Rzeszów University Press 2026
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2026.2.9

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2026; 24 (2): 289–301

ORIGINAL PAPER

Evaluation of serum and follicular fluid progranulin in relevance to BMI, oocyte, and embryo quality in Iraqi women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection

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ABSTRACT

Introduction and aim. Polycystic ovarian syndrome (PCOS) is a common endocrine-metabolic disease often associated with obesity, persistent low-grade inflammation, and suboptimal results of assisted reproductive technology (ART). The aim was to evaluate the relevance of serum and follicular progranulin (PGRN) levels in relation to intracytoplasmic sperm injection outcomes among normal and overweight/obese body mass index (BMI) women with PCOS.

Material and methods. This prospective comparative study included women diagnosed with PCOS undergoing intracytoplasmic sperm injection (ICSI) between the first of October 2024 and the first of April 2025. Baseline serum markers were measured on cycle days 2–3. Participants were categorized as having a normal BMI, group 1 (n=30), or being overweight/obese, group 2 (n=37). Fasting serum and follicular fluid progranulin (PGRN) levels were assessed on oocyte retrieval day.

Results. Women with normal BMI were younger and had significantly lower BMI and shorter infertility duration compared with overweight/obese women ($p \leq 0.05$). No statistically significant differences were observed between BMI groups in the number of retrieved oocytes, MII oocytes, fertilized oocytes, embryo grades, blastocysts, or biochemical pregnancy rate ($p > 0.05$). Numerically, normal-BMI women showed slightly higher retrieved and MII oocyte counts, whereas overweight/obese women demonstrated higher numbers of fertilized oocytes, total embryos, grade I embryos, blastocysts, and biochemical pregnancy rates; however, these differences did not reach statistical significance.

Serum and follicular fluid PGRN levels were comparable between groups ($p > 0.05$), with only limited correlations observed between follicular fluid PGRN and total oocyte count.

Conclusion. Serum and follicular fluid PGRN levels were comparable across BMI categories in women with PCOS undergoing ICSI. Although numerical variations in oocyte and embryo parameters were observed between BMI groups, most differences were not statistically significant. The findings suggest that follicular fluid PGRN may be associated with certain ovarian response parameters; however, its independent clinical relevance in predicting ART outcomes remains uncertain. Larger studies incorporating clinical pregnancy and live birth outcomes are required to clarify the potential role of follicular fluid PGRN in PCOS-related infertility.

Keywords. infertility, obesity, polycystic ovary syndrome, progranulin

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Received: 3.11.2025 / Revised: 27.01.2026 / Accepted: 31.01.2026 / Published: 30.06.2026

Al-Zori IKS, Abood MS, Mossa HAL. Evaluation of serum and follicular fluid progranulin in relevance to BMI, oocyte, and embryo quality in Iraqi women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection. *Eur J Clin Exp Med.* 2026;24(2):289–301. doi: 10.15584/ejcem.2026.2.9.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder linked to infertility, resulting from abnormal endocrine and metabolic patterns in women of reproductive age, affecting approximately 15 to 20% of this population and responsible for up to 80% of anovulation and reduced female fertility cases.[1-3] PCOS is characterized as a chronic inflammatory syndrome associated with obesity. Elevated body mass index (BMI) can influence oocyte development, fertilization processes, and embryo quality, ultimately resulting in worse pregnancy outcomes.[4-6] The extensive prevalence of obesity and overweight constitutes a significant global public health issue.[7] Since 1975, the global prevalence of obesity has nearly tripled, with 40% of women classified as overweight (BMI 25–29.9 kg/m^2) and 15% as obese (BMI≥30 kg/m^2), according to a 2016 World Health Organization (WHO) survey.[8] Obesity is a chronic illness that is increasingly prevalent worldwide and adversely affects female fertility and is inextricably associated with low-grade systemic inflammation.[9,10] Obesity-related pregnancy problems have been associated with repeated pregnancy loss, suboptimal endometrial receptivity and inadequate embryo quality in normal or post- ICSI pregnancy.[11-13]

In comparison to normal BMI-PCOS, inflammatory markers, such as PGRN, were increased in high BMI-PCOS. Since its discovery, progranulin (PGRN) has been suggested as a diagnostic and therapeutic biomarker for numerous neoplastic, neurological, and inflammatory illnesses due to its diverse functional features.[14-16] PGRN, also known as proepithelin, is an autocrine growth factor derived from plasma cells. It is a glycoprotein weighing 68–88 kDa and composed of 593 amino acids[17] serving as a precursor to granulin following a proteolytic cleavage process. PGRN is released in response to hypoxia or acidosis and participates in various complex physiological and pathological processes owing to its anti-inflammatory and pro-inflammatory properties. Evidence indicates that the complete PGRN molecule exhibits trophic and anti-inflammatory effects, whereas granulin peptides promote inflammation.[18,19]

PGRN has been implicated in the onset of insulin resistance (IR) in diabetes caused by a high-fat diet. Evidence suggests that PGRN may be associated with many autoimmune illnesses, including systemic lupus erythematosus, systemic sclerosis, multiple sclerosis, and Sjogren's syndrome. PGRN binds to TNFR1 with an affinity similar to that of TNFα, but its affinity for TNFR2 is markedly higher than that of TNFα.[20,21] The heightened immunological response, coupled with insulin resistance and hyperandrogenism resulting from obesity, negatively influences the hypothalamic-pituitary-gonadal axis at all levels and directly impacts reproduction.[22] In the context of PCOS, immune cells and regulatory immune molecules are crucial for sustaining metabolic equilibrium and modulating immunological responses. Individuals with PCOS suffer diminished progesterone levels due to oligo/anovulation. Consequently, in instances of PCOS, immune system hyperactivation transpires due to diminished progesterone levels. This phenomenon induces the synthesis of surplus estrogen, leading to the formation of multiple autoantibodies.[23] PGRN has also been reported to be linked to the infiltration of macrophages in adipose tissue.

Follicular fluid is an integral microenvironment of the growing oocyte; in addition, it mirrors local metabolic, endocrine, and inflammatory events in the ovarian follicle.[24] In contrast to serum biomarkers that reflect non-localized conditions, biomarkers detected in follicular fluid may more directly represent granulosa cell activity, oxidative stress status, and intra-follicular immune status. Thus, measuring follicular fluid PGRN in parallel with serum levels of this biomarker may be interesting since it could give further information on the role that PGRN might play not only on oocyte competence but also on embryo developmental potential in ICSI cycles.[5,25,26]

Aside from cross-sectional analysis, calculations of serum PGRN fluctuations in correlation with the early follicular phase (cycle days 2–3) and oocyte pick-up (OPU) day can provide insights regarding the inflammation and metabolic response triggered after controlled ovarian stimulation. Dynamic assessment of these relationships may help clarify whether gonadotropin exposure centers on the regulation of PGRN in cycles undergoing ICSI in women with PCOS.

A limited number of studies in the literature have compared the impact of PGRN on the etiology and pathogenesis of combined obesity and infertility across different body mass index groups in the PCOS population particularly among Iraqi infertile women, given the high incidence of obesity in the Iraqi female population.[27]

This study is, to the best of our knowledge, one of the first to investigate both serum and follicular fluid PGRN concentrations in women with PCOS and their correlations with BMI and detailed ICSI outcomes such as oocyte maturity, embryo grading, and blastocyst formation. Moreover, the comparison of PGRN dynamics pre- and post-ovarian stimulation in an Iraqi PCOS population – a physiological region that has been relatively neglected in reproductive research – offers both integrative and community-specific information to help elucidate the means through which reproductive inflammation exhibits heterogeneity across ART settings.

Aim

The aim of this study is to assess IVF/ICSI results in infertile Iraqi PCOS women, with a primary focus on the impact of BMI on ICSI outcomes and to clarify the re-

lationship between fasting serum and follicular fluid PGRN levels on OPU day, BMI and ICSI outcomes as a secondary objective.

Material and methods

Ethical approval

This study adhered to the Helsinki Declaration, and the protocol received approval from the Ethics Committee of the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University, Baghdad, Iraq (approval code: 0701-DF-2024A43 on 9/9/2024). Informed consent was obtained from each patient using a pre-prepared questionnaire.

Study setting

This prospective comparative clinical study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University/Baghdad, and included 67 Iraqi women diagnosed with PCOS who underwent ICSI between the first of October 2024 and the first of April 2025. Participants had a history of initial or recurrent IVF/ICSI attempts, and embryo transfer (ET) was predominantly conducted using frozen embryo transfer with the couple's own oocytes and sperm. The study of egg morphology obtained from each infertile female's ovaries and the assessment of embryo grading were conducted in a specialized embryology laboratory within the operating theatre. Fasting serum and follicular fluid samples for PGRN quantification were collected, centrifuged, and stored under deep freezing conditions until analysis via the enzyme-linked immunosorbent assay/sandwich ELISA technique (ELK Biotechnology), Cat: ELK10952, Lot: 54225510, sensitivity: 0.51 ng/mL, detection range: 1.56–100 ng/mL, intra-assay precision: CV%<8%, inter-assay precision: CV%<10%, using the BioTek/USA semi-automated washer and reader system.

Groups of patients

This study enrolled sixty-seven infertile women with PCOS diagnoses, who underwent controlled ovarian stimulation using a flexible antagonist protocol. They were categorized as either primary or secondary infertility. The total number of included women reported complaints of PCOS, validated by the established Rotterdam criteria (oligo- or amenorrhea, clinical and biochemical evidence of excess androgen, and subcapsular small cyst morphology observed via transvaginal ultrasound follow-up).[28] Several couples also experienced male factor infertility (mild oligo-asthenozoospermia and obstructive azoospermia were included in the study).

Patients' medical assessment

A medical history review was conducted for infertile partners with PCOS with a pre-existing questionnaire. Infertile ladies had comprehensive general and gynecological evaluations. Anthropometric measures, comprising height and weight, are utilized to compute BMI using the formula (BMI=patient's weight (kg)/ patient's height $(m)^2$). Baseline levels of FSH, LH, E_2, PRL, and TSH were assessed on menstrual cycle days 2 or 3 (CD2-3), utilizing Mini VIDAS (France-BIO-MERIEUX).

A transvaginal ultrasound, a saline infusion sonogram (SIS) or a hysterosalpingogram (HSG) was performed to evaluate the integrity of the endometrial cavity and rule out pelvic pathological conditions, such as hydrosalpinx. Semen fluid analysis for males was conducted in accordance with the WHO 2021, 6th manual.[29,30]

Controlled ovarian stimulation (GnRH antagonist protocol)

Ovulation induction was initiated on cycle day 2 or 3 using the flexible GnRH antagonist protocol for all infertile women with PCOS involved in the study. A follow-up assessment of patients' responses to controlled ovarian hyperstimulation was conducted through serial transvaginal ultrasounds and serum estradiol (E_2) levels until a minimum of three leading follicles measuring approximately 14 mm were attained. Subsequently, a daily subcutaneous administration of the GnRH antagonist cetrorelix was initiated until at least three dominant follicles measuring about 17–18 mm were achieved.[31] OPU was performed following a dual ovulation trigger, utilizing 0.2 mg decapeptyl and 250 mg ovitrelle via subcutaneous injections, approximately 34–36 hours later.

Serum and follicular fluid sample collection

Fasting serum samples for PGRN assay on CD2-3, along with fasting serum and follicular fluid samples from each participant on OPU day, were collected. These samples were frozen at -80°C after being centrifuged at 5000 rpm for 10 minutes until laboratory analysis was performed using sandwich ELISA in duplicate measurements.[31-33] The quality assessment of oocytes was conducted post-denudation in the ICSI laboratory, the ovarian sensitivity index (OSI) was recorded, and the maturation rate (MR) was evaluated, subsequently followed by sperm injection into ostensibly normal MII oocytes. The fertilization rate (FR) was documented, and an assessment of embryo quality, including the classification of various embryo grades, was conducted.[28-30] Luteal phase supplementation via micronized progesterone therapy, either by transvaginal and/or intramuscular routes, was administered. Subsequently, embryo transfer (ET) and serum B-HCG assessments were conducted fourteen days post-ET, and the biochemical pregnancy rate for all subjects was evaluated.

For primary comparative analyses between BMI groups, serum and follicular fluid PGRN levels measured

on OPU day were used, as these reflect the peri-ovulatory microenvironment during ICSI. Basal serum PGRN levels measured on cycle days 2–3 were primarily used for within-group comparison to assess dynamic changes following ovarian stimulation and were considered exploratory in relation to stimulation-induced inflammatory or metabolic responses.

Determination of inclusion and exclusion criteria

Inclusion criteria

Participants were selected based on defined criteria: couples consenting to participate in the study; female patients diagnosed with PCOS according to the Rotterdam criteria, classified by BMI as either normal or overweight/obese BMI; and women aged 18 to 45 years who provided written informed consent. Both fresh and frozen embryo transfer cycles performed under adaptable GnRH antagonist regimes were included. Cases of mild oligo-asthenozoospermia and obstructive azoospermia male factor infertility were also included.

Exclusion criteria

The exclusion criteria encompassed couples who declined participation and patients with chronic conditions such as uncontrolled diabetes mellitus, dyslipidemia, hyperthyroidism, hypothyroidism, bleeding disorders, congenital adrenal hyperplasia, hypertension, cardiovascular disease, hypogonadotropic hypogonadism, or hyperprolactinemia. Women younger than 18 or older than 45 years were excluded, as were those undergoing ovarian stimulation outside of the flexible antagonist regimen. Controlled ovarian stimulation cycles yielded empty follicles (absence of oocytes) or an unreceptive endometrium (assessed via Doppler transvaginal ultrasound by the lack of the triple-line sign in the endometrial lining and elevated pulsatility index (PI) and resistance index (RI) values), or congenital anomalies of the female reproductive tract were excluded from the study.

Study design

Sixty-seven infertile females with PCOS who participated in this prospective comparative clinical study were classified into two groups according to BMI: group 1 included 30 women with normal BMI (18.5–24.9 kg/m^2), and group 2 included 37 women classified as overweight or obese (BMI ≥25 kg/m^2). Overweight and obese women were analyzed as a single group due to insufficient statistical power to allow reliable subgroup comparisons, an approach consistent with previous PCOS and ART studies.

Both fresh and frozen embryo transfer cycles were included in the analysis. Cases of primary and secondary infertility, as well as cycles with and without mild male factor infertility, were distributed across both BMI groups and were considered background clinical characteristics. No stratified subgroup analyses were performed for these variables due to sample size considerations, and comparisons were conducted primarily according to BMI classification.

Outcome definitions

Biochemical pregnancy was defined as a positive serum β-hCG measurement 14 days after embryo transfer. Maturation rate (MR) was calculated as the number of metaphase II (MII) oocytes divided by the total number of retrieved oocytes ×100. Fertilization rate (FR) was calculated as the number of two-pronuclear (2PN) fertilized oocytes divided by the number of injected MII oocytes ×100. Embryo grading was performed according to standard morphological criteria based on blastomere number, symmetry, and fragmentation on day 3, and developmental stage assessment for morula and blastocyst formation.

Statistical analysis

All data entry and coding were performed using Microsoft Excel 365 (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were conducted using Minitab statistical software (Version 22; Minitab LLC, State College, PA, USA). Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were presented as frequencies and percentages. Data normality was assessed using the Shapiro–Wilk test. As most continuous variables demonstrated normal distribution and homogeneity of variance, parametric tests were applied. Independent samples t-tests were used to compare continuous variables between BMI groups, and the Chi-square test was used for categorical variables. Pearson's correlation coefficient (r) was used to evaluate associations between serum or follicular fluid PGRN levels and ICSI outcomes. No adjustment for multiple comparisons were performed due to the exploratory nature of the analyses. Non-significant findings were interpreted descriptively without inferring biological causality. A p-value ≤0.05 was considered statistically significant.[34]

Results

Baseline demographic and clinical characteristics

The baseline demographic and infertility characteristics of the study population are presented in Table 1. Women with normal BMI were slightly younger and had a significantly lower BMI compared with overweight/obese women. Infertility duration was significantly longer in the overweight/obese group. The distribution of primary and secondary infertility types, as well as infertility causes, did not differ significantly between BMI groups.

Table 1. Demographic characteristics of infertile PCOS women according to BMI[a]

Characteristics	Normal BMI PCOS (n=30) (Mean±SD)	Overweight/obese PCOS (n=37) (Mean±SD)	p
Age (years)	28.9±6.0	29.9±5.4	0.484*
BMI (kg/m^2)	24.2±1.4	32.4±3.8	0.001*
Infertility duration	6.0±4.5	7.9±4.7	0.001*
Types of infertility			
Primary	26 (86.7)	31 (83.8)	0.742**
Secondary	4 (13. 3)	6 (16.2)	
Causes of infertility			
Male factor	0 (0.0)	0 (0.0)	0.212**
Female factor	5 (16.7)	11 (29.7)	
Combined factor	25 (83.3)	26 (70.3)	

[a] * – independent T test was used continues variables, ** – Chi square test was used for categorical variables

Basal hormonal profile

Basal hormonal parameters measured on cycle days 2–3 are summarized in Table 2. Anti-Müllerian hormone (AMH), FSH, LH, TSH, estradiol, and prolactin levels were comparable between groups, with no statistically significant differences observed. Although minor numerical variations were noted, these did not reach statistical significance.

Table 2. Basal serum hormonal levels of infertile PCOS women on cycle day-2 based on BMI[a]

Characteristics	Normal BMI PCOS (Mean±SD)	Overweight/obese PCOS (Mean±SD)	p*
AMH (ng/mL)	5.8±2.2	5.5±3.0	0.660
FSH (mIU/mL)	6.1±2.9	6.5±2.8	0.559
LH (mIU/mL)	8.6±7.1	7.3±4.8	0.395
TSH (mIU/mL)	1.9±1.0	2.2±2.2	0.432
Basal E_2 (pg/mL)	34.0±14.5	36.7±11.4	0.396
Prolactin (ng/mL)	16.9±8.3	15.6±7.3	0.509

[a] * – independent T test was used, AMH – anti-Mullerian hormone, FSH – follicle-stimulating hormone, LH – luteinizing hormone, TSH – thyroid-stimulating hormone

Table 3. Controlled ovarian stimulation characteristics according to BMI[a]

Characteristics	Normal BMI PCOS (Mean±SD)	Overweight/obese PCOS (Mean±SD)	p*
E_2 triggering level (pg/mL)	1860±898.0	2104.0±1622.0	0.465
FSH stimulation dose (IU)	1362±527.0	1938.0±772.0	0.001
LH stimulation dose (IU)	413±477.0	622.0±454.0	0.551
Total gonadotrophin dose (IU)	1390±586.0	2190.0±1026.0	0.001
OSI	14.8±9.6	10.6± 6.7	0.042
Duration of stimulation (days)	11.2±1.1	11.2±1.4	0.931
Number of cetrotide injection (0.25mg)	3.1±0.8	3.3±0.9	0.365

[a] * – independent samples T test was used, E_2 – estradiol, OSI – total retrieved oocyte/total gonadotropin

Controlled ovarian stimulation characteristics

Stimulation-related characteristics are shown in Table 3. Overweight/obese women required significantly higher total gonadotropin and FSH doses compared with normal BMI women. In contrast, the ovarian sensitivity index (OSI) was significantly higher in the normal BMI group. Estradiol triggering levels, LH dose, duration of stimulation, and number of antagonist injections did not differ significantly between groups.

Oocyte and embryo parameters

Oocyte and embryo characteristics are summarized in Table 4. No statistically significant differences were observed between BMI groups for total retrieved oocytes, MII oocytes, maturation rate, fertilization rate, embryo grades, morula formation, blastocyst development, or number of transferred embryos ($p>0.05$).

Numerically, normal BMI women showed slightly higher retrieved and MII oocyte counts. Conversely, overweight/obese women demonstrated higher counts of fertilized oocytes, total embryos, grade I embryos, and blastocysts; however, these differences represented descriptive trends rather than statistically significant findings.

Table 4. Oocyte and embryo characteristics of infertile PCOS women according to BMI[a]

Characteristics	Normal BMI PCOS (Mean±SD)	Overweight/obese PCOS (Mean±SD)	p*
Count of retrieved oocytes	20.7±11.4	19.9±9.8	0.739
MI oocyte count	2.8±1.4	2.7±1.7	0.849
MII oocyte count	14.3±8.3	14.3±8.0	0.989
Germinal vesicle	4.4±2.7	4.9±3.7	0.655
Abnormal oocytes	4.6±4.7	3.1±1.9	0.281
Maturation rate	71.3±21.2	70.3±22.0	0.839
Fertilized oocyte 2PN	10.6 ±6.3	10.8 ±6.7	0.926
Fertilization rate	77.5±19.2	72.7±26.4	0.407
Total embryos	10.0±5.9	11.1±6.3	0.495
Day 3 grade I embryos	5.8±3.7	6.5±3.6	0.578
Day 3 grade II embryos	2.0±1.0	3.1±1.7	0.131
Day 3 grade III embryos	0.7±0.6	2.0±0.1	0.912
Day 4 morula stage embryos	5.1±5.1	4.4±3.4	0.713
Blastocyst stage embryos	1.7±1.0	3.9±3.3	0.121
Arrested embryos	5.0±3.7	4.5±3.8	0.643
Transferred embryos	2.3±0.7	2.6±0.5	0.111

[a] * – independent T test was used, MI – metaphase I, MII – metaphase II

Serum and follicular fluid PGRN levels

Serum and follicular fluid PGRN levels measured on OPU day are presented in Table 5. No statistically significant differences were detected between BMI groups for either serum or follicular fluid PGRN concentrations.

The relationship between PGRN levels and BMI is illustrated in Figures 1 and 2. Scatterplot and boxplot analyses demonstrate no clear linear association between BMI and either serum or follicular fluid PGRN levels across study groups.

Table 5. Serum PGRN and follicular fluid PGRN of infertile PCOS on oocyte pick up day according to BMI[a]

Characteristic	Normal BMI PCOS (Mean±SD)	Overweight/obese PCOS (Mean±SD)	p*
Serum PGRN (pg/mL)	6.1±1.9	5.8±1.8	0.566
Follicular fluid PGRN (pg/mL)	6.2±2.0	6.1±1.9	0.907

[a] * – independent T test was used

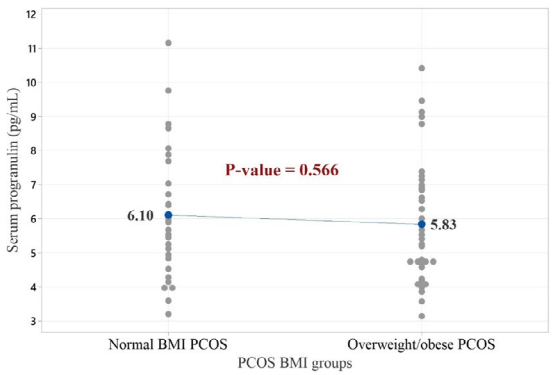

Fig. 1. Scatterplot of correlation between serum PGRN and BMI in PCOS study groups

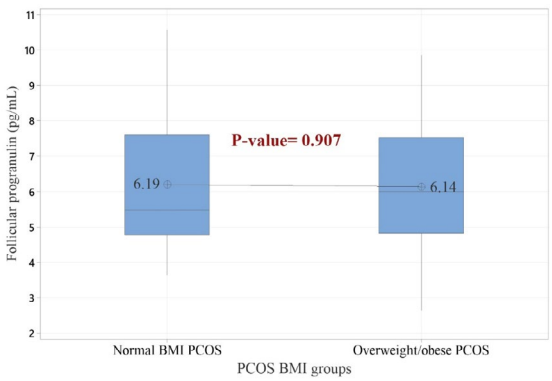

Fig. 2. Boxplot of correlation between follicular fluid PGRN and BMI in PCOS study groups

Correlation analysis with ICSI outcomes

Correlation analyses between PGRN levels and ICSI parameters are shown in Table 6. A statistically significant moderate positive correlation was observed between follicular fluid PGRN and total oocyte count. No significant correlations were identified between serum PGRN and oocyte maturity, fertilization rate, embryo grading, or number of transferred embryos. Other associations represented weak, non-significant trends.

Table 6. Correlation between serum and follicular fluid PGRN with ICSI outcomes according to BMI (r – Pearson's correlation coefficient was used)

Parameters		PCOS groups	
		Serum PGRN	Follicular fluid PGRN
Total oocyte count	r	0.063	0.312
	p	0.675	0.011
Metaphase Ioocytes	r	-0.116	0.172
	p	0.620	0.410
Metaphasell oocytes	r	0.016	0.239
	p	0.899	0.057
GV	r	0.216	0.275
	p	0.299	0.100
Maturationrate	r	-0.102	-0.030
	p	0.419	0.813
Fertilizationrate	r	-0.001	-0.161
	p	0.991	0.199
Day 3 grade 1 embryos	r	0.071	0.233
	p	0.672	0.159
Day 3 grade 2 embryos	r	-0.304	0.351
	p	0.192	0.129
Day 3 grade III embryos	r	0.306	-0.337
	p	0.694	0.663
Number of transferred embryos	r	-0.097	-0.155
	p	0.563	0.352

Pregnancy outcomes

Biochemical pregnancy outcomes are summarized in Table 7. Although the overweight/obese group showed a numerically higher biochemical pregnancy rate compared with the normal BMI group, the difference was not statistically significant.

Table 7. Biochemical pregnancy outcome in infertile PCOS women[a]

Pregnancy outcome	Normal BMI PCOS		Overweight/obese PCOS		p*
	n	%	n	%	
Positive	9	30.0	15	40.5	0.457
Negative	21	70.0	22	59.5	

[a] * – Chi -square test was used

Embryo transfer characteristics

The type of embryo transfer (fresh versus frozen) and semen source are presented in Table 8. Frozen embryo transfer cycles were more common in both groups. The distribution of embryo transfer type and semen source did not differ significantly between BMI groups.

Dynamic changes in serum PGRN

Changes between basal (cycle days 2–3) and OPU-day serum PGRN levels are shown in Table 9. Both BMI groups demonstrated a statistically significant increase in serum PGRN following ovarian stimulation. The relative increase appeared more pronounced in the normal BMI group compared with the overweight/obese group.

Table 8. Embryo transfer type and seminal fluid source used in ICSI[a]

Characteristic	Normal BMI PCOS		Overweight/obese PCOS		p*
	n	%	n	%	
Embryo transfer type					
Fresh	11	36.7	11	29.7	
Frozen	17	56.7	23	62.2	
No embryo transfer nonoembryotransfer	2	6.6	3	8.1	0.830
Seminal fluid type					
Fresh	19	63.3	28	75.7	0.724
Frozen	11	36.7	9	24.3	

[a] * – Chi -square test was used

Table 9. Comparison between basal (CD2-3) and oocyte pickup day serum PGRN levels in infertile PCOS women[a]

	Basal serum PGRN (CD2-3) (Mean ±SD) Mean±SD	OPU day serum PGRN (Mean ±SD)	Changing rate%*	p**
Normal BMI	3.7±0.3	6.4±1.6	72.9%	0.008
Overweight/obese	4.0±0.4	5.0±1.3	25.0%	0.005

[a] * – % changing rate=[OPU day – basal level/basal level]×100, ** – paired samples t-test was used to compare basal and OPU day serum PGRN levels within each group, CD – cycle day, OPU – oocyte pick-up

Discussion

This study identifies the predominant clinical phenotypes of PCOS as those with a normal BMI and those with an overweight/obese BMI.[35] The debate over the influence of hormonal abnormalities associated with PCOS on the reproductive ability of infertile women persists.[36] IR is often cited as a primary contributor to obesity, exacerbating clinical symptom severity in women with PCOS; nevertheless, it is not incorporated into the diagnostic criteria for reproductive and metabolic dysfunction.[37,38] This study divided 67 infertile women with PCOS into two groups according to their BMI status.

As reported in Table 1, the youngest group being PCOS with normal BMI (group 1: 28.9±6.0 years, p=0.484) and a longer infertility duration is reported in group 2 (7.9±4.7) with a significant difference (0.001); this may be attributed to both obesity and PCOS, corroborating the findings of the Marinelli et al. study.[39] Age is a significant determinant that affects embryo implantation.[40] A woman's fertility peaks in her late teens and early twenties, starts to decline at age thirty, and thereafter decreases more rapidly after age thirty-five. Post-forty-five, fertility diminishes markedly, making conception uncommon for women.[41] There were significant differences (p=0.001) in BMI, with normal BMI (group 1) averaging approximately 24.2±1.4 kg/m², whereas overweight/obese PCOS (group 2) presented the highest BMI at 32.4±3.8 kg/m². In group 1, primary infertility predominated over secondary infertility with combined female and male causes, showing non-significant variation (p=0.212).

Primary infertility was prevalent in the normal BMI group 1 attributed to a combination of male and female factors (PCOS).[42,43] Conversely, secondary infertility was more common in the overweight/obese PCOS group 2 [32] and this contradicts Abebe et al.[44] which reported an equal incidence of primary and secondary infertility. The female component was prevalent in group 2 due to the synergistic effects of obesity and PCOS.

Studies on the impact of obesity on oocyte quality, embryo development, mature oocyte quantity, implantation, and pregnancy rates yield inconclusive results. Genetic, environmental, and ethnic variations may account for the observed discrepancies among study participants.[45,46] Gene expression analyses performed during the window of implantation indicate that obese women with PCOS exhibit a suboptimal endometrial genetic profile and insufficient decidualisation.[47]

Table 2 demonstrates elevated AMH and LH levels, as expected in PCOS, with non-significant differences in all basal hormonal parameters (p>0.05).

Groups 1 and 2 had elevated AMH levels, consistent with findings in multiple research[48,49] which showed no significant difference. However, the present finding contrasts with findings in another study, where the causes remain unclear; still, increased BMI correlates with a reduction in AMH production from individual antral follicles due to altered granulosa cell metabolism.[50] Systemic insulin resistance is generally linked to obesity, resulting in compensatory hyperinsulinemia that modifies the responsiveness of granulosa cells and changes AMH synthesis.[51] While AMH is a dependable indicator of ovarian reserve and response to ovarian stimulation, its ability to reliably forecast live birth or pregnancy success, especially considering mother's age, remains uncertain.[52] The FSH and TSH levels on CD2-3 exhibited no significant variation between PCOS groups 1 and 2, contradicting the results of Laven 2019[53] and aligning with the findings of Saadia, 2020.[54] The serum level of LH is elevated in group 1, as corroborated by Shi et al.[55] due to the influence of obesity, which is characterized by elevated aromatase levels in adipose tissue that facilitate the conversion of androgens to estrogens. This process results in diminished pituitary gland responsiveness to GnRH and subsequent inhibition of LH, contradicting findings from multiple studies.[56] Other researchers found no significant association between BMI and elevated LH levels, noting higher LH values in lean patients and increased FSH levels in those with obesity.[57]

Basal prolactin (PRL) levels were observed to be elevated in individuals with normal BMI PCOS compared to those with overweight/obese PCOS, despite the absence of statistical significance and remaining within normal ranges (as per exclusion criteria). This finding aligns with several studies which indicate that PCOS

can present a wide spectrum of PRL levels, including higher, lower or normal levels compared to individuals without PCOS.[58-60] Clinical data suggests that prolactin (PRL) has a role in metabolic homeostasis, contingent upon its circulatory levels, since it regulates body weight activities inside adipose tissue and the pancreas. A particular PRL range value enhances metabolism.[61-63] The basal levels of E_2, TSH and PRL must be normal before the ovarian stimulation protocol commences.

The triggering levels of E_2 were elevated in group 2, with no statistically significant difference (p=0.465). Group 2 received increased doses of FSH and total gonadotrophins, demonstrating a significant difference (p=0.001, 0.001, respectively), whereas the LH dose was numerically higher, albeit with no significant variation (p=0.551). The OSI was significantly elevated in group 1 (p=0.042), as illustrated in Table 3.

Concerning E_2, levels were elevated in group 2, followed by those of group 1 PCOS, contrary to the findings of Zhou et al.[64] Estradiol is synthesized by follicular granulosa cells.[65] The serum E_2 indirectly shows the E_2 concentration in follicular fluid, which positively correlates with oocyte maturity. A higher antral follicle count and an increased number of recovered oocytes correlate with elevated E_2 levels. Xu et al.[66] determined that elevated E_2 levels did not affect pregnancy rates or live birth rates[66]; however, another trial by Li et al.[57] indicated enhanced live birth rates with E_2 levels below 5000 pg/mL and established that the E_2/oocyte ratio correlated with suboptimal reproductive implantation results due to high E_2 levels, which adversely affected endometrial receptivity.[67]

The gonadotropin requirements were elevated in overweight/obese PCOS, including both FSH dose and total gonadotropin dosages, demonstrating significant variability. The total OSI was maximal in group 1, demonstrating a considerable variance due to diminished total gonadotrophin doses requirements and an elevated count of recovered oocytes, computed as OSI=total retrieved oocytes/total gonadotrophin doses. The duration of stimulation and the number of antagonist (cetrotide) injections given were comparable in both groups. The cumulative gonadotrophin dosage needed is higher in the overweight/obese group indicating that obesity may reduce effective gonadotrophin levels, while excess adipose tissue increases leptin release, leading to relative gonadotrophin resistance.[64] Changes in pharmacodynamics, such as the absorption, bioavailability, and elimination of gonadotrophins, have been documented in obese individuals.[39]

All the parameters listed in Table 4 showed non-significant variability ($p > 0.05$); however, group 2 had a numerically larger number of fertilized oocytes, as well as total and high-quality grade 1 embryos, blastocyst embryos, and transferred embryos compared to group 1.

The quantity of retrieved oocytes was greater in PCOS group 1, while not statistically significant, suggesting a more robust ovarian response. This aligns with prior work indicating that a greater quantity of oocytes was extracted in individuals with normal BMI PCOS compared to those who are overweight/obese with PCOS,[64,68] and contrasts with other research.[7]

The mature MII oocytes showed no significant variation, although the PCOS group 1 displayed a greater quantity, in contrast to Rahman et al.[59,60] Moreover, MI oocytes revealed no significant intergroup differences.

Germinal vesicle counts were more frequent in the PCOS group 2, despite no significant difference, attributed to oocyte spindle abnormalities and disarray associated with PCOS and obesity,[54] indicating both heightened follicular activity and a potential compromise in oocyte uniformity, although abnormal oocytes were predominant in group 1.

In group 2, the quantities of fertilised oocytes and total embryos exhibited a similar trend, being more prevalent than in group 2; however, no statistical variability was observed. Nonetheless, maturation and fertilization rates remained statistically comparable between both groups, suggesting that the increased yield did not influence per-oocyte competence, which contradicts the assertion made by Zhou et al.[64] who indicated that an increase in BMI correlates with a reduction in the number of transferable embryos.

Group 2 produced a higher number of grade I embryos, contradicting the findings of many studies.[67-69] In addition, grade II and III embryos were more prevalent in the PCOS group 2, although no significant differences were seen. This phenomenon may be attributed to alterations in follicular fluid composition and metabolic dysfunction associated with obesity.[70,71] Although the morula, blastocyst, and arrested embryos exhibited no statistical differences, the quantities of morula embryos were greater in group 1, but blastocysts were more prevalent in group 2. Arrested embryos were comparable in both PCOS groups, suggesting that the increased embryo quantity may be counterbalanced by developmental attrition. The quantity of transferred embryos was higher in overweight/obese PCOS; however, no significant changes were observed to substantiate the general trend of increased embryo availability in this demographic, which should inform personalized embryo transfer techniques. The maturation and fertilization rates showed no significant difference, indicating that the higher yield did not impact per-oocyte competence.

The mean serum PGRN levels were not significantly elevated in PCOS group 1,[16,62] compared to group 2, contradicting the findings of Gorkem et al.,[72] which reported elevated serum PGRN levels associated with increased BMI, consistent with previous research in both humans and animals. Miehle et al.[19] demonstrated ele-

vated serum PGRN levels in individuals with lipodystrophy and established that this increase may arise from visceral adipose tissue and muscle.[19] PGRN is posited to facilitate development and angiogenesis following the expansion of adipose tissue in obesity.[73]

Likewise, follicular fluid PGRN levels demonstrated a similar trend, peaking in group 1 with no statistically significant difference when compared to group 2 PCOS women. In normal BMI PCOS individuals, adipose tissue secretes PGRN irrespective of BMI.[16]

The persistent absence of statistical significance, despite the observable numerical trend in group 1, indicates that BMI and PCOS status likely do not affect PGRN levels in serum or follicular microenvironments, either separately or together. These findings suggest that PGRN, although biologically significant, is unlikely to function as an independent diagnostic or stratification biomarker in relation to obesity or PCOS-associated infertility. Zhou et al.[73] noted that the levels of PGRN and PGRN mRNA are elevated in the granulosa cells of ovaries impacted by PCOS,[13] and that follicular fluid PGRN concentrations in PCOS inversely correlate with the number of retrieved oocytes, suggesting inflammatory disruptions and a possible role in forecasting ICSI outcomes.

A significant difference was found only between the total oocyte count and the follicular fluid PGRN level, which showed a moderate positive correlation ($p=0.011$, $r=0.312$). In contrast, there was a non-significant variation with negative correlations observed for the maturation rate, the fertilization rate, and the number of transferred embryos, as shown in Table 6.

In Table 7, a higher pregnancy rate was reported in group 2 with a non-significant difference, suggesting that a combination of endocrine and metabolic factors influenced these rates, with 15 out of 37 women (40.5%) attaining a positive biochemical pregnancy,[68] while group 1 exhibited a pregnancy rate of 30.0% (9/30), contrasting with Al-Yasiry et al.[47] and indicating a notable inconsistency despite an expected beneficial metabolic profile in normal-weight PCOS. These findings challenge the conventional notion that normal weight is inherently associated with optimal fertility outcomes and instead highlight the potentially advantageous reproductive responsiveness in PCOS patients, particularly those with increased BMI.

Table 8 reveals that patients with PCOS constituted the majority undergoing frozen embryo transfers, suggesting that clinicians may have opted to postpone the transfer in these high-responder patients, particularly those with PCOS, due to potential complications such as ovarian hyperstimulation syndrome (OHSS) or suboptimal endometrial receptivity conditions assessed via Doppler evaluation of subendometrial vascularity.[74-76]

The lowest proportion of cycles without embryo transfer in both PCOS groups suggested enhanced oocytes production and embryo availability, and the results indicated that a freeze-all strategy for PCOS patients enhanced the live birth rate, diminished the incidence of OHSS, and lowered the rate of miscarriages.[77,78] The elevated concentrations of steroid hormones during stimulated cycles may have modified endometrial receptivity, elucidating why frozen embryo transfers are expected to produce better outcomes than fresh transfers.[79] Freeze-all cycles are effective for high responders but not for intermediate or low responders or women of advanced maternal age.[80]

Most of the ICSI cycles used fresh sperm preparation especially group 2 with no statistical significance ($p> 0.05$), as reported in Table 8.

Table 9 indicates that there is significant variation between basal and OPU day fasting serum PGRN level ($p<0.05$) which may indicate a possible metabolic and inflammatory response to gonadotrophin administration. It is worth noting that we preferred to use an antagonist protocol in this study due to its advantages in comparison to a long agonist protocol.

Study limitations

This study has several limitations that require attention. The absence of live birth data restricts the ability to thoroughly assess the ultimate clinical effects of the treatments. The restricted sample size and selection of certain factors may limit the generalizability of the findings. A notable limitation is the lack of essential clinical objectives, such as implantation rate, clinical pregnancy, and live birth outcomes.

This research primarily focused on hormonal profiles, ovarian response, embryo quality, and oocyte development; however, these additional endpoints are crucial for a comprehensive evaluation of the significance of BMI in relation to serum and follicular fluid PGRN in PCOS.

Conclusion

PGRN levels in the serum and follicular fluid microenvironments may remain unaffected by BMI in PCOS, either independently or collectively, as evidenced by the consistent absence of statistical significance despite observable numerical trends in normal BMI PCOS individuals. A larger cohort of patients within the designated age range is necessary to elucidate the relationship between PGRN, PCOS, and BMI. In the overweight/obese PCOS group, increased embryo maturity was noted, potentially supporting the hypothesis of a threshold-dependent effect of PGRN on ovarian function. In individuals with normal BMI PCOS, elevated PGRN levels in follicular fluid may exceed a medically acceptable threshold, thereby compromising oocyte quality and embryonic developmental potential. Conversely, obese/overweight PCOS

may remain below this threshold, resulting in relatively preserved follicular function and improved assisted reproductive outcomes. The variation in serum PGRN levels following ovarian stimulation represents a research gap warranting further investigation in larger patient cohorts.

Acknowledgements

The authors express gratitude to the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/AL-Nahrain University for the resources that facilitated the completion of the work.

Declarations

Funding

The authors receive no external financial support.

Author contributions

Conceptualization, I.K.S.A. and M.S.A.; Methodology, H.A.L.M.; Software, I.K.S.A.; Validation, M.S.A. and H.A.L.M.; I.K.S.A. and M.S.A.; Formal Analysis, I.K.S.A.; Investigation, I.K.S.A..; Resources, X.X.; Data Curation, I.K.S.A. and H.A.L.M.; Writing – Original Draft Preparation, I.K.S.A.; Writing – Review & Editing, M.S.A.; Visualization, M.S.A. and H.A.L.M.; Supervision, M.S.A. and H.A.L.M.; Project Administration, H.A.L.M.; Funding Acquisition, I.K.S.A.

Conflicts of interest

The authors stated that there are no conflicts of interest.

Data availability

The data underpinning the findings of this investigation can be obtained from the corresponding author upon request.

Ethics approval

This study adhered to the Helsinki Declaration, and the protocol received approval from the Ethics Committee of the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies at Al-Nahrain University, Baghdad, Iraq (Approval Code: 0701-DF-2024A43 on 9/9/2024).

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