quality and 0.92 (95% CI: -0.13, -0.05, p < 0.00001) for embryo quality. This indicates that a longer duration of stimulation is associated with a decreased likelihood of producing high-quality oocytes. Furthermore, the Agonist Protocol exhibited a higher likelihood of oocyte quality compared

to the Antagonist Protocol 1.1 (95% CI: 0.03, 0.21, p = 0.007), as illustrated in (Table 5).

Table 4: Parameter of Pregnancy with different protocols

	GnRH Antagonist (N = 102)	GnRH Agonist (N = 130)	P. Value
Chemical pregnancy (n,%)	46 (45.5%)	72 (55.4%)	0.177
Clinical pregnancy (n,%)	41 (40.6%)	70 (53.8%)	0.062
Ongoing pregnancy (n,%)	36 (35.6%)	59 (45.4%)	0.175

 Table 5: Poisson Multiple Regression model for quality of embryo and Oocyte

	IRR	95% CI	P-Value
Quality of Oocyte			
Duration of Simulation	0.94	-0.09: -0.04	0.00001
Antagonist protocol			
Agonist protocol	1.1	0.03: 0.21	0.007
Quality of Embryo			
Duration of Simulation	0.92	-0.13: -0.05	0.00001

IRR = Incidence Rate Ratio, CI = Confidence Interval

DISCUSSION

As a result, the impact that stimulation techniques have on the efficiency of in vitro fertilization and intracytoplasmic sperm injection processes is of the highest significance. In order to develop embryos of a good grade, it is not possible to use eggs of a low quality. It is possible for ovarian stimulation to have an effect on the quality of oocytes and embryos through the course of three basic characteristics. The inhibition of pituitary hormones using GNRH agonists or antagonists, the encouragement of follicular growth by the injection of FSH or HMG, and the utilization of a "trigger" to stimulate the ultimate maturity and release of follicles are all strategies that are utilized. These are only few of the methods that are utilized. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures, the use of GnRH agonists has resulted in a decrease in the number of cycles that have been terminated, as well as an increase in the quantity of oocytes that have been recovered and an increase in the fertility rate. In addition, the fertility rate has increased^[7].

Following that, the introduction of GnRH antagonists, which suppress the pituitary gland in a significant and quick manner, made it possible to employ treatment tactics that were less harsh and more specifically tailored to the individual. The initial increase in hormone production as well as the following indications of oestrogen deficiency were both avoided by using this strategy^[8]. Comparing GnRHa cycles with GnRH antagonist cycles, the initial investigations consistently revealed that the use of antagonists resulted in somewhat reduced pregnancy rates^[9].

The purpose of this study was to explore the influence that a multiple dosage regimen of GnRH antagonists, as compared to a prolonged regimen of GnRH agonists, has on the quality of oocytes and embryos that are produced during in *vitro* fertilisation (IVF) and intracoupling in *vitro* fertilisation (ICSI) cycles.

Regarding the characteristics that were existing at the beginning of the study, the current investigation found that there was no statistically significant difference between the two groups that were being analyzed. This was discovered concerning the characteristics that were present. Based on the findings of a study that was conducted by Cota et al.,^[10], it was found that the average age of the agonist group was 33.2 years, whereas the average age of the antagonist group was 32.5 years. Comparatively, those in the group that was treated with antagonists had infertility for 4.1 years, while those in the group that was treated with agonists experienced it for an average of 4.4 years. In addition, the group that worked with the antagonist experienced 14 instances of secondary infertility, which accounts for 43.8% of the total. On the other hand, the group that worked against the antagonist experienced 7 instances, which accounts for 21.9% of the actual total. In spite of this, it did not appear that their conclusions were in agreement with the findings of our inquiry into the elements that contribute to infertility. Infertility can be caused by a number of causes, including the male factor, the idiopathic factor, the tubal factor, and the combination of the male factor and the tubo-peritoneal problem, as indicated by the findings of their research. In addition, Geng et al.,[11] concurred with the findings that we gave, which were presented earlier. According to the results of the research, it was found that the average age of the group that was considered to be the antagonist was 31 years old, whereas the average age of the group that was considered to be the agonist was 30 years old. Additionally, the duration was 3.6 minutes on average for both of the groups being compared.

According to the findings of this study, there was not a statistically significant difference between the groups in terms of the features of stimulation. Both Cota *et al.*^[10] and Geng *et al.*^[11] reported that there were no statistically significant differences between the two groups in terms of the GnRH doses. These doses were determined by the number of ampoules that were used and the duration of the stimulation. The findings of both groups provided evidence that this was the case. In contrast to the findings that were published by Lee *et al.*^[12,13], our research discovered that there was a substantial difference between the two groups in terms of the length of ovarian stimulation. our finding represents a considerable departure from the findings that were published. To provide a more precise explanation, our findings revealed that the group of patients who were given GnRH antagonists experienced a significantly longer period of ovarian stimulation (P < 0.001).

From the results of this inquiry, it was found that there was no significant difference between the two groups in terms of the amount and structure of the oocytes that were collected. A larger number of immature oocytes was produced as a result of the GnRH antagonist therapy; however, this number did not approach a threshold that is regarded to be clinically significant. A further observation made by Cota et al.[10] was that the amount of recovered oocytes did not differ between the two groups in a manner that was statistically significant. The antagonist group was found to have a significantly larger amount of recovered oocytes (P = 0.57), as was revealed in the research studies. The results of the investigation demonstrated that the antagonist group produced a greater quantity of mature and immature oocytes during the experiment. An injection of 3.75 milligrammes of a GnRH agonist was shown to successfully suppress levels of LH for a period of eight weeks, according to a study that was carried out not too long ago by Ren et al.^[14]. Specifically, a significant inhibition of the pituitary gland was found to be the root source of this suppression. The presence of low amounts of luteinizing hormone (LH) had a detrimental effect on the early stages of oocyte development, which resulted in a reduction in the total number of oocytes that were obtained, as shown by their findings. A considerable increase in the number of recovered oocytes was seen in the group that was given the agonist, as discovered by Murber et al. (2015). A greater number of completely formed oocytes were found in the group that was treated with agonists, according to the findings of the study. On the other hand, the group that was treated with GnRH antagonists had a higher percentage of oocytes that seemed abnormal.

In terms of the fertilisation rate, the number of embryos, or the number of embryos that were of a healthy quality, the findings of the current research indicate that there was no statistically significant difference between the group that was given GnRH antagonist and the control group. This was the case regardless of whether the group was given the GnRH antagonist or not. According to the results of our research, Geng et al.[11] found that the group that utilized GnRH antagonists experienced an average of 1.21±0.92 embryos transferred during the process. On the other hand, the group that utilized GnRH agonists witnessed an average of 1.19±0.95 embryos transferred during the process. In contrast to one another, the two groups had a set of characteristics that were significantly different. In addition, the utilization of GnRH antagonist medication led to a high-quality embryo rate of 79.26 \pm 28.48 instances, whereas the utilization of the GnRH agonist regimen resulted in a rate of 78.33 ± 24.98 cases, as was indicated in the same study. According to the findings

of a study that was conducted in 2014 by Meng et al., cryopreserved embryos that were obtained from the GnRH antagonist regimen revealed implantation and pregnancy rates that were unaffected by the regimen. According to the findings of the research that was carried out by Al-Inany et $al^{[16]}$ and Lee et $al^{[12]}$, the quality of the oocytes and embryos that were produced from donors who underwent GnRH antagonist therapy was comparable to that of donors who had GnRH agonist treatment. These findings were discussed with relation to oocvte donor cycles after they were presented. Murber *et al.*^[15], on the other hand, found that those who completed the GnRH agonist regimen had much higher rates of fertilisation, in addition to a greater number of recovered embryos and embryos of a higher grade. This was the case regardless of whether or not the individuals had completed the regimen. There was a lack of information that was accessible regarding the media that was utilized, and this limited the amount of information that was available.

When the two groups were compared with regard to the indications of pregnancy, there was no noticeable difference between them. The findings that were published by Geng *et al.*^[11], Lee *et al.*^[12], Murber *et al.*^[15], and Qing *et al.*^[17] in their individual research were all in agreement with one another. The findings of Surrey *et al.*^[18] indicate that individuals who received GnRH agonist medication for a period of three months saw significantly higher rates of continuing to carry a pregnancy to term. Researchers Ren *et al.*^[14] did a study in which they discovered that treatment with a GnRH agonist that was given to a woman for a lengthy period of time has the ability to increase the likelihood of the woman becoming pregnant.

This study demonstrated that there is a significant and favorable connection between the amount of time that stimulation was applied and the quality of the oocytes and embryos. This link was found to exist within the scope of this investigation. An other observation that was found was that there was a significant association between the utilization of the agonist regimen and the quality of the oocytes. This proved to be a significant finding. A valid predictor of ovarian reserve, responsiveness to controlled ovarian hyperstimulation (COH), and the number of oocytes and embryos obtained is the quantity of anti-Mullerian hormone (AMH), as demonstrated by Lee et al.^[12]. This was demonstrated by the fact that the amount of AMH is a valid indicator. In light of the findings of the research that was conducted, this was proved. According to their findings, the utilization of agonist treatment was also demonstrated to have a significant association with the quality of the oocytes and embryos that were extracted.^[19,20] is the coordinates that have been brought to your attention. A study that was conducted on the topic by Yang et al.^[9] revealed that the length of time that the gonadotropin stimulation regimen was provided had a range of impacts on the maturity of oocytes and the likelihood that conception would be successful. The findings of this study were presented in the literature. Furthermore, it has been demonstrated that the long-term treatment with GnRH agonist results in a higher rates of pregnancy when compared to the antagonist regimen^[21]. When compared to our findings, other studies have shown that there is a direct correlation between the length of time that stimulation was administered and the quality of the oocytes and embryos that were recovered^[22-24]. This is in contrast to our findings.

CONCLUSION

The GnRH antagonist protocol had yielded more immature oocytes than agonist protocol but this finding didn't reach a clinical significance. While fertilization rates and embryo parameters were similar, stimulation duration correlated significantly with oocyte and embryo quality. Additionally, the GnRH Agonist protocol showed a positive association with oocyte quality thus favorably influences some parameters of early embryo development dynamics.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

- Xia M, Zheng J. Comparison of clinical outcomes between the depot gonadotrophin-releasing hormone agonist protocol and gonadotrophin-releasing hormone antagonist protocol in normal ovarian responders. BMC Pregnancy and Childbirth. 2021;21(1):372.
- Casati L, Ciceri S, Maggi R, Bottai D. Physiological and pharmacological overview of the gonadotropin releasing hormone. Biochemical Pharmacology. 2023:115553.
- Li F, Lu R, Zeng C, Li X, Xue Q. Development and validation of a clinical pregnancy failure prediction model for poor ovarian responders during IVF/ICSI. Frontiers in Endocrinology. 2021;12:717288.
- Bakhtiari M, Babaei T, Safarpour M, Esmaeili M, Asgari R. Investigating the Factors Affecting the ICSI (microinjection) Success in Infertile People Referred to an Infertility Treatment Center in Western Iran from 2011 to 2017. Journal of Obstetrics, Gynecology and Cancer Research. 2020;5(3):115-25.

- Gowramma G, Nayak S, Cholli N. Intrinsic and extrinsic factors predicting the cumulative outcome of IVF/ICSI treatment. Int J Innov Technol Explor Eng (IJITEE). 2019;9:269-73.
- Tuan NC, Dzhemlikhanova LK, Makhmadaliyeva MR, Kogan IY, Niauri DA, Krikheli IO, *et al.* Main characteristics of IVF/ICSI protocols in patients with suboptimal response to controlled ovarian stimulation. Journal of obstetrics and women's diseases. 2021;70(1):109-18.
- Kadoura S, Alhalabi M, Nattouf AH. Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/ICSI cycles of polycystic ovary syndrome women: a systematic review and metaanalysis. Scientific reports. 2022;12(1):4456.
- Ciebiera M, Madueke-Laveaux OS, Feduniw S, Ulin M, Spaczyński R, Zgliczyńska M, *et al.* GnRH agonists and antagonists in therapy of symptomatic uterine fibroids–current roles and future perspectives. Expert Opinion on Pharmacotherapy. 2023;24(16):1799-809.
- 9. Yang R, Guan Y, Perrot V, Ma J, Li R. Comparison of the long-acting GnRH agonist follicular protocol with the GnRH antagonist protocol in women undergoing in *vitro* fertilization: a systematic review and meta-analysis. Advances in Therapy. 2021;38:2027-37.
- Cota AMM, Oliveira JBA, Petersen CG, Mauri AL, Massaro FC, Silva LF, *et al.* GnRH agonist versus GnRH antagonist in assisted reproduction cycles: oocyte morphology. Reproductive Biology and Endocrinology. 2012;10:1-10.
- Geng Y, Xun Y, Hu S, Lai Q, Jin L. GnRH antagonist versus follicular-phase single-dose GnRH agonist protocol in patients of normal ovarian responses during controlled ovarian stimulation. Gynecological Endocrinology. 2019;35(4):309-13.
- Lee JR, Kim SH, Kim SM, Jee BC, Ku S-Y, Suh CS, *et al.* Follicular fluid anti-Müllerian hormone and inhibin B concentrations: comparison between gonadotropin-releasing hormone (GnRH) agonist and GnRH antagonist cycles. Fertility and sterility. 2008;89(4):860-7.
- 13. Nikmard F, Aflatoonian B, Hosseini E, Aflatoonian A, Bakhtiyari M, Aflatoonian R. A comparative study on the results of agonist and antagonist protocols based on serum AMH levels in patients undergoing intracytoplasmic sperm injection. International Journal of Reproductive BioMedicine. 2016;14(12):769.

- 14. Ren J, Sha A, Han D, Li P, Geng J, Ma C. Does prolonged pituitary down-regulation with gonadotropin-releasing hormone agonist improve the live-birth rate in in *vitro* fertilization treatment? Fertility and sterility. 2014;102(1):75-81.
- 15. Murber Á, Fancsovits P, Ledó N, Gilán ZT, Rigó J, Urbancsek J. Impact of GnRH analogues on oocyte/ embryo quality and embryo development in in *vitro* fertilization/intracytoplasmic sperm injection cycles: a case control study. Reproductive Biology and Endocrinology. 2009;7:1-8.
- Al-Inany H, Abou-Setta A, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. Reproductive biomedicine online. 2007;14(5):640-9.
- 17. Qing X, He L, Ma Y, Zhang Y, Zheng W. Systematic review and meta-analysis on the effect of adjuvant gonadotropin-releasing hormone agonist (GnRH-a) on pregnancy outcomes in women with endometriosis following conservative surgery. BMC Pregnancy and Childbirth. 2024;24(1):237.
- Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in *vitro* fertilization-embryo transfer in patients with endometriosis. Fertility and sterility. 2002;78(4):699-704.

- 19. Silberstein T, MacLaughlin D, Shai I, Trimarchi J, Lambert-Messerlian G, Seifer D, *et al.* Müllerian inhibiting substance levels at the time of HCG administration in IVF cycles predict both ovarian reserve and embryo morphology. Human Reproduction. 2006;21(1):159-63.
- Ebner T, Sommergruber M, Moser M, Shebl O, Schreier-Lechner E, Tews G. Basal level of anti-Müllerian hormone is associated with oocyte quality in stimulated cycles. Human Reproduction. 2006;21(8):2022-6.
- Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins J, *et al.* Circulating Progesterone Levels and Ongoing Pregnancy Rates in Controlled Ovarian Stimulation Cycles for in *Vitro* Fertilization: Analysis of over 4000 Cycles. Obstetrical & Gynecological Survey. 2011;66(1):27-8.
- 22. Yoldemir T. Does the duration of gonadotropin stimulation affect embryo quality on post-retrieval day 3? Gynecological Endocrinology. 2011;27(5):324-30.
- Martin JR, Mahutte NG, Arici A, Sakkas D. Impact of duration and dose of gonadotrophins on IVF outcomes. Reproductive biomedicine online. 2006;13(5):645-50.
- 24. Chuang M, Zapantis A, Taylor M, Jindal SK, Neal-Perry GS, Lieman HJ, *et al.* Prolonged gonadotropin stimulation is associated with decreased ART success. Journal of assisted reproduction and genetics. 2010;27:711-7.