JRME

Journal of Reproductive Medicine and Embryology

Comparison between Agonist & Antagonist Risks and Outcome

Ahmed Mashaly[1,2,3]*, Ashraf Abo Ali[3,4], Yasser Elkassar[3,5].

[1]*Obstetrics and Gynecology Department, Damanhour National Medical Institute, Egypt.*
[2]*RYADA Fertility Center, Damanhour, Egypt.*
[3]*Egyptian Foundation of Reproductive Medicine and Embryology (EFRE), Egypt.*
[4]*Madina ICSI Fertility Center, Madina women's hospital, Alexandria, Egypt.*
[5]*Obstetrics and Gynecology Department, Faculty of Medicine, Alexandria University, Egypt.*

Dr. Ahmed Mashaly, MD is the Head of the Obstetrics and Gynecology department in Damanhor Medical National Institute. He is the Founder and Clinical Director of Reyada Fertility Center, and Founder and Deputy Chairman of Lady Care Hospital for Women's Health. He is a Consultant of reproductive medicine.

Abstract

Background: An essential part of ovarian stimulation in Invitro Fertilization /Intra-Cytoplasmic Sperm Injection (IVF/ICSI) involves co-medication to prevent premature luteinization. Controlled ovarian hyperstimulation (COH) is a fundamental step. Most published reviews have insufficiently accounted for various patient populations, who are likely to be of relevance since they strongly differ about ovarian responsiveness, particularly in relation to the long agonist and antagonist protocols. Both protocols are effective in blocking premature LH surges. The main two approaches for this are pituitary desensitization with prolonged daily administration of a gonadotrophin-releasing hormone (GnRH) agonist or an instant blockade of the pituitary luteinizing hormone (LH) secretion with a GnRH antagonist.

Objective: The study aimed to compare the risk and outcome of agonist and antagonist stimulation protocols.

Materials and Methods: This study was carried out in ART Unit of RIYADA fertility center for the year 2020-2021 including 320 patients. Patients were subdivided into two groups: The long protocol group (n = 241) was stimulated by the GnRH agonist long protocol, and the Antagonist Group (n = 79) was stimulated by the antagonist protocol.

Results: The multiple logistic regression analysis for different risk factors of pregnancy, was significant, and the significant items were protocol used (long protocol), young age, high number of oocytes, the three items gave a high pregnancy rate if combined.

Conclusion: The study concluded that the long protocol shows a high pregnancy rate in certain patient groups who fulfill the following criteria; age less than 37 years; Number of oocytes less than 15.

Keywords: GnRH; PCO; COH; LH.

JRME® Volume. 1, Issue no. 2, July 2024
 https://jrme.journals.ekb.eg/article_338916.html

Original article

Introduction

Effectively addressing infertility, a source of distress for couples, is paramount, given its 15% prevalence within the first year of marriage. The introduction of the gonadotropin-releasing hormone (GnRH agonist) in the 1980s represented a crucial advancement in assisted reproductive technology (1, 2). Over the subsequent two decades, the GnRH agonist has established itself as the "gold standard" for ovarian stimulation, particularly in the long protocol. This protocol initiates increased production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. These hormonal changes lead to reduced ovarian stimulation, suppression of folliculogenesis, and a significant decline in circulating estrogen to menopausal levels within three weeks. This effect is achieved through the continuous administration of the GnRH agonist, resulting in the down-regulation of GnRH receptors and subsequent reduction in LH and FSH levels (3, 4) The continuous use of the GnRH agonist plays a crucial role in preventing the early LH surge, thereby reducing the risk of ovarian hyperstimulation syndrome (5). This risk mitigation is attributed to the GnRH agonist's ability to desensitize the pituitary gland (6). In the late 1990s, the GnRH antagonist emerged as an alternative approach, as suggested by specific studies (7-9).
Patients treated with the Gonadotropin-releasing hormone (GnRH) agonists protocol demonstrated a significantly higher number of oocyte retrieved and mature oocyte production.

High numbers of oocytes produced with the agonist long protocol suggested that the protocol also improved the number of embryos produced. Therefore, the GnRH agonist long protocol may be beneficial with regard to a high cumulative pregnancy rate (9).

Nevertheless, the use of agonists came with several drawbacks, including an initial undesirable surge in gonadotropin secretion (flare-up effect) and an extended treatment duration before desensitization. This not only leads to increased treatment costs but also prolonged hormonal exposure, resulting in menopausal symptoms induced by profound gonadotropin suppression. On the flip side, discontinuation of agonist treatment did not promptly restore pituitary responsiveness, complicating luteal phase support (10). Lastly, high risk of ovarian hyperstimulation syndrome (OHSS) occurrences in GnRH agonist protocols (11). High dose Gonadotropin. In addition to that the GnRH agonist long protocol implies a longer treatment duration and probability of ovarian cyst formation.
Several modifications to the classic 'long protocol' for agonist use were proposed to streamline treatment and enhance IVF outcomes, such as the short protocol or ultrashort protocol. However, pregnancy rates achieved with these protocols were not as high as those obtained with the long protocol (9).

GnRH antagonists operate with a complexity distinct from agonists, employing a completely different mechanism to impede gonadotropin secretion. These antagonists competitively bind to GnRH receptors, thwarting the influence of endogenous GnRH pulses on the pituitary (12). Within hours of antagonist administration, there is a notable reduction in gonadotropin secretion, without the occurrence of a flare-up effect. Additionally, discontinuing GnRH antagonist treatment leads to a swift and predictable restoration of the pituitary-gonadal axis (13), as the pituitary receptor system remains intact. It has the advantage of shorter duration of the ovarian stimulation and the low dose of Gonadotrophin stimulation hence lower risk of developing ovarian hyperstimulation syndrome (OHSS).

In addition, with the standard ‘long agonist protocol’ approximately 25 daily subcutaneous injections are needed, whereas antagonists require around 5 daily subcutaneous injections. Moreover, it has no risk of cyst formation and less cost (14-16).

Nevertheless, GnRH antagonist has the disadvantage of low follicular production, lower pregnancy and implantation rates because of low LH levels and impaired estrogen secretion. In addition, GnRH antagonist is less flexible and the risk of OHSS still persists when HCG is used for the final maturation.

Unlike GnRH agonists, the effectiveness of antagonist treatment is strongly contingent on dosage, depending on the equilibrium between the existing endogenous GnRH and the administered antagonist (17). Upon entering the circulation, GnRH antagonists promptly exert adverse effects on any developing follicle or corpus luteum, with anticipated uterine bleeding within 48 hours. Crucially, within 6 to 8 hours of administration, any impending LH surge is effectively obstructed (18).

Shortly after the integration of GnRH agonists into assisted reproductive technology (ART), it became evident that, in addition to preventing premature LH surges, their usage came with several advantages. These benefits included the retrieval of a greater number of cumulus-oocyte complexes, subsequently increasing the availability of embryos for transfer and cryopreservation. The superiority of GnRH agonists in enhancing the likelihood of pregnancy, compared to situations without downregulation, was affirmed by one of the initial meta-analyses in the field of reproductive medicine (19).

A number of systematic reviews have appeared over the past decade (20-23). The most recent review indicates that overall GnRH antagonists do not compromise effectiveness and significantly prevent OHSS (24).

Most reviews have insufficiently accounted for various patient populations, such as ovulatory women, women with polycystic ovary syndrome (PCOS), or women with poor ovarian response. This is likely to be of relevance since these women strongly differ with regard to ovarian responsiveness, particularly in relation to the long agonist and antagonist protocols. Both protocols are effective in blocking premature LH surges.

Materials and Methods

The data file of a cohort of 320 patients was revised and subdivided into 2 groups according to the protocols prescribed: group 1 (n = 241) was stimulated by GnRH agonist long protocol, and group 2 (n = 79) was stimulated by antagonist protocol.

In GnRH agonist long mid-luteal protocol (agonist group), triptorelin 0.1 mg daily s.c. injection started on day 21 of the preceding cycle (3 days before the discontinuation of oral contraceptive pills (OCP) for 2 weeks), and complete downregulation was diagnosed if estimated E2 < 50 pg/ml. Then, recombinant FSH (rFSH), s.c. injection was started at a dose of 150 IU/day (the dose was modified according to the response), and both the agonist and recombinant were continued until the day of triggering.

As soon as three follicles with a mean diameter of ≥ 17 mm were reached, 5000 IU of HCG was administered i.m. once and 36 h before ovum pick up. Oocyte retrieval was performed assisted by transvaginal ultrasound-guided double-lumen needle aspiration. All embryos were transferred under abdominal ultrasound guidance.

Luteal phase support with 400 mg of micronized progesterone (was initiated for 14 days after the embryo transfer. Embryo transfer was canceled, and elective embryo cryopreservation was performed in cases of early OHSS detected 3 days post-oocyte retrieval that could possibly lead to life-threatening OHSS or in cases fulfilling one or more of the criteria for hospitalization.

The primary outcome measure was the incidence rate of OHSS. Secondary outcome measures were the clinical pregnancy rate (CPR), number of oocytes retrieved, number of embryos transferred, fertilization rate, cancelation rate, duration of stimulation, total dose of stimulation, and E2 concentration on the day of HCG administration. Clinical pregnancy is defined as the presence of a gestational sac with fetal heartbeat detected in 6–7 weeks of gestation.

Selection Criteria for Patients

Inclusion Criteria

- Patient age (less than 47 years)
- Levels of AMH that (less than 6.0 ng/ml)
- Absence of pelvic pathology such as endometriotic cysts, fibroids, and uterine

abnormality such as a bicornuate uterus assessed by transvaginal ultrasound.

Exclusion Criteria

- The exclusion criterion is patients in antagonist protocols who are triggered by the agonist.

Criteria for IVF Protocol Selection

- The decision is based on the benefits and shortcomings of each treatment option, and most importantly on the patient's response. Gonadotropin stimulation patients fall under three categories based on their response: (I) high responders; (II) intermediate responders and (III) poor responders.
- Most commonly, FSH level, oocyte number, cycle cancellation rate, gonadotrophin dose, and E2 levels are used as criteria for defining poor ovarian response.

Statistical Analysis

Qualitative data were described using numbers and percentages. Comparison between different groups regarding categorical variables was tested using the Chi-square test. Significance test results are quoted as two-tailed probabilities. The significance of the obtained results was judged at the 5% level.

Results

The age of the Long Protocol group ranged The age of the Long Protocol group ranged from 19.0 to 45.00 years with a mean±SD. of 31.29±5.97 years, while the age of the antagonist Protocol group ranged from 20.0 to 47.00 years with a mean±SD. of 32.32±7.15 years. There is no statistically significant difference in age between the two studied groups (p=.209). The AMH ranged from 0.1 – 8.5 with mean±S.D 2.26±1.68 in the Long Protocol Group, while ranged from 0.00 to 16.2 with a mean±S.D. of 2.50±3.31. There is no statistically significant difference in AMH between the two studied groups (p=0.405). The number oocyte ranged from 0.00 to 45.00 with a mean±SD. of 12.87±7.49 in the Long Protocol Group, while ranged from 0.00 to 58.00 with a mean±SD. of 12.41±12.61.There is no statistically significant difference in age between the two studied groups (p=0.690) (table 1).

Table 1: Comparison between the two patients in the different protocols regarding age, AMH, and number of oocytes.

	Long protocol "n=241"	Antagonist "n=79"	P value
Age	19.0-45.0 31.29±5.97	20.0-47.0 32.32±7.15	0.209
AMH (ng/ml)	0.1-8.5 2.26±1.68	0.0-16.2 2.50±3.31	0.405
No. of oocyte	0.0-45.0 12.87±7.49	0.0-58.0 12.41±12.61	0.690

p: p-value for comparing between the two studied groups. Statistically significant at *p*<.05.

In the Long Protocol Group, the mean age of the pregnant women was 29.63±5.40 years and in the non-pregnant women was 31.29±5.97 years. There is a statistically significant older age in non-pregnant women compared with pregnant women (p=0.021). In the Antagonist Protocol Group, the mean age of the pregnant women was 29.25±6.55 years and in the non-pregnant women was 34.52±7.15 years. There is a statistically significant older age in non-pregnant women compared with pregnant women (p=0.020).

In the Long Protocol Group, the mean AMH ng/ml of the pregnant women was 2.69±1.74 ng/ml and in the non-pregnant women was 1.65±1.32 ng/ml. There is a statistically significant Higher AMH in pregnant women compared with non-pregnant women (p=0.011). In the Antagonist Protocol Group, the mean AMH ng/ml of the pregnant women was 2.66±12.47 ng/ml and in the non-pregnant

Table 2: Comparison between pregnant and non-pregnant in the two protocols regarding age, AMH, and number of oocytes.

	Long protocol "n=241"		P value	Antagonist "n=79"		P value
	Pregnant	Non pregnant		Pregnant	Non pregnant	
Age	29.63±5.40	33.11±6.19	0.021*	29.25±6.55	34.52±7.15	0.02*
AMH	2.69±1.74	1.65±1.32	0.011*	2.66±2.47	0.96±1.27	0.001*
No. of oocytes	14.42±6.60	10.76±6.23	0.0045*	13.88±7.27	6.21±6.51	0.026*

p: p-value for comparing between the two studied groups. Statistically significant at *p*<.05.

women was 0.96±1.27 ng/ml. There is a statistically significant Higher AMH in pregnant women compared with non-pregnant women (p=0.001) (table 2).

In the Long Protocol Group, the mean number of oocytes of the pregnant women was 14.42±6.60, and in the non-pregnant women was 10.76±6.32. There is a statistically significant higher number of oocytes in pregnant women compared with non-pregnant women (p=0.0045). In the Antagonist Protocol Group, the mean number of oocytes of the pregnant women was 13.88±7.27.60 and in the non-pregnant women was 6.21±6.51. There is a statistically significant higher number of oocytes in pregnant women compared with non-pregnant women (p=0.026) (table 2).

Comparison between the two protocols regarding different affected risk factors revealed that the general success rate of the Long Protocol was 54.50% and in the Antagonist Protocol was 32%.00. There was a statistically significant higher success rate in the Long Protocol compared with the Antagonist protocol (p=0.0045) (table 3). According to age, patients with less than 37 years had a success rate of 60.00% in the Long Protocol and 32.50% in the Antagonist protocol with a statistically significant higher success rate in the Long Protocol compared with the Antagonist protocol for women less than 37 years old (p=.0008). However, for women more than 37 years old the success rate in the Long Protocol was 32.50%, and in the Antagonist, protocol was 30.00% with no statistically significant difference in success rate between both studied protocols (p=0.096) (table 3). Concerning AMH, for less than 1.0 ng\ml, the success rate was 42.00% in the Long Protocol and 27.50% in the Antagonist protocol with no statistically significant difference in success rate between both protocols (p=.096). For more than 1.0 ng\ml, the success rate in the Long Protocol was 60.00%, and in the Antagonist, protocol was (70.00%) with no statistically significant difference in success rate between both studied protocols (p=0.210) (table 3).

When the number of oocytes was less than 15 oocytes, the success rate was 51.50% in the Long Protocol and 25.00% in the Antagonist protocol. There was a statistically significant higher success rate in the Long Protocol compared with the Antagonist Protocol (p=.0013). However, when the number of oocytes was more than 15 oocytes, the success rate was

58.80% in the Long Protocol and 50.00% in the Antagonist protocol. There was no statistically significant difference in the success rate between both studied protocols (p=0.376) (table 3). For the number of PCO patients, the success rate of the Long Protocol was 77.00% and in the Antagonist Protocol was 100.00%. There was a statistically significant higher in success rate in Antagonist protocol compared with Long Protocol (p=.046) (table 3).

Table 3: Comparison between two protocols regarding different affected risk factors (Statistics for the year 2020,2021 - 320 cases)

	Protocol	Long protocol	Antagonist	X^2 P value
	Total case	**241**	**79**	**12.28**
	Clinical pregnancy rate	**54.50%**	**32%**	**0.0045***
	Freeze all	**48**	**32**	
		According to Age		
less than 37 years	Total case	191 cases	63 cases	**15.41**
	Clinical pregnancy rate	**60%**	**32.50%**	**0.0008***
	Freeze all	38	26	
more than 37 years	Total case	50 cases	16 cases	**0.031**
	Clinical pregnancy rate	**32.50%**	**30%**	**0.95 N.S.**
	Freeze all	10	6	
		According to AMH		
less than 1.0 ng\ml	Total case	78 cases	41 cases	**2.76**
	Clinical pregnancy rate	**42%**	**27.50%**	**0.096**
	Freeze all	15	12	
more than 1.0 ng\ml	Total case	163 cases	38 cases	**1.56**
	Clinical pregnancy rate	**60%**	**70%**	**0.21**
	Freeze all	33	22	
		According to NO. Of oocytes		
less than 15 oocytes	Total case	137 cases	45 cases	**10.25**
	Clinical pregnancy rate	**51.50%**	**25%**	**0.0013***
	Freeze all	24	13	
more than 15 oocytes	Total case	104 cases	34 cases	**0.780**
	Clinical pregnancy rate	58.80%	50%	**0.376**
	Freeze all	24	20	
		According to PCOS patients		
	total case	39 cases	14 cases	**3.11**
	freeze all	12 cases	12 cases	**0.046***
	Clinical pregnancy rate	**77%**	**100.0%**	

χ^2: Chi-square test
p: p-value for comparing between the two groups

Table 4 shows the multiple logistic regression analysis for different risk factors of pregnancy, revealing that the model was significant, and the significant items were protocol used (long protocol), young age, and high number of oocytes, the three items gave a high pregnancy rate if combined.

Table 4: Multiple logistic regression analysis of different risk factors that affect the pregnancy rate (Model Summary).

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.413	.171	.160	.67881

ANOVA

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	29.841	4	7.460	16.190	.0001*
Residual	145.146	315	.461		
Total	174.988	319			

a. Dependent Variable: Outcome

Coefficients

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	.572	.264		4.169	.0031*
Group	-.022	.089	-.013	-3.251	.002*
Age	-.006	.007	-.049	-2.058	.0391*
AmH	.091	.022	.270	1.136	.082
No. oocyte	.013	.006	.162	2.395	.017*
PCO	.011	.0054	.107	1.03	.107

a. Dependent Variable: Outcome

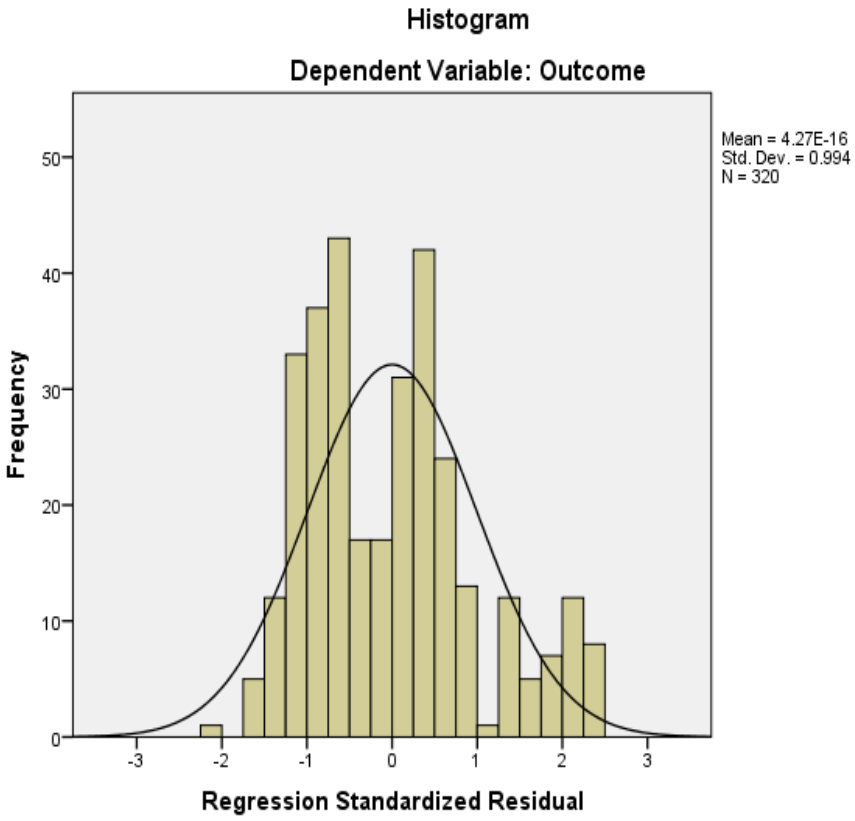

Figure 1. Histogram of multiple logistic regression analysis for different risk factors of pregnancy. The model was significant, and the significant items were protocol used (long protocol), young age, and a high number of oocytes, the three items gave a high pregnancy rate if combined.

Discussion

The long GnRH agonist (GnRH-a) protocol is a conventional protocol, probably the most widely used throughout the world even now. It allows a good predictability of the work in IVF units, implies a low cancelation rate, and allows a relatively high number of pre-ovulatory follicles of retrieved oocytes and, as a consequence, of embryos available for transfer, thus leading to a satisfactory pregnancy rate. The relatively recent introduction of GnRH antagonists in clinical practice has provided another option for ovarian stimulation in IVF. The introduction of GnRH antagonists (GnRH-ant) in assisted reproductive technologies (ART) to prevent LH surge seemed to open up a new way towards a more Unlike the indirect pituitary suppression induced by GnRH-a, GnRH-ant administration causes immediate and dose-related inhibition of gonadotrophin release by competitive occupancy of the GnRH receptors in the pituitary.

In recent times, the benefits of GnRH-antagonist (GnRH-ant) have become increasingly evident, as it has been promoted and applied in assisted reproductive technology (ART) treatments. In comparison to GnRH agonists (GnRH-a), GnRH-ant competitively binds to the GnRH receptor in the pituitary gland without

waiting for receptor exhaustion and desensitization, eliminating the 'flare-up' effect. It swiftly inhibits gonadotropin secretion within a few hours, preventing excessive pituitary inhibition. As a result, GnRH-ant effectively reduces gonadotropin consumption and significantly shortens the treatment duration (25, 26). The findings of Zhu et al. (2022) study (27), indicate that the GnRH-ant group exhibited a notably shorter stimulation duration and lower gonadotropin dosage compared to the GnRH-a group, consistent with previous research (28, 29).

In the current study, there was no statistically significant difference in basic data of the age, AMH, and number of oocytes (p=0.209, p=0.405, and p=0.690, respectively). The comparison between pregnant and non-pregnant women in each protocol group revealed that there was a statistically significant relation between pregnancy and young age, high AMH, and High number of oocytes in both protocols.

Pinto et al (2009), examined the predictive capacity of the stimulation protocol and explored potential associations between different stimulation protocols and the outcomes of the treatment (30). The study demonstrated that the chances of achieving pregnancy were observed to rise until the age of 30, after which they declined, particularly sharply for women aged 40 and above. these findings align with prior studies in terms of female age, number of attempts, and endometrial thickness (31, 32).

There was a statistically significant higher success rate in the long protocol compared with the antagonist protocol in general. The most significant risk factors that affect in long protocol success rate were patients with age less than 37 years, and patients with a number of oocytes less than 15 oocytes, Finally, the PCO was a significant factor that affected the success rate in antagonist protocol.

Yang et al. (2021), meta-analysis indicated that, within the general IVF population, the long-acting agonist protocol remains the preferred treatment, yielding a higher ongoing pregnancy rate compared to the antagonist protocol (33). However, for individuals with PCOS and poor ovarian response, the GnRH antagonist protocol appears to be the standard choice due to its association with a lower risk of ovarian hyperstimulation syndrome (OHSS) (16). Some studies have reported no significant difference in live birth rates between the long-acting GnRH agonist and antagonist protocols (34-39).

Laqqan et al (2021), revealed a significant negative correlation between the number of retrieved oocytes, the anti-Müllerian hormone (AMH) level, and the basal level of follicle-stimulating hormone (FSH) (40). Conversely, a noteworthy positive association was observed between the number of retrieved oocytes, mature oocytes, immature oocytes, and fertilized oocytes; the number of embryos transferred; and AMH level. Similar findings demonstrated that antral follicle count (AFC) was closely linked to the serum AMH level on the third day of the menstrual cycle in women facing infertility issues (41,42). A review manuscript reported that five studies showed a correlation between AFC and AMH similar to the number of oocytes retrieved, while four other studies indicated that AMH was either less effective or more effective (43).

Laqqan et al. (2021), identified a notable rise in anti-Müllerian hormone (AMH) levels, estradiol (E2) levels on human chorionic gonadotropin (hCG) day, the number of retrieved oocytes (both mature and immature), fertilized oocytes, embryos transferred, and ß-human chorionic gonadotropin (ß-hCG) values among the responder groups (40). Additionally, a significant decrease was observed in age, basal E2 levels, and the rate of oocyte fertilization within the responder groups.

All the results mentioned align with a prior study conducted by Seifer et al. (2002) demonstrating a connection between circulating anti-Müllerian hormone (AMH) levels and the ovarian response to gonadotropin treatment. Their research indicated that women with ≥ 11 oocytes retrieved exhibited serum AMH concentrations 2.5 times higher than those of women with ≤ 6 oocytes retrieved (44). This finding is consistent with the support from other studies as well (45,46).

In Laqqan et al. (2021), study, the cutoff values for age and AMH as predictors of poor response were > 31.5 years (AUC= 0.675) and < 1.45 ng/ml (AUC= 0.894), respectively (40). These findings align with previous studies that identified the cutoff value of AMH for predicting poor ovarian response to be between 0.30 and 1.40 ng/ml (47-49). Another meta-analysis including 28 studies of women undergoing assisted reproductive technology (ART) indicated that AMH (area under the curve, AUC= 0.78) is a more reliable predictor of poor response to ovarian stimulation than age (AUC= 0.61) (50).

Additionally, the La Marca et al. (2010), study observed that low AMH cutoff values (0.1 to 1.66 ng/mL) have 76% sensitivity and 79% specificity for predicting a poor response to gonadotropin stimulation (51). However, these findings contradict another study that identified the cutoff value for AMH distinguishing a poor response from a normal response as 0.1 to 2.97 ng/ml (52). This discrepancy was supported by Kelsey et al.'s study, which reported that the best cutoff value for AMH in predicting a poor response was 0.7 ng/mL (53).

The optimal cutoff values for AMH and age indicating a high response in this study were > 3.55 ng/mL (AUC= 0.888) and < 27.5 years (AUC= 0.613), respectively. The AMH cutoff value is consistent with a systematic review of two studies that used AMH to predict a high response to gonadotropin stimulation, revealing that high AMH cutoff values (3.36 to 5.0 ng/mL) have sensitivities and specificities ranging between 53% and 90.5% and 70% and 94.9%, respectively (51,52). In contrast, these findings do not align with a previous article that identified the cutoff for AMH level in predicting a high stimulation response as > 4.89 ng/mL (AUC= 0.82, sensitivity= 55%, specificity = 85%) (49).

Depalo et al. (2009) evaluated the response to treatment in a group of patients undergoing IVF and randomised to receive GnRH-antagonist or the GnRH-agonist. The average counts of retrieved oocytes and mature oocytes were notably higher in the agonist group compared to the antagonist group ($p < 0.02$ and $p < 0.01$, respectively). However, there were no significant differences between the two groups in terms of embryo quality, implantation rate, clinical pregnancy rates, ongoing pregnancy rate, and miscarriage rate. The study concluded that superior follicular growth and oocyte maturation

are attained with GnRH agonist treatment. Nevertheless, both regimens appear to exhibit comparable efficacy in terms of implantation and pregnancy rates (54).

Kadoura et al. (2022), conducted a systematic review and meta-analysis to consolidate the existing evidence and provide a comprehensive comparison of the effects of Conventional GnRH antagonist protocols, which are the most frequently utilized GnRH antagonist protocols, and GnRH agonist protocols on in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes in women with polycystic ovary syndrome (PCOS) (55). The study evidence suggests that employing the Conventional GnRH antagonist protocol in women with polycystic ovary syndrome (PCOS) is linked to reduced consumption of gonadotropins (high-quality evidence), a shorter duration of stimulation (very low-quality evidence), thinner endometrial thickness on hCG day (moderate-quality evidence), lower estradiol (E2) levels on hCG day (moderate-quality evidence), a lower number of retrieved oocytes (low-quality evidence), and a lower incidence of ovarian hyperstimulation syndrome (OHSS) (low-quality evidence). Importantly, these outcomes do not compromise the clinical pregnancy rate (high-quality evidence), ongoing pregnancy rate (high-quality evidence), or live birth rate (low-quality evidence). Additionally, comparable multiple pregnancy rates (MPR) (very low-quality evidence) and miscarriage rates (MR) (very low-quality evidence) have been observed between the GnRH antagonist protocols and the Long GnRH agonist protocol. Similarly, the overall risk of cycle cancellation is comparable between the two groups (very low-quality evidence). However, it is noteworthy that more cycles have been canceled due to poor ovarian response in the GnRH antagonist protocols (very low-quality evidence), while similar rates of cancellation due to the risk of OHSS have been observed in both groups (very low-quality evidence).

Likewise, Winkler et al. (2010), observed that GnRH antagonist administration resulted in a dose-dependent decrease in granulosa cell aromatase within a granulosa cell culture model. In contrast, the GnRH agonist demonstrated a dose-dependent stimulation of aromatase. The cumulative impact of these effects, along with the potential of GnRH antagonists to decrease the number of retrieved oocytes, could contribute to their protective effect in reducing the incidence of ovarian hyperstimulation syndrome (OHSS) during controlled ovarian stimulation (COS) (56).

The studies by Lambalk et al (2017), and Xiao et al (2013), have demonstrated that the use of GnRH antagonist in polycystic ovary syndrome (PCOS) subjects is linked to lower incidences of ovarian hyperstimulation syndrome (OHSS) (57, 58). Additionally, findings from Pundir et al indicated lower incidences of severe-moderate OHSS (ovarian hyperstimulation syndrome), although not for mild OHSS, in the GnRH antagonist protocols, which aligns with our study results. Moreover, we observed lower consumption of gonadotropins and a shorter duration of stimulation in GnRH antagonist protocols compared to the Long GnRH agonist protocol, consistent with previous review findings (59, 60).

However, Lin et al (2014), and Griesinger et al. (2006), did not find

significant differences in the OHSS rate between GnRH antagonist protocols and the Long GnRH agonist protocol. Furthermore, Griesinger et al. (2006), did not observe any significant variations in gonadotropin consumption among different GnRH analogue protocols. This discrepancy might be attributed to the limited number of studies included in the meta-analyses that investigated these effects in those reviews (60, 61).

In contrast to Kadoura et al (2022),(55) results, previous reviews did not show significant differences between GnRH antagonist protocols and GnRH agonist protocols regarding estradiol (E2) levels on hCG day or the number of retrieved oocytes(16,20, 55, 58-59) except for the review by Lin et al. (2014), which reported a lower number of retrieved oocytes in the GnRH antagonist protocols. This discrepancy could be due to differences in the inclusion and exclusion criteria of studies, as all previous reviews included both Early and Conventional GnRH antagonist protocols, while ours specifically focused on Conventional protocols (60).

Zhu et al (2022), examined the clinical results and assessed the safety for both mothers and neonates associated with gonadotropin-releasing hormone antagonist (GnRH-ant) and gonadotropin-releasing hormone agonist (GnRH-a) protocols (27). The study concluded that the GnRH-ant protocol exhibited similarity to the GnRH-a protocol in terms of clinical outcomes, obstetric and perinatal outcomes, while also presenting a lower risk of ovarian hyperstimulation syndrome (OHSS). Opting for the GnRH-ant protocol is advisable for individuals seeking an effective and safe outcome with shorter treatment duration.

In the Zhu et al. (2022), study, the moderate-severe OHSS incident rate and multiple pregnancy rate of the GnRH-ant group were significantly lower than those of the GnRHa group (27), which was consistent with previous reports (62-64). The follicle development of the GnRH-ant protocol is not as synchronous as that of the GnRH-a protocol, and the gonadotropin dosage and estrogen levels on trigger day were lower, which may be the reasons for reducing the occurrence of OHSS (62).

However, the limitation of this study is the small sample size, therefore Future studies with a large sample size are needed in order to confirm these results.

Conclusions

The study concluded that the long protocol shows a high pregnancy rate in certain patient' groups who fulfill the criteria of age less than 37 years and number of oocytes less than 15.

References

1. Porter RN, Smith W, Craft IL, Abdulwahid NA, Jacobs HS. Induction of ovulation for in-vitro fertilisation using buserelin and gonadotropins. Lancet 1984;2(8414):1284-5.
2. Fleming R, Adam A, Barlow D, Black W, MacNaughton M, Coutts J. A new systematic treatment for infertile women with abnormal hormone profiles. BJOG BJOG-INT J OBSTET GY 1982;89(1):80-3.
3. Edmonds DK. Dewhurst's textbook of obstetrics & gynaecology: Wiley Online Library; 2007.
4. Al-Mousawi BJ, Al-Azzam MA, Al-Zahawi B, Fawzi HA. Agonist Versus Antagonist in Intracytoplasmic Sperm Injection Cycles: Which Is the Best? Int J Women Health Rep Sci 2020;8(3):285-9.

5. Rizk B, Smitz J. Ovarian hyperstimulation syndrome after superovulation using GnRH agonists for IVF and related procedures. Hum Reprod 1992;7(3):320-7.
6. Daya S. Gonadotropin releasing hormone agonist protocols for pituitary desensitization in in vitro fertilization and gamete intrafallopian transfer cycles. Cochrane Database Syst Rev 2000;10.1002/14651858.Cd001299(2):Cd001299.
7. Olivennes F, Frydman R. Friendly IVF: the way of the future? Hum Reprod 1998;13(5):1121-4.
8. Cheung LP, Lam PM, Lok IH, Chiu TT, Yeung SY, Tjer CC, et al. GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial. Hum Reprod 2005;20(3):616-21.
9. Tarlatzis BC, Kolibianakis EM. GnRH agonists vs antagonists. Best Pract Res Clin Obstet Gynaecol 2007;21(1):57-65.
10. Smitz J, Erard P, Camus M, Devroey P, Tournaye H, Wisanto A, et al. Pituitary gonadotrophin secretory capacity during the luteal phase in superovulation using GnRH-agonists and HMG in a desensitization or flare-up protocol. Hum Reprod 1992;7(9):1225-9.
11. Forman RG, Frydman R, Egan D, Ross C, Barlow DH. Severe ovarian hyperstimulation syndrome using agonists of gonadotropin-releasing hormone for in vitro fertilization: a European series and a proposal for prevention. Fertil Steril 1990;53(3):502-9.
12. Reissmann T, Felberbaum R, Diedrich K, Engel J, Comaru-Schally AM, Schally AV. Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of infertility: an overview. Hum Reprod 1995;10(8):1974-81.
13. Kenigsberg D, Littman BA, Hodgen GD. Medical hypophysectomy: I. Dose-response using a gonadotropin-releasing hormone antagonist. Fertil Steril 1984;42(1):112-5.
14. Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2016;4(4):Cd001750.
15. Behery MA, Hasan EA, Ali EA, Eltabakh AA. Comparative study between agonist and antagonist protocols in PCOS patients undergoing ICSI: a cross-sectional study. Middle East Fertil Soc J 2020;24:1-7.
16. Lambalk C, Banga F, Huirne J, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017;23(5):560-79.
17. Felberbaum R, Reissmann T, Zoll C, Küpker W, al-Hasani S, Diedrich C, et al. [GnRH antagonists in gynecology: initial results within the scope of controlled ovarian hyperstimulation]. Gynakol Geburtshilfliche Rundsch 1995;35 Suppl 1:113-7.
18. Klingmüller D, Schepke M, Enzweiler C, Bidlingmaier F. Hormonal responses to the new potent GnRH antagonist Cetrorelix. Acta Endocrinol (Copenh) 1993;128(1):15-8.
19. Hughes EG, Fedorkow DM, Daya S, Sagle MA, Van de Koppel P, Collins JA. The routine use of gonadotropin-releasing hormone agonists prior to in vitro fertilization and gamete intrafallopian transfer: a meta-analysis of randomized controlled trials. Fertil Steril 1992;58(5):888-96.
20. Griesinger G, Diedrich K, Devroey P, Kolibianakis E. GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Hum Reprod Update 2006;12(2):159-68.
21. Al‐Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin‐releasing hormone antagonists for assisted reproductive technology. Cochrane Database of Systematic Reviews 2016, (4).
22. Youssef MA, Van der Veen F, Al‐Inany HG, Griesinger G, Mochtar MH, Aboulfoutouh I, et al. Gonadotropin‐releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles. Cochrane Database of Systematic Reviews 2011, (1).
23. Xiao J-s, Su C-m, Zeng X-t. Comparisons of GnRH antagonist versus GnRH agonist protocol in supposed normal ovarian

responders undergoing IVF: a systematic review and meta-analysis. PloS one 2014;9(9):e106854.
24. Youssef H, Thabet M, Emam M, El Azab S, Al-Inany H. Early initiation of gonadotropin-releasing hormone antagonist versus long agonist protocols in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection cycles. EBWHJ 2016;6(2):68-74.
25. Luo X, Pei L, Li F, Li C, Huang G, Ye H. Fixed versus flexible antagonist protocol in women with predicted high ovarian response except PCOS: a randomized controlled trial. BMC Pregnancy Childbirth 2021;21(1):1-7.
26. Papamentzelopoulou M, Stavros S, Mavrogianni D, Kalantzis C, Loutradis D, Drakakis P. Meta-analysis of GnRH-antagonists versus GnRH-agonists in poor responder protocols. Archives of Gynecology and Obstetrics 2021;304:547-57.
27. Zhu J, Xing W, Li T, Lin H, Ou J. GnRH antagonist protocol versus GnRH agonist long protocol: a retrospective cohort study on clinical outcomes and maternal-neonatal safety. FRONT ENDOCRINOL 2022;13:875779.
28. Klement AH, Berkovitz A, Wiser A, Gonen O, Amichay K, Cohen I, et al. GnRH-antagonist programming versus GnRH agonist protocol: a randomized trial. EUR J OBSTET GYN R B 2015;185:170-3.
29. Trenkić M, Popović J, Kopitović V, Bjelica A, Živadinović R, Pop-Trajković S. Flexible GnRH antagonist protocol vs. long GnRH agonist protocol in patients with polycystic ovary syndrome treated for IVF: comparison of clinical outcome and embryo quality. Ginekol Pol 2016;87(4):265-70.
30. Pinto F, Oliveira C, Cardoso MF, Teixeira-da-Silva J, Silva J, Sousa M, et al. Impact of GnRH ovarian stimulation protocols on intracytoplasmic sperm injection outcomes. Reprod Biol Endocrinol 2009;7(1):1-10.
31. Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. Lancet 1996;348(9039):1402-6.
32. Frattarelli JL, Bergh PA, Drews MR, Sharara FI, Scott Jr RT. Evaluation of basal estradiol levels in assisted reproductive technology cycles. Fertil Steril 2000;74(3):518-24.
33. 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. Adv Ther 2021;38(5):2027-37.
34. Zhao Z, Hao G, Cui N. Impact of long protocol in early follicular phase of patients with polycystic ovary syndrome who undergone in vitro fertilizaton-embryo transfer on clinical outcomes. Chin J Fam Plan 2018;26:709-13.
35. Kolibianakis EM, Albano C, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Initiation of gonadotropin-releasing hormone antagonist on day 1 as compared to day 6 of stimulation: effect on hormonal levels and follicular development in in vitro fertilization cycles. J Clin Endocrinol Metab 2003;88(12):5632-7.
36. Bosch E, Valencia I, Escudero E, Crespo J, Simón C, Remohí J, et al. Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertil Steril 2003;80(6):1444-9.
37. Seow KM, Lin YH, Hsieh BC, Huang LW, Huang SC, Chen CY, et al. Characteristics of progesterone changes in women with subtle progesterone rise in recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonist cycle. Gynecol Obstet Invest 2010;70(1):64-8.
38. Bosch E, Valencia I, Escudero E, Crespo J, Simón C, Remohí J, et al. Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertil Steril 2003;80(6):1444-9.
39. Al-Inany HG, Youssef MA, Aboulghar M, Broekmans F, Sterrenburg M, Smit J, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev 2011;10.1002/14651858.CD001750.pub3 (5):Cd001750.
40. Laqqan MM, Yassin MM. Predictive factors of ovarian response to GnRH antagonist stimulation protocol: AMH and age are potential candidates. Middle East Fertil Soc J 2021;26(1):1-11.

41. Umarsingh S, Adam JK, Krishna SBN. The relationship between anti-Müllerian hormone (AMH) levels and pregnancy outcomes in patients undergoing assisted reproductive techniques (ART). PeerJ 2020;8:e10390.
42. Fanchin R, Schonäuer LM, Righini C, Guibourdenche J, Frydman R, Taieb J. Serum anti‐Müllerian hormone is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3. Hum Reprod 2003;18(2):323-7.
43. Huang J, Lin J, Gao H, Wang Y, Zhu X, Lu X, et al. Anti-müllerian hormone for the prediction of ovarian response in progestin-primed ovarian stimulation protocol for IVF. FRONT ENDOCRINOL 2019;10:325.
44. Seifer DB, MacLaughlin DT, Christian BP, Feng B, Shelden RM. Early follicular serum müllerian-inhibiting substance levels are associated with ovarian response during assisted reproductive technology cycles. Fertil Steril 2002;77(3):468-71.
45. Yassin MM, Sharif FA, Laqqan MM. Anti-mullerian hormone as a predictor of ovarian reserve and ovarian response in IVF women from Gaza strip. IJRM (Iran J Reprod Med) 2013;11(4):261.
46. Vural B, Cakiroglu Y, Vural F, Filiz S. Hormonal and functional biomarkers in ovarian response. Archives of gynecology and obstetrics 2014;289:1355-61.
47. Saleh H, Saleh H. Comparison between antral follicle count and anti-Müllerian hormonal level in the prediction of ovarian response and pregnancy outcome in intracytoplasmic sperm injection patients: implications in personalizing ovarian stimulation. 2020.
48. Neves AR, Blockeel C, Griesinger G, Garcia-Velasco JA, La Marca A, Rodriguez I, et al. The performance of the Elecsys® anti-Müllerian hormone assay in predicting extremes of ovarian response to corifollitropin alfa. Reprod Biomed Online 2020;41(1):29-36.
49. Zheng H, Chen S, Du H, Ling J, Wu Y, Liu H, et al. Ovarian response prediction in controlled ovarian stimulation for IVF using anti-Müllerian hormone in Chinese women: A retrospective cohort study. J Med 2017;96(13).
50. Broer SL, Dólleman M, Van Disseldorp J, Broeze KA, Opmeer BC, Bossuyt PM, et al. Prediction of an excessive response in in vitro fertilization from patient characteristics and ovarian reserve tests and comparison in subgroups: an individual patient data meta-analysis. Fertil Steril 2013;100(2):420-9. e7.
51. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC, et al. Anti-Müllerian hormone (AMH) as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010;16(2):113-30.
52. La Marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. Hum Reprod Update 2014;20(1):124-40.
53. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WHB. A validated model of serum anti-müllerian hormone from conception to menopause. PloS one 2011;6(7):e22024.
54. Depalo R, Lorusso F, Palmisano M, Bassi E, Totaro I, Vacca M, et al. Follicular growth and oocyte maturation in GnRH agonist and antagonist protocols for in vitro fertilisation and embryo transfer. Gynecol Endocrinol 2009;25(5):328-34.
55. 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 meta-analysis. Sci Rep 2022;12(1):4456.
56. Winkler N, Bukulmez O, Hardy DB, Carr BR. Gonadotropin releasing hormone antagonists suppress aromatase and anti-Müllerian hormone expression in human granulosa cells. Fertil Steril 2010;94(5):1832-9.
57. Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017;23(5):560-79.
58. Xiao J, Chen S, Zhang C, Chang S. Effectiveness of GnRH antagonist in the treatment of patients with polycystic ovary syndrome undergoing IVF: a systematic review and meta analysis. Gynecological Endocrinology 2013;29(3):187-91.

59. Pundir J, Sunkara SK, El-Toukhy T, Khalaf Y. Meta-analysis of GnRH antagonist protocols: do they reduce the risk of OHSS in PCOS? Reprod Biomed Online 2012;24(1):6-22.
60. Lin H, Li Y, Li L, Wang W, Yang D, Zhang Q. Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. PloS one 2014;9(3):e91796.
61. Griesinger G, Diedrich K, Tarlatzis BC, Kolibianakis EM. GnRH-antagonists in ovarian stimulation for IVF in patients with poor response to gonadotrophins, polycystic ovary syndrome, and risk of ovarian hyperstimulation: a meta-analysis. Reprod Biomed Online 2006;13(5):628-38.
62. Toftager M, Bogstad J, Bryndorf T, Løssl K, Roskær J, Holland T, et al. Risk of severe ovarian hyperstimulation syndrome in GnRH antagonist versus GnRH agonist protocol: RCT including 1050 first IVF/ICSI cycles. Hum Reprod 2016;31(6):1253-64.
63. Qiao J, Zhang Y, Liang X, Ho T, Huang HY, Kim SH, et al. A randomised controlled trial to clinically validate follitropin delta in its individualised dosing regimen for ovarian stimulation in Asian IVF/ICSI patients. Hum Reprod 2021;36(9):2452-62.
64. Bonduelle M, Oberyé J, Mannaerts B, Devroey P. Large prospective, pregnancy and infant follow-up trial assures the health of 1000 fetuses conceived after treatment with the GnRH antagonist ganirelix during controlled ovarian stimulation. Hum Reprod 2010;25(6):1433-40.