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## The Metabolic-Endocrine Axis: Interplay Between Follicular Adiponectin and Igf-I In Determining Oocyte Competence and ICSI Outcomes

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**ABSTRACT: Background:** Ovarian response and follicular development are regulated through complex interactions between metabolic and endocrine pathways. adiponectin and insulin-like growth factor-1 (igf-1) are key mediators involved in metabolic homeostasis, follicular growth, and oocyte maturation. their role within the follicular microenvironment may influence ovarian response and assisted reproductive outcomes in women undergoing intracytoplasmic sperm injection (icsi). Aim of the Study: evaluate the associations of serum and follicular fluid adiponectin and IGF-1 levels with ovarian response, hormonal profiles, oocyte characteristics, embryo quality, and pregnancy outcomes in women undergoing icsi.

**Subjects and Methods:** This prospective comparative study enrolled 120 infertile women scheduled for ICSI at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Iraq. According to ovarian response, the women were allocated into three equal groups of 40 each: poor responders, normal responders, and hyper responders. Serum samples were drawn on two occasions—at the day of oocyte retrieval and again on the day of embryo transfer—whereas follicular fluid was aspirated during the retrieval procedure itself. Adiponectin and IGF-1 levels in the collected specimens were quantified by enzyme-linked immunosorbent assay (ELISA).

The relationship of these two markers with ovarian response, hormonal indices, oocyte characteristics, embryo grade, and pregnancy outcome was then examined statistically.

**Results:** Serum and follicular fluid adiponectin and IGF-1 levels differed significantly among ovarian response groups, with the highest values observed in hyper responders ( $p < 0.001$ ). Both biomarkers showed significant positive correlations with anti-müllerian hormone, estradiol, and luteinizing hormone levels. Adiponectin and IGF-1 were also positively associated with total oocyte count and mature metaphase II oocytes. Furthermore, elevated levels of both biomarkers were significantly associated with high-quality grade 1 embryos. However, neither adiponectin nor IGF-1 demonstrated a significant association with pregnancy outcomes.

**Conclusion:** Adiponectin and IGF-1 are closely associated with ovarian responsiveness, endocrine regulation, oocyte maturation, and embryo quality in women undergoing IVF. These biomarkers may serve as useful indicators of ovarian activity and follicular competence; however, their value in predicting pregnancy outcomes remains limited.

## 1. INTRODUCTION

Infertility is recognized as a pressing public health concern worldwide, with an estimated 10–15% of couples of reproductive age experiencing the condition. As a result, recourse to assisted reproductive technologies (ART), and particularly intracytoplasmic sperm injection (ICSI), has expanded markedly over the past few decades. Yet in spite of the notable progress achieved in controlled ovarian stimulation regimens and in embryology laboratory practice, marked variability persists in how women respond to ovarian stimulation, in the developmental competence of their oocytes, and in the final outcomes of ICSI cycles.<sup>(1,2)</sup> Adiponectin is a hormone secreted by adipocytes that plays a central role in regulating glucose metabolism, insulin sensitivity, and the maintenance of cellular energy balance. By activating adenosine monophosphate-activated protein kinase (AMPK), it modulates steroidogenesis within the ovary and contributes to the proper functioning of granulosa cells. Adiponectin receptors have also been localized in ovarian tissue, which lends further support to the notion that the hormone is directly engaged in follicular development and other aspects of reproductive physiology. Deviations from normal adiponectin concentrations have been linked to a number of metabolic disturbances, including obesity, insulin resistance, and polycystic ovary syndrome (PCOS)—conditions that are commonly seen in women presenting with infertility.<sup>(3,4)</sup>

Another molecule of considerable importance to ovarian function is insulin-like growth factor-1 (IGF-1). It stimulates granulosa cell proliferation, drives follicular growth, and supports steroid hormone synthesis by activating the PI3K/Akt and MAPK signalling cascades. IGF-1 also sensitises follicles to circulating gonadotropins—most notably FSH—and in doing so participates in the processes of follicular recruitment, dominant follicle selection, and final oocyte maturation. It is conceivable, therefore, that differences in IGF-1 bioactivity account, at least in part, for the heterogeneous ovarian response seen in women undergoing IVF.<sup>(5,6)</sup> Recent studies have suggested a close interaction between metabolic and growth-related pathways within the follicular environment. Adiponectin-mediated metabolic regulation may influence IGF-1 signaling, while IGF-1 activity may alter cellular energy demands and metabolic balance within developing follicles. This bidirectional crosstalk is believed to be essential for maintaining optimal follicular growth and oocyte developmental competence.<sup>(7,8)</sup> Nevertheless, the clinical significance of these biomarkers in predicting ovarian response and embryological outcomes remains incompletely understood.

### *Aim of study*

To examine how adiponectin and insulin-like growth factor-1 (IGF-1), measured in both serum and follicular fluid, relate to ovarian response, hormonal profile, oocyte competence, embryo quality, and pregnancy outcome in women undergoing intracytoplasmic sperm injection (ICSI).

## 2. SUBJECTS AND METHODS

### 2.1. subjects

This prospective comparative study was conducted at the high institute of infertility diagnosis and assisted reproductive technologies, Al-Nahrain University, Baghdad, Iraq. 120 women that participated in this study should be undergoing IVF treatment,

poor, normal, or hyper ovarian responders. patients with or without polycystic ovary syndrome (pcos). couples with normal semen parameters (normozoospermia).

## **2.2. procedure**

Each woman enrolled in the study was subjected to a thorough work-up that began with the recording of her medical and reproductive history, followed by a general physical and gynaecological examination and calculation of body mass index (BMI). A hormonal panel was then obtained, comprising anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinising hormone (LH), estradiol (E2), prolactin (PRL), and thyroid-stimulating hormone (TSH). Ovarian reserve and the overall reproductive status of each participant were further assessed by transvaginal ultrasound scanning.

### **2.2.1 ovarian stimulation and icsi procedure**

For controlled ovarian stimulation, a flexible gonadotropin-releasing hormone (GnRH) antagonist regimen was adopted. Recombinant FSH was commenced on day 2 of the menstrual cycle, and its starting dose was tailored to the individual characteristics of each patient. once two or more follicles had attained a mean diameter of 17–18 mm, ovulation was triggered by an injection of human chorionic gonadotropin (hCG). Oocyte retrieval was carried out 34 to 36 hours later under transvaginal ultrasound guidance. Mature oocytes at the metaphase II (MII) stage were selected for ICSI, and successful fertilisation was verified by the appearance of two pronuclei (2pn) on the following morning. the resulting embryos were maintained in culture up to day 3, at which point each was scored morphologically prior to transfer. Clinical pregnancy was confirmed 14 days after embryo transfer..

### **2.2.2 biochemical analysis and sample collection**

Venous blood was drawn on two occasions, namely the day of oocyte retrieval (ORD) and again on the day of embryo transfer (ETD), while follicular fluid was aspirated during the retrieval procedure itself. The collected specimens were centrifuged at 5000 rpm for 10 minutes; the resulting serum and follicular fluid fractions were then aliquoted and kept frozen at  $-20^{\circ}\text{C}$  pending biochemical analysis.

Concentrations of adiponectin and insulin-like growth factor-1 (IGF-1) in both biological fluids were determined with commercially supplied enzyme-linked immunosorbent assay (ELISA) kits, the procedures being carried out in accordance with the instructions provided by each manufacturer..

### **2.2.3 assessment of oocyte and embryo characteristics**

oocytes were classified after denudation into germinal vesicle (gv), metaphase i (mi), and metaphase ii (mii) stages. fertilization rate was calculated as follows:

$$\text{fertilization rate (\%)} = (\text{number of fertilized oocytes [2pn]} / \text{number of injected mii oocytes}) \times 100$$

embryo quality was assessed morphologically and categorized according to standard embryological criteria.

## **2.3. pilot study**

Prior to commencement of the main study, a pilot phase was carried out involving ten infertile women who were undergoing ICSI and fulfilled the predefined eligibility criteria. The aim of this preliminary stage was to test the feasibility of recruiting eligible participants, to verify that sample collection could be performed smoothly, and to ensure that the laboratory assays and the data-recording sheets were workable in practice. The ten women enrolled at this stage were excluded from the final statistical analysis. Findings from the pilot phase indicated that the overall protocol was practicable and that the ELISA procedures yielded reliable measurements of adiponectin and IGF-1 in both serum and follicular fluid; consequently, no substantial amendments to the study design were deemed necessary..

## **2.4. reliability**

to ensure the reliability and reproducibility of laboratory measurements, serum and follicular fluid adiponectin and igf-1 concentrations were determined using standardized commercially available elisa kits according to the manufacturer's instructions. all samples were analyzed under identical laboratory conditions, and calibration procedures were performed before each assay run. internal quality control samples were included to verify assay accuracy and consistency. duplicate measurements

were performed when necessary, and laboratory personnel were blinded to participants' ovarian response categories to minimize measurement bias.

the analytical procedures demonstrated acceptable precision and reproducibility throughout the study period, ensuring the reliability of the obtained biochemical data.

## 2.5. ethical considerations

Formal ethical clearance was secured from the local Medical Ethics Committee of Al-Nahrain University in Baghdad, Iraq, as well as from the Institutional Review Board (IRB) of Mansoura University, Egypt (approval code: MDP.24.9.166).

## 2.6 statistical analysis

All statistical computations were carried out with the Statistical Package for the Social Sciences (SPSS), version 23.0. The distribution of each continuous variable was first inspected by means of the Kolmogorov–Smirnov and Shapiro–Wilk tests. Variables that approximated a normal distribution were summarised as mean  $\pm$  standard deviation (SD), whereas those that departed from normality were expressed as the median

## 3. RESULTS

the adiponectin and igf-1 concentrations differed significantly among the ovarian response groups. hyper responders exhibited the highest serum and follicular fluid levels of both biomarkers, whereas lower concentrations were observed in poor responders. these findings suggest a positive association between adiponectin, igf-1, and ovarian responsiveness during controlled ovarian stimulation. (table 1).

**Table 1.** adiponectin and igf-1 levels across ovarian response groups

| marker      | sample           | poor responders<br>median (iqr) | normal responders<br>median (iqr) | hyper responders<br>median (iqr) | p-value |
|-------------|------------------|---------------------------------|-----------------------------------|----------------------------------|---------|
| adiponectin | serum (ord)      | 7.39 (2.12)                     | 5.18 (2.86)                       | 9.43 (2.22)                      | <0.001* |
|             | follicular fluid | 8.44 (2.36)                     | 4.62 (1.65)                       | 10.05 (2.34)                     | <0.001* |
|             | serum (etd)      | 5.66 (6.37)                     | 5.52 (2.19)                       | 10.28 (1.59)                     | <0.001* |
| igf-1       | serum (ord)      | 201.72 (70.55)                  | 137.70 (56.85)                    | 457.84 (166.21)                  | <0.001* |
|             | follicular fluid | 254.45 (28.70)                  | 173.48 (136.36)                   | 378.29 (44.41)                   | <0.001* |
|             | serum (etd)      | 271.42 (139.18)                 | 164.59 (95.09)                    | 324.77 (68.76)                   | <0.001* |

1. \*ord: oocyte retrieval day; etd: embryo transfer day.

\*significant at  $p < 0.05$ .

**Table 2** show that both adiponectin and igf-1 demonstrated significant positive correlations with amh, estradiol, and lh levels, indicating their close relationship with ovarian reserve and follicular steroidogenic activity. in contrast , no meaningful correlations were observed with fsh except for a weak negative association between serum adiponectin on etd and fsh . (table 2)

**Table 2.** correlation of adiponectin and igf-1 with hormonal parameters

| marker      | sample           | amh (r) | estradiol trigger (r) | lh (r) | fsh (r) |
|-------------|------------------|---------|-----------------------|--------|---------|
| adiponectin | serum (ord)      | 0.323*  | 0.322*                | 0.333* | -0.054  |
|             | follicular fluid | 0.187   | 0.276*                | 0.287* | -0.022  |

| marker | sample           | amh (r) | estradiol trigger (r) | lh (r) | fsh (r) |
|--------|------------------|---------|-----------------------|--------|---------|
|        | serum (etd)      | 0.440*  | 0.400*                | 0.372* | -0.211* |
| igf-1  | serum (ord)      | 0.390*  | 0.403*                | 0.441* | -0.110  |
|        | follicular fluid | 0.458*  | 0.514*                | 0.468* | -0.150  |
|        | serum (etd)      | 0.204   | 0.243*                | 0.154  | 0.018   |

\*spearman correlation coefficient.

\*significant at  $p < 0.05$ .

**Table 3** presents the higher adiponectin and igf-1 levels were significantly associated with increased total oocyte yield and mature (mii) oocyte numbers. these results indicate that both biomarkers may contribute to follicular development and oocyte maturation, reflecting improved ovarian performance in women undergoing icsi.

**Table 3.** correlation of adiponectin and igf-1 with oocyte characteristics

| marker      | sample           | total oocytes (r) | gv oocytes (r) | mii oocytes (r) |
|-------------|------------------|-------------------|----------------|-----------------|
| adiponectin | serum (ord)      | 0.363*            | 0.424*         | 0.311*          |
|             | follicular fluid | 0.259*            | 0.271*         | 0.200           |
|             | serum (etd)      | 0.440*            | 0.311*         | 0.381*          |
| igf-1       | serum (ord)      | 0.462*            | 0.379*         | 0.405*          |
|             | follicular fluid | 0.462*            | 0.391*         | 0.420*          |
|             | serum (etd)      | 0.257*            | 0.267*         | 0.238*          |

\*gv: germinal vesicle; mii: metaphase ii.

\*significant at  $p < 0.05$ .

(**Table 4**). describes the significant positive correlations were identified between adiponectin and igf-1 levels and grade 1 embryo formation. however, neither biomarker showed significant associations with grade 2 or grade 3 embryos, suggesting a potential role in supporting the development of high-quality embryos rather than overall embryo production.

**Table 4.** correlation of adiponectin and igf-1 with embryo quality

| marker      | sample           | grade 1 embryos (r) | grade 2 embryos (r) | grade 3 embryos (r) |
|-------------|------------------|---------------------|---------------------|---------------------|
| adiponectin | serum (etd)      | 0.241*              | -0.049              | -0.122              |
| igf-1       | serum (ord)      | 0.241*              | -0.123              | -0.162              |
|             | follicular fluid | 0.282*              | -0.097              | -0.128              |

\*spearman correlation coefficient.

\*significant at  $p < 0.05$ .

**Table 5** shows the overall, adiponectin and igf-1 were positively associated with ovarian response, reproductive hormonal profiles, oocyte competence, and embryo quality. nevertheless, neither biomarker demonstrated predictive value for pregnancy

outcomes, indicating that implantation and clinical pregnancy are influenced by additional factors beyond follicular metabolic and growth-related pathways.

**Table 5.** summary of associations between biomarkers and clinical outcomes

| variable                | adiponectin                      | igf-1                            |
|-------------------------|----------------------------------|----------------------------------|
| ovarian response        | significant positive association | significant positive association |
| amh                     | positive correlation             | positive correlation             |
| estradiol (e2)          | positive correlation             | positive correlation             |
| lh                      | positive correlation             | positive correlation             |
| total oocyte count      | positive correlation             | positive correlation             |
| mii oocytes             | positive correlation             | positive correlation             |
| grade 1 embryos         | positive correlation             | positive correlation             |
| pregnancy outcome       | no significant association       | no significant association       |
| age                     | significant negative correlation | significant negative correlation |
| bmi                     | no significant association       | no significant association       |
| duration of infertility | no significant association       | no significant association       |

*Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; E2, estradiol; ELISA, enzyme-linked immunosorbent assay; ETD, embryo transfer day; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GV, germinal vesicle; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IGF-1, insulin-like growth factor-1; IQR, interquartile range; LH, luteinising hormone; MII, metaphase II; ORD, oocyte retrieval day; PRL, prolactin; SD, standard deviation; TSH, thyroid-stimulating hormone.*

## 4. DISCUSSION

The present study investigated the relationship between serum and follicular fluid adiponectin and insulin-like growth factor-1 (igf-1) concentrations and ovarian response, hormonal profiles, oocyte competence, embryo quality, and pregnancy outcomes in women undergoing icsi. the findings demonstrated significant associations between both biomarkers and ovarian responsiveness, reproductive hormonal parameters, oocyte maturation, and embryo quality. however, neither adiponectin nor igf-1 showed predictive value for pregnancy outcomes.

one of the principal findings of the current study was the significantly higher concentrations of adiponectin and igf-1 observed among hyper responders compared with poor and normal responders. these findings suggest that both biomarkers are closely related to follicular activity and ovarian reserve. hyper responders typically exhibit enhanced follicular recruitment and greater sensitivity to gonadotropin stimulation, which may explain the elevated concentrations of metabolic and growth-related factors within both the systemic circulation and follicular microenvironment. similar observations have been reported by qin et al. and mehta et al., who demonstrated positive associations between adiponectin, igf-1, and ovarian responsiveness during assisted reproductive procedures.<sup>(9,10)</sup>

A further finding of the present work was that adiponectin concentrations correlated positively, and to a significant degree, with several reproductive hormones, most notably AMH, estradiol, and LH. Although adiponectin has long been regarded primarily as an adipose-tissue hormone concerned with glucose homeostasis and the regulation of insulin sensitivity, a growing body of evidence now points to actions that go well beyond metabolism. Through the AMP-activated protein kinase (AMPK) pathway, adiponectin appears to influence granulosa cell metabolism directly and to modulate the steroidogenic machinery of the ovary. The positive link between adiponectin and estradiol observed in our cohort is therefore consistent with earlier reports in which adiponectin was shown to support granulosa cell activity and to play a role in the maturation of the developing follicle.<sup>(11,12,13)</sup>

likewise, igf-1 exhibited strong positive correlations with amh, estradiol, and lh. igf-1 is a well-established regulator of folliculogenesis and ovarian steroidogenesis. through activation of pi3k/akt and mapk signaling pathways, igf-1 promotes granulosa cell proliferation, enhances aromatase activity, and increases follicular sensitivity to fsh. the strong relationship

between igf-1 and hormonal indicators of ovarian activity observed in this study is consistent with previous experimental and clinical investigations demonstrating the central role of igf-1 in follicular growth and dominant follicle selection.<sup>(14,15)</sup>

another important finding was the positive association between both biomarkers and oocyte characteristics. higher adiponectin and igf-1 concentrations were associated with greater total oocyte yield and increased numbers of mature mii oocytes. adiponectin may improve oocyte developmental competence through optimization of cellular energy metabolism, whereas igf-1 promotes granulosa cell survival and follicular growth. these mechanisms may explain the significant correlations observed between biomarker concentrations and oocyte maturation parameters.<sup>(16,17)</sup>

the present study further demonstrated significant associations between adiponectin, igf-1, and the development of high-quality grade 1 embryos. these findings suggest that both biomarkers contribute not only to oocyte maturation but also to subsequent embryonic developmental potential. previous studies have reported that follicular fluid igf-1 concentrations are associated with embryo quality and implantation potential. similarly, metabolic regulators such as adiponectin have been implicated in mitochondrial function, cellular energy regulation, and early embryogenesis. therefore, elevated concentrations of these biomarkers may reflect a more favorable follicular environment capable of supporting embryo development.<sup>(18,19)</sup>

despite their significant associations with ovarian response and embryo quality, neither adiponectin nor igf-1 predicted pregnancy outcomes. this finding is consistent with previous reports indicating that biomarkers reflecting follicular competence do not necessarily predict implantation success or clinical pregnancy. pregnancy achievement is a multifactorial process involving embryo quality, endometrial receptivity, immunological tolerance, vascular remodeling, and embryo-maternal communication. consequently, although adiponectin and igf-1 appear to be valuable indicators of ovarian function, their predictive ability may be limited to the earlier stages of reproduction.<sup>(20,21)</sup>

an additional observation in the present study was the significant inverse relationship between both biomarkers and advancing maternal age. this finding agrees with the established decline in ovarian reserve and follicular quality associated with reproductive aging. age-related alterations in granulosa cell function, mitochondrial activity, and follicular fluid composition may contribute to reduced adiponectin and igf-1 concentrations, thereby affecting ovarian responsiveness and reproductive potential.<sup>(22,23)</sup>

from a clinical perspective, the findings suggest that adiponectin and igf-1 may serve as complementary biomarkers to conventional ovarian reserve markers such as amh and estradiol. their assessment in serum and follicular fluid could provide additional information regarding follicular competence and ovarian responsiveness, particularly in women with metabolic disturbances such as obesity and polycystic ovary syndrome. incorporation of metabolic and growth-related biomarkers into individualized ovarian stimulation strategies may contribute to improved patient stratification and optimization of icsi outcomes.<sup>(24,25)</sup>

Among the strengths of the present work is the fact that adiponectin and IGF-1 were quantified in parallel within two biological compartments — the systemic circulation and the follicular microenvironment — and that their behaviour was traced against a fairly wide spectrum of reproductive endpoints. A number of limitations, however, must be openly conceded. Recruitment was confined to a single tertiary centre, and the sample, although adequate for the comparisons undertaken, remained modest in size; live birth, arguably the most clinically meaningful outcome, was not captured within our observation window. Nor did the protocol extend to other metabolic or inflammatory mediators that might have shed additional light on the mechanisms involved. Larger, multicentre studies with longer-term follow-up will therefore be needed before the prognostic value of these two markers in assisted reproduction can be established with confidence.<sup>(26,27)</sup>

## CONCLUSION

The findings of this study indicate that adiponectin and insulin-like growth factor-1 (IGF-1) bear a meaningful relationship to several aspects of the ICSI cycle — namely ovarian response, the reproductive hormonal milieu, the maturational status of the retrieved oocytes, and the morphological quality of the resulting embryos. Both markers were present at higher concentrations, in serum as well as in follicular fluid, among women classified as hyper responders, and their levels moved in the same direction as established indicators of ovarian reserve, the total oocyte yield, the number of mature oocytes recovered, and the proportion of good-grade embryos obtained. On the other hand, no clear link could be established between either biomarker and the achievement of clinical pregnancy. It would appear, therefore, that adiponectin and IGF-1 hold promise as indicators of ovarian

function and follicular competence, even though their usefulness for forecasting pregnancy on a case-by-case basis remains, for the time being, limited

## **recommendations**

1. measurement of these biomarkers alongside conventional ovarian reserve markers, such as amh and estradiol, may improve the evaluation of ovarian function.
2. future studies should investigate the combined predictive value of metabolic, endocrine, embryological, and endometrial biomarkers for improving pregnancy outcome prediction.
3. large-scale multicenter studies with longer follow-up periods are recommended to validate the clinical utility of adiponectin and igf-1 in assisted reproductive technologies.
4. more research needed to explore the molecular mechanisms linking adiponectin and igf-1 signaling pathways to follicular development, embryo competence, and reproductive success.

## **STUDY LIMITATIONS**

Several caveats need to be borne in mind when the present results are interpreted. To begin with, all participants were recruited from a single infertility centre, and the extent to which our observations can be extrapolated to other patient populations or to different clinical contexts is therefore uncertain. Second, the sample size; although it proved sufficient to expose the principal associations of interest, it may have lacked the power needed to detect more subtle effects, particularly those relating to pregnancy. Third, the reproductive endpoint chosen for analysis was clinical pregnancy rather than live birth, the latter being the outcome that ultimately matters most to couples seeking assisted reproduction. A further point worth raising is that the biochemical investigation was deliberately restricted to two metabolic-endocrine mediators, namely adiponectin and IGF-1; numerous other molecules with established roles in folliculogenesis, implantation, and the embryo–endometrial dialogue were left outside the scope of the present enquiry. These reservations notwithstanding, the work makes a meaningful contribution to the understanding of how adiponectin and IGF-1 relate to ovarian response, oocyte competence, and embryo quality in the context of ICSI treatment.

## **REFERENCES**

- [1] mousa m, al-jefout m, alsafar h, kirtley s, lindgren cm, missmer sa, et al. prevalence of common gynecological conditions in the middle east: systematic review and meta-analysis. *frontiers in reproductive health*. 2021. doi:10.3389/frph.2021.661360.
- [2] motlagh asghari k, nejadghaderi sa, alizadeh m, sanaie s, sullman mjm, kolahi aa, et al. burden of polycystic ovary syndrome in the middle east and north africa region, 1990–2019. *sci rep*. 2022;12(1). doi:10.1038/s41598-022-11006-0
- [3] dermolo m, ansa m, siferih m. ovarian response to controlled stimulation and its predictors in a limited-resource setting. *bmc womens health*. 2024;24(1). doi:10.1186/s12905-024-02991-7
- [4] chang q, wang s, mai q, zhou c. impact of obesity on proteomic profiles of follicular fluid-derived small extracellular vesicles: a comparison between pcos and non-pcos women. *journal of ovarian research* . 2025;18(1). doi:10.1186/s13048-025-01703-5
- [5] lazzarino g, pallisco r, bilotta g, listorti i, mangione r, saab mw, et al. altered follicular fluid metabolic pattern correlates with female infertility and outcome measures of in vitro fertilization. *int j mol sci*. 2021;22(16). doi:10.3390/ijms22168735
- [6] revelli a, plane ld, casano s, molinari e, massobrio m, rinaudo p. follicular fluid content and oocyte quality: from single biochemical markers to metabolomics. *reproductive biology and endocrinology*. 2009. doi:10.1186/1477-7827-7-40
- [7] zhang y, he c, he y, zhu z. follicular fluid metabolomics: tool for predicting icsi outcomes of different infertility causes. *reproductive sciences*. 2025. doi:10.1007/s43032-024-01664-y
- [8] barbe a, bongrani a, mellouk n, estienne a, kurowska p, grandhay e j, et al. mechanisms of adiponectin action in fertility: an overview from gametogenesis to gestation in humans and animal models in normal and pathological conditions. *international journal of molecular sciences*. 2019. doi:10.3390/ijms20071526
- [9] grandhay e j, hmadeh s, plotton i, levasseur f, estienne a, leguevel r, et al. the adiponectin agonist, adiporon, inhibits steroidogenesis and cell proliferation in human luteinized granulosa cells. *mol cell endocrinol*. 2021;520. doi:10.1016/j.mce.2020.111080

- [10] hayes e, winston n, stocco c. molecular crosstalk between insulin-like growth factors and follicle-stimulating hormone in the regulation of granulosa cell function. *reproductive medicine and biology*. 2024. doi:10.1002/rmb2.12575
- [11] bezerra més, barberino rs, menezes vg, gouveia bb, macedo tjs, santos jms, et al. insulin-like growth factor-1 (igf-1) promotes primordial follicle growth and reduces dna fragmentation through the phosphatidylinositol 3-kinase/protein kinase b (pi3k/akt) signalling pathway. *reprod fertil dev*. 2018;30(11). doi:10.1071/rd17332
- [12] motobayashi y, izawa-ishizawa y, ishizawa k, orino s, yamaguchi k, kawazoe k, et al. adiponectin inhibits insulin-like growth factor-1-induced cell migration by the suppression of extracellular signal-regulated kinase 1/2 activation, but not akt in vascular smooth muscle cells. *hypertension research*. 2009;32(3). doi:10.1038/hr.2008.19
- [13] yamauchi t, kamon j, minokoshi y, ito y, waki h, uchida s, et al. adiponectin stimulates glucose utilization and fatty-acid oxidation by activating amp-activated protein kinase. *nat med*. 2002;8(11). doi:10.1038/nm788
- [14] schindler m, pendzialek m, joanna grybel k, seeling t, gürke j, fischer b, et al. adiponectin stimulates lipid metabolism via ampk in rabbit blastocysts how does a maternal diabetic hyperadiponectineamia affect signal transduction and lipid metabolism in rabbit preim- plantation blastocysts? *human reproduction advanced access publication on may*. 2017;32(4).
- [15] schindler m, pendzialek m, grybel kj, seeling t, gürke j, fischer b, et al. adiponectin stimulates lipid metabolism via ampk in rabbit blastocysts. *human reproduction*. 2017;32(7). doi:10.1093/humrep/dex087
- [16] orisaka m, miyazaki y, shirafuji a, tamamura c, tsuyoshi h, tsang bk, et al. the role of pituitary gonadotropins and intraovarian regulators in follicle development: a mini-review. *reproductive medicine and biology*. 2021. doi:10.1002/rmb2.12371
- [17] dri m, klinger fg, de felici m. the ovarian reserve as target of insulin/igf and ros in metabolic disorder-dependent ovarian dysfunctions. *reproduction and fertility*. 2021. doi:10.1530/raf-21-0038
- [18] li w, murtaza i, ali t. the adiponectin-depression nexus: a brief review of mechanisms and therapeutic opportunities. *metabolic brain disease*. 2026. doi:10.1007/s11011-025-01757-w
- [19] moore lg, wesolowski sr, lorca ra, julian cg. ampk: accumulating evidence in support of its role in dual regulation of vascular function and metabolism during human pregnancy. *acta physiologica*. 2025. doi:10.1111/apha.70093
- [20] goto m, iwase a, ando h, kurotsuchi s, harata t, kikkawa f. pten and akt expression during growth of human ovarian follicles. *j assist reprod genet*. 2007;24(11). doi:10.1007/s10815-007-9156-3
- [21] pan y, pan c, zhang c. unraveling the complexity of follicular fluid: insights into its composition, function, and clinical implications. *journal of ovarian research* . 2024. doi:10.1186/s13048-024-01551-9
- [22] mendoza c, ruiz-requena e, ortega e, cremades n, martinez f, bernabeu r, et al. follicular fluid markers of oocyte developmental potential. *human reproduction*. 2002;17(4). doi:10.1093/humrep/17.4.1017
- [23] dai s, zhang h, yang f, shang w, zeng s. effects of igf-1 on the three-dimensional culture of ovarian preantral follicles and superovulation rates in mice. *biology (basel)*. 2022;11(6). doi:10.3390/biology11060833
- [24] mehta bn, chimote nm, chimote mn, chimote nn, nath nm. follicular fluid insulin like growth factor-1 (ff igf-1) is a biochemical marker of embryo quality and implantation rates in in vitro fertilization cycles. *j hum reprod sci*. 2013;6(2). doi:10.4103/0974-1208.117171
- [25] mao j, whitworth km, spate ld, walters em, zhao j, prather rs. regulation of oocyte mitochondrial dna copy number by follicular fluid, egf, and neuregulin 1 during in vitro maturation affects embryo development in pigs. *theriogenology*. 2012;78(4). doi:10.1016/j.theriogenology.2012.04.002
- [26] demirel e, kelekçi s, aydoğmuş s, kızıltuğ n, eriş s. endometriosis and implantation failure: review. *türkiye klinikleri jinekoloji obstetrik*. 2015. doi:10.5336/gynobstet.2013-3816
- [27] mrozikiewicz ae, ożarowski m, jędrzejczak p. biomolecular markers of recurrent implantation failure— a review. *international journal of molecular sciences*. 2021. doi:10.3390/ijms221810082