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Cycle Day 2 Serum Levels of Insulin-Like Growth Factor-1 as a Prognostic Indicator for Poor Responders to Controlled Ovarian Hyperstimulation

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Abstract

Objective: This study aimed to compare serum insulin-like growth factor (IGF)-1 levels on cycle day 2 among poor ovarian responders, age-matched normal responders, and high responders undergoing in vitro fertilization (IVF). The investigation sought to understand the potential correlation between IGF-1 levels and ovarian response, with a focus on advanced maternal age and poor ovarian response.

Methods: Conducted at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies in Baghdad, this clinical experiment involved 30 infertile individuals. The primary outcome measures included Cycle Day 2 IGF-1 serum levels, anti-Müllerian hormone (AMH) levels, antral follicle count (AFC), and retrieved oocytes. Secondary outcomes comprised intrauterine pregnancy, live birth, unfavorable pregnancy outcomes, oocyte maturation, and fertilization. Participants were categorized based on antral follicle count: Group 1 (≤3 AFC) and Group 2 (4 to 10 AFC).

Results: In participants with usual responses, 72.5% had 4–10 AFC, while poor responders had ≤3 AFC in 27.5% of cases. Poor responders exhibited higher mean ages, lower mean AMH, and higher mean IGF-1 levels. However, poor responders and normal responders showed similar mean FSH levels. Female age positively correlated with FSH and IGF-1, while negatively correlating with AMH. The study also indicated negative correlations between female AMH, FSH, and IGF-1, along with a positive correlation between IGF-1 and FSH.

Conclusion: The findings suggest that FSH, AMH, and IGF-1 readings in fertility-assessed women can serve as indicators of ovarian age and reserve. The observed correlations with age imply a diminishing ovarian function. This study contributes valuable insights into the relationship between serum IGF-1 levels, ovarian response, and aging, particularly in the context of poor ovarian responders undergoing IVF.
Keywords: Cycle, insulin-like growth factor-1, prognostic, poor responders, ovarian hyperstimulation

Introduction

Patients classified as poor responders, constituting around 10% of women undergoing in vitro fertilization (IVF),[1] present a significant challenge in treatment. The European Society of Human Reproduction and Embryology defines poor ovarian response by at least two of three criteria: advanced maternal age, a previous poor ovarian response cycle, and an abnormal ovarian reserve test.[2] Treatment options for these patients are limited, and the efficacy of various strategies, such as estrogen pretreatment for follicular synchronization, remains debated. While estrogen pretreatment is widely used, its overall impact on follicular growth is not well-understood, and effective prognostic tools for cycle optimization are lacking. Studies have shown that exogenous estradiol (E2) can delay the increase in plasma follicle-stimulating hormone (FSH), aiding in the synchronization of endogenous and exogenous FSH stimuli.[3] However, findings regarding the impact of luteal estradiol (LE) treatment on IVF outcomes are mixed. Some studies suggest no significant effect on cycle outcomes, recommending its use primarily for scheduling IVF retrievals.[4] Others, like a meta-analysis by Reynolds et al., indicate potential benefits for poor responders, such as reduced cycle cancellation risk and increased chances of clinical pregnancy, attributed to better synchronization of follicles for controlled ovarian hyperstimulation (COH).[5] Additionally, the role of estrogen in modulating other aspects of follicular development, such as its interaction with growth hormone (GH) and insulin-like growth factor 1 (IGF-1), is noted.[6,7] Estradiol can antagonize GH receptor function and reduce GH-induced hepatic IGF-1 synthesis. IGF-1, a polypeptide secreted by the liver in response to GH, is crucial in amplifying gonadotropin hormonal action during follicular growth.[8] Decreased GH/IGF-1 signaling is associated with reproductive issues, as seen in conditions like Laron syndrome and certain genetic variations in the African Pygmy tribe, where fertility is affected.[9,10] The aim of study is to study whether patients exhibiting poor ovarian response have abnormal levels of serum insulin-like growth factor (IGF)-1 on cycle day 2 when compared with age-matched normal and high responders.

Method

Clinical trial study of 30 patients were included in the final analysis. The study sample collected at the infertility center of High Institute of Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain University/ Baghdad/ Iraq from period January 2022 to July 2023. Primary outcome measures included, as follows:

1. Cycle day 2 IGF-1 serum levels (in nanograms per milliliter).
2. Anti Mullerian hormone levels (AMH) (in nanograms per milliliter) serum levels measured within 1 year from the index cycle.

3. Antral follicle count (AFC).
4. Number of retrieved oocytes.

Levels of IGF-1 were analyzed in serum specimens collected by venipuncture, in the early morning of the second day of a menstrual cycle. These values were determined using Immulite 2000 enzyme-labeled chemiluminescent immunometric assay. Serum AMH levels were determined using Access2 ELISA kit. Secondary outcome measures included, as follows:

1. intrauterine pregnancy (defined as the presence of a yolk sac and/or fetal pole within the uterine cavity as determined by transvaginal ultrasound between 5 and 7 weeks of gestation)
2. live birth
3. negative pregnancy outcome (defined as serum β-human chorionic gonadotropin [hCG] level <5 mIU/mL 11 days after day 3 embryo transfer, or 9 days after blastocyst transfer
4. maturation rate of oocyte: number of meiosis II out of total harvested
5. fertilization rate: number of 2 pronuclei out of total meiosis II.

Females classified into 2 groups;
Group 1; 3 AFC or less.
Group 2; 4–10 AFC.

Statistical analysis done by SPSS 22, person correlation shows the correlation between continuous data. T test used for evaluation differences between mean and median of continues variables. *P*-value less or equal to 0.05 is consider significant.

Results

According to Figure 1; females classified as normal respond have 4-10 AFC represented 72.5% of cases and poor response they have ≤3 AFC represented 27.5% of all cases.

As shown in Table 1; there is significant increase in mean age of females in poor response AFC group than normal response AFC, also there is significant decrease in mean AMH of females in poor response AFC group than normal response AFC, while there is highly significant increase in mean IGF-1 of females in poor response AFC group than normal response AFC. No any significant difference in mean FSH of females in poor response AFC group than normal response AFC.

As shown in Table 2; there is significant positive correlation between Age of females and FSH, IGF-1, and significant negative correlation between Age of females and AMH. Also the table show significant negative correlation between AMH of females and FSH, IGF-1. While significant positive correlation between IGF-1 and FSH.

Discussion

The results you mentioned indicate a clear distinction in ovarian response based on antral follicle count (AFC) in women undergoing fertility treatments. Antral follicle count is a key marker used in reproductive medicine to assess ovarian reserve, which is the capacity of the ovary to provide egg cells that are capable of fertilization resulting in a healthy and successful pregnancy. **Normal Responders (4–10 AFC – 72.5% of cases):** Representing the majority (72.5%) of cases, women in this group with an AFC ranging from 4 to 10 suggest a moderate ovarian reserve.[11] This categorization indicates that these women are likely to have an adequate response to ovarian stimulation in IVF treatments, with a lower risk of complications such as ovarian hyperstimulation syndrome (OHSS).[12] They generally have better prospects for successful egg retrieval and IVF outcomes.[13] **Poor Responders (≤3 AFC – 27.5% of cases):** Accounting for 27.5% of the cohort, women with an AFC of 3 or less are classified as poor responders, indicating a diminished ovarian reserve.[14] This group faces

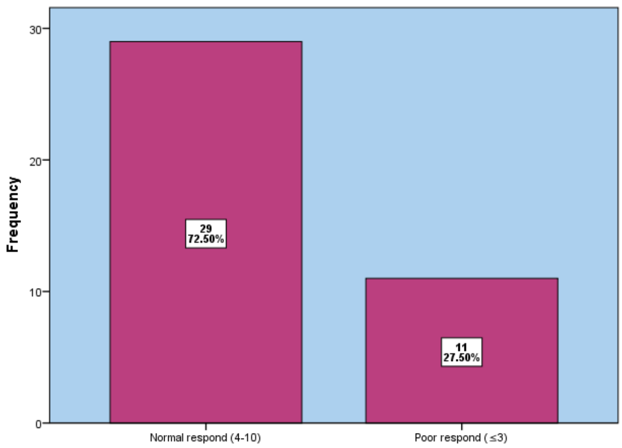

Fig. 1 **Distribution of females according to follicles count (poor, normal, good response).**

Table 1. **Difference mean of IGF according to patients with poor & normal response**

Variables	AFC	*N*	Mean	Std. deviation	*P*-value
Age	Poor respond (≤3)	11	34.27	3.03	0.001
	Normal respond (4–10)	29	30.07	3.45	
AMH	Poor respond (≤3)	11	1.72	0.36	0.014
	Normal respond (4–10)	29	2.07	0.31	
FSH	Poor respond (≤3)	11	6.97	0.81	0.09
	Normal respond (4–10)	29	6.47	0.69	
IGF-1	Poor respond (≤3)	11	395.91	50.06	0.0001
	Normal respond (4–10)	29	251.79	64.05	

P-value ≤0.05 (significant).

Table 2. **Correlation between (age, AMH, SFH, IGF-1)**

		AMH	FSH	IGF-1
Age	Pearson correlation	–0.765**	0.430**	0.622**
	Sig.	0.0001	0.006	0.0001
AMH	Pearson correlation		–0.334*	–0.508**
	Sig.		0.035	0.001
FSH	Pearson correlation			0.421**
	Sig.			0.007

P-value ≤0.05 (significant).

increased challenges in fertility treatments, including higher rates of cycle cancellation and lower success rates in achieving pregnancy through IVF.[15] Antral Follicle Count is measured using transvaginal ultrasonography and is a critical factor in tailoring IVF protocols.[16] However, it should be considered alongside other factors like age, hormone levels, and overall health in comprehensive fertility assessments.[17] The classification into normal and poor responders based on AFC is key to setting realistic expectations for treatment, selecting appropriate stimulation protocols, and effectively managing potential risks associated with fertility treatments.[18]

The data you've provided outlines significant differences in mean age, Anti-Müllerian Hormone (AMH) levels, Insulin-like Growth Factor 1 (IGF-1) levels, and Follicle-Stimulating Hormone (FSH) levels between women classified as poor responders and normal responders based on Antral Follicle Count (AFC) in IVF treatments. Here's a discussion of these findings: There is a significant increase in the mean age of females in the poor response AFC group compared to the normal response group. Advanced maternal age is a well-known factor associated with diminished ovarian reserve and poorer response to ovarian stimulation in IVF.[19] Aging ovaries often have fewer available follicles, which can be reflected in a lower AFC.[20] This association aligns with the finding that the poor response group, which typically has a lower AFC, also has a higher mean age.

There is a significant decrease in mean AMH levels in the poor response AFC group compared to the normal response group. AMH, a hormone produced by growing follicles, is a marker of ovarian reserve. Lower levels of AMH indicate a reduced number of antral and preantral follicles, typically seen in women with diminished ovarian reserve.[21] This finding is consistent with the observed lower AFC in the poor response group, as both reflect a reduced ovarian reserve.

There is a highly significant increase in mean IGF-1 levels in the poor response AFC group compared to the normal response group. The relationship between IGF-1 levels and ovarian response is complex. IGF-1 is known to play a role in follicular development and steroidogenesis.[22] The elevated IGF-1 levels in poor responders might indicate a compensatory mechanism in response to diminished ovarian reserve, possibly to enhance follicular sensitivity to gonadotropins.[23]

There is no significant difference in mean FSH levels between the poor response and normal response AFC groups. FSH is a primary regulator of ovarian function and follicular growth. The lack of significant difference in FSH levels between the two groups is intriguing, as higher FSH levels are typically expected in women with lower ovarian reserve.[24] This could suggest that FSH, while a useful marker, may not always correlate directly with ovarian reserve as measured by AFC or AMH levels.[25]

The observed correlations in your data provide insightful connections between age, FSH (Follicle-Stimulating Hormone), IGF-1 (Insulin-like Growth Factor 1), and AMH (Anti-Müllerian Hormone) in women undergoing fertility assessments or treatments. Here's a brief discussion of these findings: With increasing age, there's typically an increase in FSH levels, which is indicative of declining ovarian reserve.[26] As ovarian function diminishes, the body compensates by producing more FSH to stimulate the ovaries. The rise in IGF-1 with age might reflect a physiological response to declining ovarian function, possibly to enhance follicular sensitivity and optimize the remaining ovarian reserve.[20] AMH levels decline with age, reflecting the natural decrease in ovarian reserve and the number of antral follicles.[27] This inverse relationship is a key factor in fertility assessments. Lower AMH levels correlating with higher FSH levels align with the understanding that as the ovarian reserve diminishes (reflected by lower AMH), the body increases FSH secretion in an attempt to stimulate the ovaries.[28] The negative correlation between AMH and IGF-1 might indicate that as ovarian reserve decreases, there's an adaptive increase in IGF-1, possibly as a compensatory mechanism.[29] The positive correlation between IGF-1 and FSH could suggest a linked role in ovarian aging and response. As ovarian function decreases with age (and hence a decrease in AMH), both FSH and IGF-1 levels increase, possibly reflecting the body's attempt to maintain ovarian function and follicular development.[30]

Conclusion

The interplay of age, FSH, AMH, and IGF-1 levels in women undergoing fertility assessments reveals key insights into ovarian aging and reserve. An increase in FSH and IGF-1 levels with advancing age, coupled with a decrease in AMH, highlights the diminishing ovarian function over time. The observed hormonal correlations underscore the complexity of ovarian aging and its implications for fertility treatments, emphasizing the need for tailored approaches in reproductive medicine based on individual hormonal profiles.

Conflict of Interest

None.

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