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Original Article

Does Insulin-Like Growth Factor-I Level Associate with Pregnancy Outcomes in Primary and Secondary Infertile Women Undergoing In Vitro Fertilization? A Prospective Cohort Study

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Abstract

Background: Infertility, which affects 8%–12% of couples worldwide and 21.9% of couples in Pakistan in particular, is a major reproductive health issue. In vitro fertilization (IVF) has emerged as a prevalent therapeutic intervention. Recent studies have identified insulin-like growth factor-I (IGF-I) as a promising biomarker for assessing embryo viability and predicting implantation outcomes in IVF procedures.

Objective: To evaluate the relationship between IGF-I levels and IVF outcomes in women with primary and secondary infertility.

Materials and methods: This prospective cohort study included 133 infertile women (99 with primary infertility and 34 with secondary infertility) aged 20-45 years. IGF-I levels were measured using an ELISA kit. Participants were grouped based on infertility type and cause of infertility. Statistical analyses included the Mann-Whitney U test, Pearson chi-square test, Kruskal-Wallis test, and Pearson correlation coefficient.

Results: Women with secondary infertility had significantly higher IGF-I levels compared to those with primary infertility (279.40±85.89 ng/ml vs. 239.11±74.55 ng/ml, p=0.02). Male factors were the predominant cause of infertility in both groups. Patients with male-factor infertility had the highest IGF-I levels (267.1±77.6 ng/ml). Significant positive correlations were found between IGF-I levels and the number of oocytes fertilized (r=0.398, p<0.01), oocytes retrieved (r=0.326, p<0.01), oocytes at metaphase II (r=0.386, p<0.01), and cleaved embryos (r=0.369, p<0.01).

Conclusion: This study demonstrates a positive correlation between IGF-I levels and various IVF outcomes. Higher IGF-I levels were associated with improved oocyte retrieval, fertilization, and embryo development.

Keywords

embryo development, infertility, insulin-like growth factor-I, in vitro fertilization, oocyte quality

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INTRODUCTION

According to the World Health Organization (WHO), the clinical debility of a couple to achieve pregnancy within or after 12 months of regular sexual intercourse without using any contraceptive method is termed infertility.[1] This condition is categorized into two types: primary infertility, when a couple cannot achieve pregnancy after a year or more of unprotected intercourse, and secondary infertility, which occurs when a couple has previously conceived but is now unable to do so again.[2] Infertility is estimated to affect around 8%–12% of couples worldwide, and in some areas such as the Middle East, Eastern Europe, Central Asia, South Asia, and Africa it is reaching up to 30%. [3] Estimates suggest that about 21.9% of people in Pakistan live with infertility, with primary infertility accounting for 4% of those affected.[4] Of all the factors contributing to infertility, the female component accounts for 40%–55%, the male component 30%–40%, with 10% due to both partners, and 10% unknown.[5] Data on the prevalence and factors of infertility in Pakistan is scarce.[6] Male infertility can result from substandard sperm parameters, including low concentration, poor motility, or abnormal morphology. Female infertility may stem from issues with the uterus, ovaries, fallopian tubes, or endocrine system.[6,7]

Globally, people use assisted reproductive technologies (ART) like in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to treat infertility. Numerous factors affect the likelihood of clinical pregnancy outcomes in ART. Securing a suitable embryo for implantation depends on various internal and external factors, with the female hormonal environment playing a crucial role.[8] Evidence suggests that various growth factors contribute to ontogeny, with insulin-like growth factor-I (IGF-I) standing out for its unique functions and potential impact.[9] The action of IGF-I depends on its site of secretion.[10] As an ovarian IGF system member, it is thought to have direct effects on human granulosa cells; moreover, it also regulates follicular activity.[9,11] IGF-I and gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) function in an autocrine way to promote follicular development and survival as an anti-atretic hormone and secretion of steroids.[11] IGF-I is also thought to exhibit aromatase activity along with estrogen production by growing follicles, and studies revealed that during embryogenesis, IGF-I has a major role in regulating the cell cycle.[12] Moreover, it has been presented as a plausible and potential biomarker of embryo quality, as well as being responsible for successful implantation rates in IVF cycles.[11,13] The utilization of IVF as a therapeutic measure for infertility has witnessed a notable increase in Pakistan, but it is complex and risky. Many women face challenges in conceiving and suffer from miscarriages due to poor egg quality.[9,13] Given the resource-intensive nature of IVF treatment, assessing outcomes beforehand is crucial to reducing patient burden. This involves evaluating embryo and oocyte status pre-implantation to improve desirable outcomes and minimize risks.

AIMS

This study aims to evaluate the outcomes and cost-effectiveness of IVF by assessing IGF-I levels in women with primary and secondary infertility. It seeks to understand IGF-I's role in predicting successful pregnancy outcomes, including the number of eggs retrieved and the quality of embryos. The findings have the potential to inform and influence IVF treatment decisions, thereby reducing costs and minimizing the risks associated with redundant interventions.

MATERIALS AND METHODS

Study design, site, and population

This was a prospective cohort study that was conducted in collaboration with the Basic Medical Sciences Institute and Jinnah Postgraduate Medical Centre at the Australian Concept Infertility Clinic in Karachi for a period of 12 months. The Open Epi calculator was used to determine the sample size. Based on an expected sensitivity and specificity of 80%, a 5% margin of error, and a 95% confidence level, the required sample size was calculated to be 133.

During data collection, samples were chosen using a convenient sampling technique. After securing consent, study subjects were categorized into two groups depending on the causes and manifestations of infertility. One hundred thirty-three infertile females of the age group 20–45 who had been infertile for more than two years and had a regular ovulation cycle (duration: 25–35 days) with no abnormalities in the morphology of either of the two ovaries were included in the study. Women under 20 and over 45 years of age who previously failed IVF/ICSI and had ovarian pathologies or endometriosis were excluded from the study.

Laboratory parameters

We performed a full family history check and general medical examination on both partners to rule out likely causes of infertility. For the study, we used an IGF-I ELISA kit to measure IGF-I levels in lab samples. This kit uses a sandwich ELISA method. The kit's product number was SEA-050Hu, and it could detect IGF-I levels between 0.19 and 12 ng/ml.

Patient grouping

We divided the participants into two groups, group A1 and group A2, based on their type of infertility according to the WHO definition of infertility. Group A1 included women with primary infertility. Group A2 consisted of women with secondary infertility. **Fig. 1** illustrates the flow of patients in the study. To minimize bias, patients in groups A1

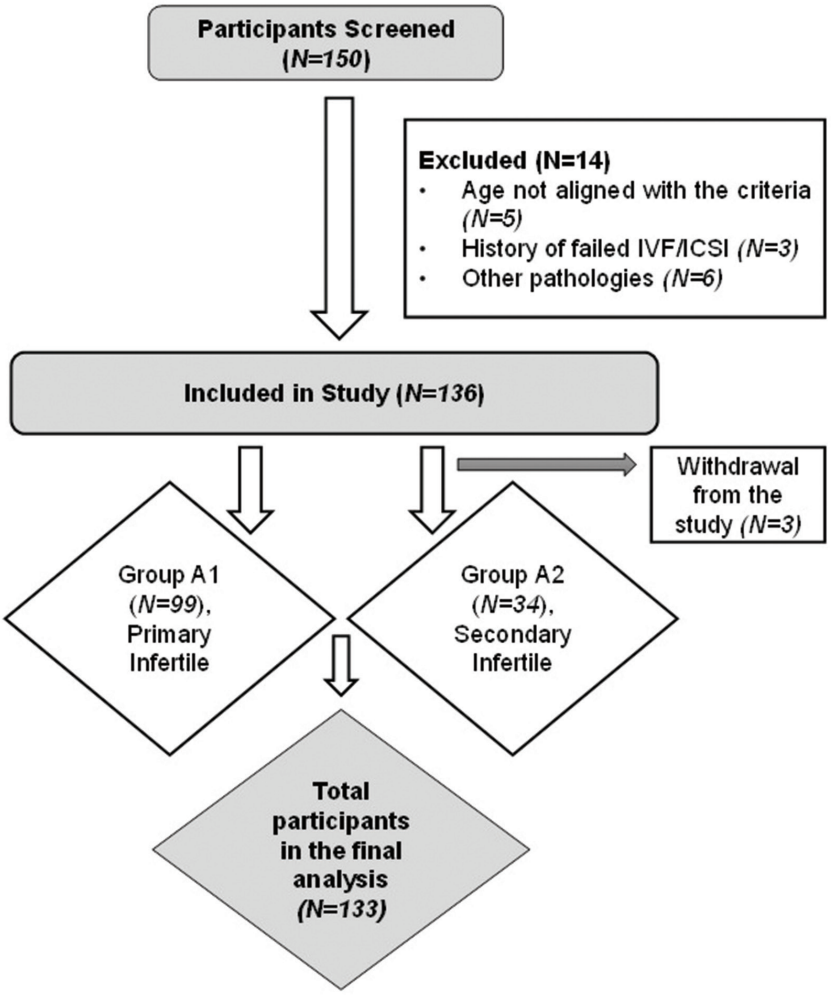

Figure 1. Patient flow chart.

and A2 were evaluated for factors contributing to their infertility. Selection bias was minimized by strictly following study criteria, and measurement bias was prevented using standardized procedures, calibrated equipment, and a validated IGF-I ELISA kit with a specified detection range.

Ethical considerations

The study procedure followed the ethical guidelines of the institutional and national research committees, as well as the Helsinki Declaration. JPMC's institutional review committee granted ethical authorization, and all subjects provided informed consent. The information gathered throughout the research was kept entirely confidential.

Statistical analysis

The data were analyzed using IBM SPSS 23.0. Mean and standard deviation were presented for quantitative data, while percentages and counts were reported for qualitative variables. The Mann-Whitney U test was used to compare age, BMI, duration of infertility, and IGF-I levels between primary and secondary infertility. The Pearson chi-square test assessed the association between the type and causes of infertility. The Kruskal-Wallis test was used to compare age, BMI, and IGF-I levels across different causes of infertility, with post hoc analysis using Tukey's HSD test for BMI and IGF-I levels. The Pearson coefficient of correlation was used to measure the strength of the relationship between IGF-I, the number of oocytes fertilized, the number of oocytes retrieved, the number of oocytes in metaphase II, and the number of cleaved embryos. P-values ≤0.05 were considered statistically significant. Scatter plots were used to depict the correlations between IGF-I levels and other variables.

RESULTS

Among the 133 samples, 99 females had primary infertility (A1), while 34 had secondary infertility (A2). The mean age, BMI, and duration of infertility among group A1 and A2 are shown in **Table 1**. A comparison of IGF-I levels between the two groups revealed that females in group A1

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had a mean IGF-I level of 239.11±74.55, whereas those in group A2 had a mean level of 279.40±85.89. This indicates significantly higher IGF-I levels in the A2 group, with a p-value of 0.02 as determined by the Mann-Whitney U Test **(Table 1)**.

Table 1. Comparison of quantitative characteristics between the types of infertility

Characteristics	A1 (n=99)		A2 (n=34)		p-value
	Mean	SD	Mean	SD	
Age	31.51	4.45	32.59	4.41	0.37
BMI (kg/m^2)	25.88	2.72	25.35	3.14	0.57
Duration of infertility (years)	5.21	3.92	6.76	5.03	0.12
IGF-I (ng/ml)	239.11	74.55	279.40	85.89	0.02*

By using Mann Whitney U Test, *p<0.05 was deemed significant. SD: standard deviation; BMI: body mass index; IGF-I: insulin-like growth factor-I

Fig. 2 illustrates the association between the causes of infertility in groups A1 and A2. Among all participants in group A1 (primary infertile females), male factors are the main cause of infertility, accounting for 61 (61.6%) cases, followed by female factors and unexplained causes, which account for 24 (24.2%) and 14 (14.1%) cases, respectively. Among the patients in group A2 (secondary infertile females), 26 (76.5%) reported male factors as the cause of infertility, while 4 (11.8%) attributed it to female factors, and 4 (11.8%) had unexplained causes. The chi-square test showed no significant association between the cause and type of infertility.

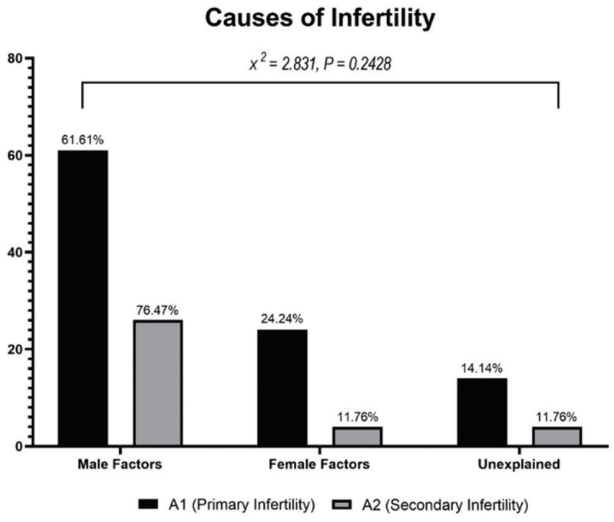

Figure 2. Association between causes of infertility among groups A1 and A2.

Table 2 presents the mean comparison of age, BMI, and IGF-I levels across different causes of infertility. Higher levels of IGF-I were observed in patients with male factors identified as the cause of their infertility. Specifically, the results indicated that the mean IGF-I level in patients whose cause of infertility is due to male factors was 257.1±7.6. In contrast, the mean IGF-I level for patients whose cause of infertility is due to female factors was 232.6±46.5, and for those with unexplained infertility, the mean IGF-I level was 190.0±95.2. The Tukey HSD post hoc test for BMI showed a significant difference between the male factors and female factors groups (mean difference = 1.58, p=0.02), with the male factors group having a higher BMI. No significant differences in BMI were found between the male factors and the unexplained groups or between the female factors and the unexplained groups. For IGF-I levels, a significant difference was observed between the male factors and the unexplained groups (mean difference = 77.04, p<0.01), with the male factors group showing higher levels. However, no significant differences were found between the other groups (**Table 3**).

Table 4 presents the result of correlation coefficients and corresponding significant p-values for IGF-I levels and various reproductive parameters in females undergoing IVF treatment. IGF-I shows a 39.8% positive correlation with the number of oocytes fertilized (r=0.398, p<0.01), a 32.6% positive correlation with the number of oocytes retrieved per patient (r=0.326, p<0.01), a 38.6% positive correlation with the number of oocytes at metaphase II (r=0.386, p<0.01), and a 36.9% positive correlation with the number of cleaved embryos (r=0.369, p<0.01).

Linear regression analysis shows a positive relationship between IGF-I levels and various reproductive outcomes, such as the number of oocytes retrieved, fertilized, at metaphase II, and embryos cleaved **(Fig. 3)**. Although the positive slopes indicate increasing reproductive outcomes with higher IGF-I levels, the R^2 values are relatively low. IGF-I levels explain 10.6% of the variability in the number of oocytes retrieved **(Fig. 3A)**, 15.8% in the number of oocytes fertilized **(Fig. 3B)**, 14.9% in the number of metaphase II oocytes **(Fig. 3C)**, and 13.6% in the number of embryos cleaved **(Fig. 3D)**.

DISCUSSION

Infertility is emotionally and mentally challenging. WHO ranks it as the fifth most serious disability worldwide. While infertility has many causes, advancements in ART methods, particularly IVF and ICSI, have increased hope for couples seeking help.[13] ART is a complex process requiring high precision and skill, with egg extraction being particularly challenging for women undergoing infertility treatment.[9,13,14] Laboratory studies have confirmed the regulatory role of IGF-I in human reproduction. IGF-I influences granulosa cell differentiation and stimulates steroidogenesis in cultured granulosa and luteinizing

Table 2. Mean comparison of characteristics across causes of infertility

Parameters	Cause of infertility						p-value
	Male factors (n=87)		Female factors (n=28)		Unexplained (n=18)		
	Mean	SD	Mean	SD	Mean	SD	
Age	31.59	4.00	32.11	6.15	32.22	3.52	0.38
BMI	26.08	2.99	24.50	1.90	26.06	2.84	<0.01*
IGF-I	267.1	77.6	232.6	46.5	190.0	95.2	<0.01*

*p-value <0.05 was considered significant using the Kruskal-Wallis test

Table 3. Multiple comparisons of significant characteristics across causes of infertility

Parameters	Comparison	Mean difference	p-value
BMI	Male factors vs. Female factors	1.58	0.02*
	Male factors vs. Unexplained	0.02	0.99
	Female factors vs. Unexplained	−1.56	0.15
IGF-I	Male factors vs. Female factors	34.44	0.09
	Male factors vs. Unexplained	77.04	<0.01*
	Female factors vs. Unexplained	42.60	0.15

*p<0.05 was considered significant for mean difference using Tukey's HSD test

Table 4. Correlation analysis of IGF-I and various reproductive parameters using Pearson correlation

Parameters		IGF-I	No of oocytes fertilized	No of oocytes retrieved / patient	No of oocytes metaphase II
IGF-I	*r*	1			
	p				
Number of oocytes fertilized	*r*	0.398	1		
	p	<0.01*			
Number of oocytes retrieved / patient	*r*	0.326	0.933	1	
	p	<0.01*	<0.01*		
Number of oocytes metaphase II	*r*	0.386	0.989	0.953	1
	p	<0.01*	<0.01*	<0.01*	
Number of cleaved embryos	*r*	0.369	0.99	0.932	0.984
	p	<0.01*	<0.01*	<0.01*	<0.01*

**p*<0.05 was considered significant for correlation

granulosa cells.[15-17] Many studies have explored markers to predict ovarian and follicular responses to stimulation, aiming to improve ART outcomes. Our research focuses on IGF-I as a biochemical marker for IVF success. Its critical role in early development and potential as an embryo quality indicator makes it a promising predictor of IVF results.

Most participants in our study had primary infertility. We found no significant differences in age, BMI, or infertility duration between primary (A1) and secondary (A2) infertility groups. However, IGF-I levels were significantly higher in group A2. Male factors were the main cause of infertility in both groups. We found no significant association between infertility type and cause. Patients with male factor infertility had higher IGF-I levels compared to those with female factor or unexplained infertility. We observed an inverse relationship between BMI and IGF-I levels, with lower BMI subjects showing higher IGF-I concentrations. Statistical analysis revealed a significant difference in BMI between male factor and female factor infertility groups (p=0.02). The results of our study show that the IGF-I levels positively correlated with the number of oocytes fertilized, retrieved, at metaphase II, and cleaved embryos. Linear

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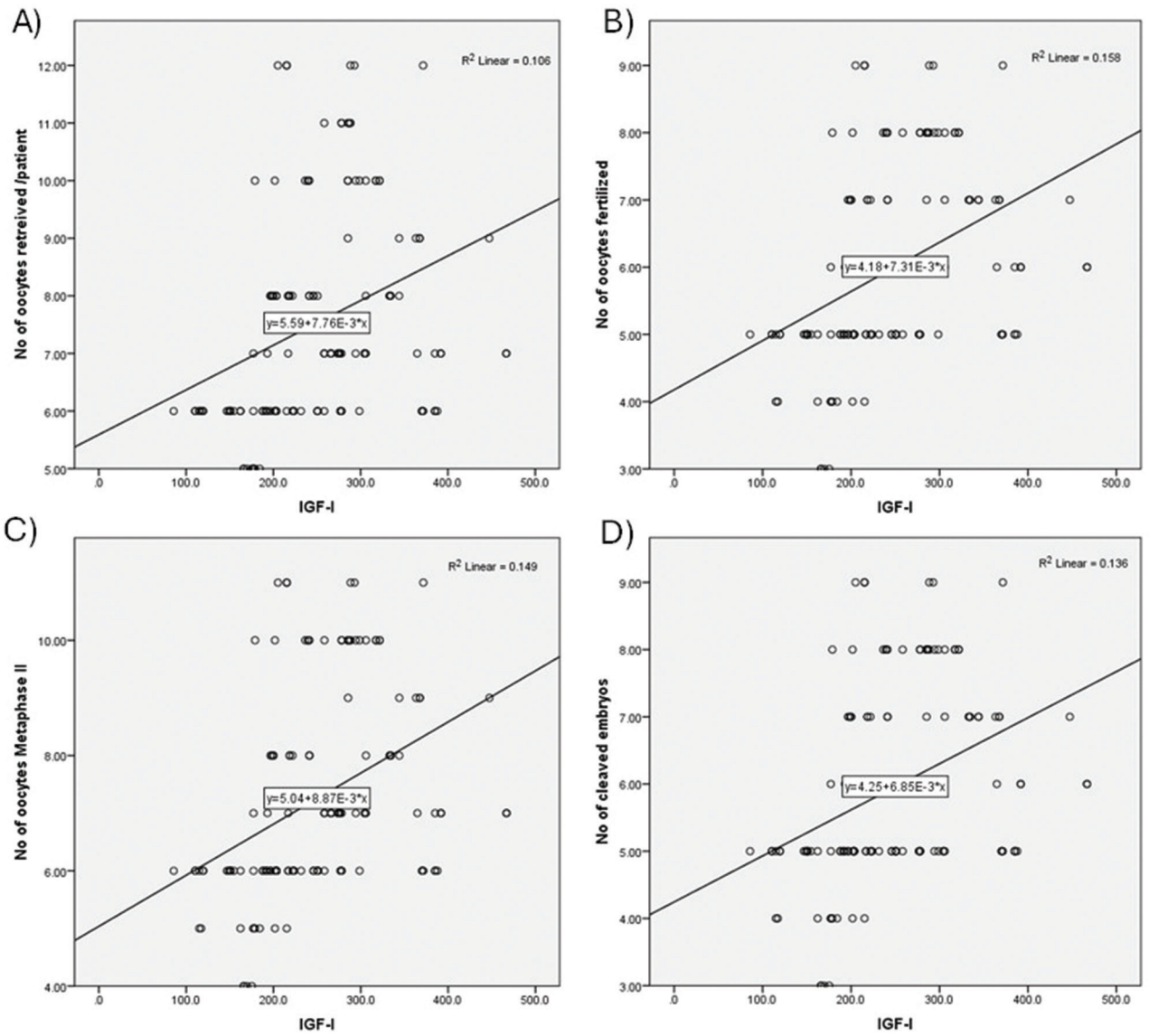

Figure 3. Correlation of IGF-I with various reproductive parameters. **A**) Correlation between IGF-I levels and the number of oocytes retrieved; **B**) Correlation between IGF-I levels and the number of oocytes fertilized; **C**) Correlation between IGF-I levels and number of oocytes in metaphase II; **D**) Correlation between IGF-I levels and number of embryos cleaved.

regression analysis showed positive relationships between IGF-I levels and these reproductive outcomes. These findings highlight IGF-I's potential role in reproductive outcomes, particularly in male factor infertility, and suggest that higher IGF-I levels may benefit certain reproductive parameters.

Our findings align with those of Afradiasbagharani et al., who suggest a positive role for IGF-I in ovulation and folliculogenesis regulation.[9] Similarly, our study and the results reported by Mehta et al. showed that elevated IGF-I levels could alter regulatory mechanisms in ovarian follicular genesis, facilitating primary and antral follicle activation and development. This creates an optimal environment for embryo growth, potentially increasing pregnancy likelihood in subsequent cycles. Mehta et al. found that higher follicular fluid (FF) IGF-I levels were associated with better fertilization, cleavage, blastocyst formation, and top-quality embryos. The clinical pregnancy rate was significantly higher in the high IGF-I group (38.3%) compared to the low IGF-I group (20%) (p=0.02). They reported significantly higher cleavage rates in patients with high IGF-I levels (p=0.001) and strong correlations between high IGF-I levels and embryo quality (Pearson r=0.3894) and clinical pregnancy (Pearson r=0.5972). Their ROC curve data showed a threshold value of FF IGF-I for clinical pregnancy (>58.5 ng/mg protein, sensitivity 89.58%, specificity 60.24%).[18] In a pilot study by Scheffler et al., with the aims to analyze the association between oocyte cohort quality and follicular levels of growth hormone (GH) and IGF-I, they found higher GH and IGF-I levels in normal oocyte cohorts compared to abnormal ones, with significantly lower fertilization rates in the abnormal cohort group. They

concluded that higher follicular levels of GH and IGF-I were associated with better oocyte quality and maturation.[19] Another study noted a positive correlation between follicular IGF-I and the number of mature oocytes[20], although some studies did not find these associations.[21,22] Whereas, according to a Cochrane systematic review, it was reported that GH treatment improves ovarian response, leading to more oocytes, embryos, and higher pregnancy and live birth rates in poor responders.[23] Studies also showed that adding IGF-I to the culture medium during in vitro maturation of human oocytes results in more mature oocytes[24,25] and, IGF-I works synergistically with gonadotropins, enhancing ovarian responsiveness to FSH and LH by increasing their receptor expression levels[26,27].

However, Imterat et al. reported no association between IGF-I levels and pregnancy rate.[28] This discrepancy may be due to their inclusion of polycystic ovarian syndrome (PCOS) patients, whom we excluded. The ovarian microenvironment is crucial for normal physiology, and ovulatory disorders like PCOS can directly affect IGF-I levels.[29] Rehman et al. also found no relationship between IGF-I and pregnancy following IVF therapy, possibly due to different IVF protocols; they used an ultrashort regimen for ovarian hyperstimulation, while we used the standard protocol.[4] A 2022 study by Duzok et al. reported that GH levels did not correlate with ovarian reserve markers, despite the known role of GH in granulosa cell function.[30] It is interesting to mention the study conducted by Gleicher N and colleagues, where they divided women into three IGF-I level groups: low (<132 ng/mL), normal (132–202 ng/mL), and high (>202 ng/mL). Cycle cancellations were lowest in the high IGF-I group (11.6%) and highest in the low IGF-I group (25.0%), showing an inverse correlation between IGF-I levels and cycle cancellation rates. While oocyte numbers, pregnancy, and live birth rates did not significantly differ, the normal IGF-I group showed the highest trend in oocyte numbers and the best outcomes. This supports their hypothesis that GH supplementation may primarily improve IVF outcomes in women with low IGF-I levels, potentially explaining the conflicting results in the literature about GH use in IVF. GH supplementation seems beneficial mainly for women with low IGF-I levels, aligning with its physiological role in the ovaries. Overall, their findings suggest that higher IGF-I levels reduce cycle cancellations and indicate that IGF-I could be a marker for selecting women who might benefit from GH supplementation in IVF, explaining the varied results in GH use in IVF treatments.[31] Whereas, in a study conducted in China by Hou HY and colleagues using an aged mouse model, it was found that GH increased the number of antral follicles and retrieved oocytes most effectively at a medium dosage, followed by high and then low dosages. The enhancements correlated with increased ATP levels, more frequent homogeneous mitochondrial distribution, and improved mitochondrial membrane potential. The authors suggested that GH improves mitochondrial function in oocytes.[32] Our study adds to the evidence supporting the role of IGF-I in reproductive outcomes, particularly in IVF treatments. The positive correlations between IGF-I levels and various reproductive parameters align with several previous studies, although conflicting results across different research settings highlight the complexity of IGF-I's role in fertility.

CONCLUSION

This study demonstrates a significant positive correlation between IGF-I levels and various IVF outcomes, including oocyte retrieval, fertilization, and embryo development. Women with secondary infertility showed higher IGF-I levels than those with primary infertility, and patients with male factor infertility had the highest levels. These findings support the potential use of IGF-I as a biomarker for predicting IVF success, which could lead to more personalized and cost-effective treatments. However, the relatively low R^2 values indicate that IGF-I levels alone cannot fully predict outcomes, highlighting the complexity of fertility. Future research should focus on standardizing protocols, establishing definitive IGF-I thresholds, and exploring its use in combination with other biomarkers. These results contribute to our understanding of IGF-I's role in reproductive biology and represent a step towards more personalized fertility treatments, potentially improving IVF success rates and offering new hope to those struggling with infertility.

Limitations

The use of a convenient sampling technique and conducting the study at a single center may limit the generalizability of the findings. The lack of long-term follow-up precludes assessment of the sustained impact of IGF-I levels on pregnancy outcomes. Potential confounding factors, such as lifestyle and genetic predispositions, were not fully accounted for, which could influence the results. The study's focus on only IGF-I, along with the relatively low R^2 values, shows that a multifactor approach is needed to better predict IVF outcomes. Financial constraints prevented the inclusion of other biomarkers, which could have provided a more comprehensive analysis. Future research should include multi-center studies, longitudinal follow-up, and combined biomarker analysis to enhance predictive accuracy and applicability.

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Conflict of Interest

The authors declare no conflicts of interest.

Disclaimer

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Author contributions

Conceptualization: Huma Salahuddin, Rehana Rehman, Sadia Rehman, and Muhammad Raza Sarfraz; *writing of initial drafts*: Huma Salahuddin, Sadia Rehman, and Muhammad Raza Sarfraz; *review and editing*: Raheela Rafiq, Fatima Rehman, and Muhammad Raza Sarfraz; *project supervision*: Rehana Rehman, Huma Salahuddin, and Sadia Rehman; *data curation*: Raheela Rafiq and Fatima Rehman; *software*: Muhammad Raza Sarfraz; *data analysis*: Huma Salahuddin, Sadia Rehman, and Muhammad Raza Sarfraz; *resources*: Huma Salahuddin, Sadia Rehman, and Muhammad Raza Sarfraz. All authors approved the final manuscript before submission to the journal.

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Связан ли уровень инсулиноподобного фактора роста I с исходами беременности у женщин с первичным и вторичным бесплодием, проходящих процедуру экстракорпорального оплодотворения? Проспективное когортное исследование

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Резюме

Введение: Бесплодие, которое затрагивает 8% - 12% пар во всём мире и 21,9% пар в Пакистане в частности, является серьёзной проблемой репродуктивного здоровья. Экстракорпоральное оплодотворение (ЭКО) стало распространённым терапевтическим вмешательством. Недавние исследования выявили инсулиноподобный фактор роста-I (IGF-I) как перспективный биомаркер для оценки жизнеспособности эмбриона и прогнозирования результатов имплантации при процедурах ЭКО.

Цель: Оценить связь между уровнями IGF-I и результатами ЭКО у женщин с первичным и вторичным бесплодием.

Материалы и методы: Это проспективное когортное исследование включало 133 бесплодные женщины (99 с первичным бесплодием и 34 с вторичным бесплодием) в возрасте 20–45 лет. Уровни IGF-I измеряли с помощью набора ELISA. Участники были сгруппированы на основе типа бесплодия и причины бесплодия. Статистический анализ включал U-тест Манна-Уитни, критерий хи-квадрат Пирсона, тест Краскела-Уоллиса и коэффициент корреляции Пирсона.

У женщин с вторичным бесплодием были значительно более высокие уровни IGF-I по сравнению с женщинами с первичным бесплодием (279.40 ± 85.89 ng/ml против 239.11 ± 74.55 ng/ml, p = 0.02). Мужской фактор был преобладающей причиной бес-

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плодия в обеих группах. У пациентов с мужским фактором бесплодия были самые высокие уровни IGF-I (267.1 ± 77.6 ng/ml) . Значимые положительные корреляции были обнаружены между уровнями IGF-I и количеством оплодотворенных ооцитов (r = 0.398, p<0.01), извлечённых ооцитов (r = 0.326, p<0,01), ооцитов в метафазе II (r = 0.386, p<0.01) и дробленых эмбрионов (r = 0.369, p<0.01).

Заключение: Это исследование демонстрирует положительную корреляцию между уровнями IGF-I и различными результатами ЭКО. Более высокие уровни IGF-I были связаны с улучшенным извлечением ооцитов, оплодотворением и развитием эмбриона.

Ключевые слова

развитие эмбриона, бесплодие, инсулиноподобный фактор роста-I, экстракорпоральное оплодотворение, качество ооцитов