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Research Article

Influence of Obesity and Insulin Resistance on the Reproductive Outcome of Iraqi Women Undergoing Intracytoplasmic Sperm Injection

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Abstract

Background: Insulin resistance (IR) is commonly associated with obesity, which plays a role in the pathogenesis of reproductive disorders. ***Objectives***: To evaluate the impact of insulin resistance and obesity on ICSI outcomes in Iraqi infertile females. ***Methods***: Ninety women who were unable to conceive received an intracytoplasmic sperm injection and have various infertility causes; Age range: 18–40 participated in this prospective clinical cross-sectional study. Three groups of patients were formed based on their body mass index (BMI) rankings. The ovarian hyperstimulation antagonist protocol was administered to all women. Serum glucose, insulin and HOMA-IR were measured for all participants on the ovum pickup day. In addition, the results of ICSI were determined. ***Results***: The insulin levels and HOMA-IR were significantly higher in obese females than in overweight and normal weight groups. There was significantly lower BMI, waist/hip ratio, and HOMA-IR in pregnant females when compared with non-pregnant ladies. There is a significant negative correlation between fasting insulin, HOMA-IR with metaphase II oocytes, maturation rate, grade 1 embryos and pregnancy outcome. The cutoff values of fasting serum insulin and HOMA-IR levels were ≤ 4.64 (ng/ml) and ≤ 1.1, respectively, as predictors of positive pregnancy in women undergoing ICSI. ***Conclusions***: Insulin resistance impairs the ICSI outcomes of infertile women. Furthermore, obesity may increase the risk of insulin resistance in infertile women; therefore, enhancing HOMA-IR and BMI will positively impact ICSI outcomes.

Keywords: HOMA-IR, Insulin resistance, ICSI, Obesity.

تأثير السمنة ومقاومة الأنسولين على النتائج التناسلية للنساء العراقيات اللواتي يخضعن لحقن الحيامن المجهري

الخلاصة

الخلفية: ترتبط مقاومة الأنسولين عادة بالسمنة، والتي تلعب دورا في التسبب في الاضطرابات التناسلية. **الأهداف**: تقييم تأثير مقاومة الأنسولين والسمنة على نتائج حقن الحيامن المجهري لدى الإناث العراقيات المصابات بالعقم. **الطريقة**: تلقت تسعون امرأة غير قادرات على الحمل حقنة الحيامن المجهرية ولديهن أسباب مختلفة للعقم. الفئة العمرية: 18-40 شارك في هذه الدراسة السريرية المقطعية المحتملة. تم تشكيل ثلاث مجموعات من المرضى بناء على تصنيفات مؤشر كتلة الجسم. تم إعطاء بروتوكول مضاد فرط تحفيز المبيض لجميع النساء. تم قياس الجلوكوز في الدم والأنسولين و HOMA-IR لجميع المشاركين في يوم التقاط البويضة. بالإضافة إلى ذلك، تم تحديد نتائج الحقن المجهري. **النتائج**: كانت مستويات الأنسولين و HOMA-IR أعلى بشكل ملحوظ في الإناث البدينات مقارنة بمجموعات الوزن الزائد والوزن الطبيعي. كان هناك انخفاض ملحوظ في مؤشر كتلة الجسم، ونسبة الخصر/الورك، و HOMA-IR في الإناث الحوامل مقارنة بالسيدات غير الحوامل. هناك علاقة سلبية كبيرة بين الأنسولين الصائم، HOMA-IR مع بويضات الطور الثاني، معدل النضج، أجنة الدرجة 1 ونتائج الحمل. كانت القيم الفاصلة لمستويات الأنسولين في المصل الصيام HOMA-IR 4.64 ≤نانوغرام/مل و ≥ 1.1، على التوالي، كتنبؤات للحمل الإيجابي لدى النساء اللائي يخضعن للحقن المجهري. **الاستنتاجات**: مقاومة الأنسولين تضعف نتائج الحقن المجهري للنساء المصابات بالعقم. علاوة على ذلك، قد تزيد السمنة من خطر مقاومة الأنسولين لدى النساء المصابات بالعقم. لذلك ، فإن تعزيز HOMA-IR ومؤشر كتلة الجسم سيؤثر بشكل إيجابي على نتائج الحقن المجهري.

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INTRODUCTION

Insulin, a hormone consisting of 51 amino acids, plays a crucial role in glucose homeostasis, fat production, cell growth and metabolism. Insulin regulates sex hormone metabolism by increasing androgen synthesis, accumulating a large number of immature follicles, and inhibiting the formation of dominant follicles [1]. Insulin resistance (IR) is defined as the relative insensitivity or diminished reactivity of peripheral tissues to the hormone's biological regulatory effects, as well as increased insulin production to maintain blood sugar stability [2]. Insulin resistance may inhibit the use of glucose by muscles, release free fatty acids, and activate the inflammatory system. as well as being linked with oxidative stress, obesity, and metabolic syndrome (i.e., impaired glucose tolerance, dyslipidemia, and type 2 diabetes) [3]. The homeostasis model assessment of insulin resistance (HOMA-IR) is a simplified technique that may be utilized for clinical reasons and has been verified. It was first described under the name HOMA by Matthews et al. in 1985 as a model of the relationship between insulin and glucose dynamics under fasting conditions to predict insulin resistance [4]. Obesity and malnutrition are both associated with reproductive disorders due to a significant correlation between reproductive capability and adipose tissue metabolism [5]. Obesity, particularly central obesity, can result in a lipid metabolism issue, cause and raise the severity of insulin resistance, create a high amount of free fatty acids, and initiate a vicious loop involving these variables [6]. A body mass index (BMI) of 30 kg/m^2 is considered obesity based on the WHO classification [7]. Obesity, a common metabolic condition, has been characterized as an excessive or abnormal fat buildup in the body. It has become a global issue that is commonly related to metabolic and endocrine diseases like type 2 diabetes, cardiovascular disease and reproductive abnormalities [8] and has a deleterious impact on fertility, pregnancy, and future generations' health [4,8]. Obesity reduces fertility; females with a body mass index (BMI) ≥ 30 kg/m2 had a 2.7-fold higher risk of infertility [9]. Furthermore, obesity has been shown to impede adipose tissue storage capacity due to restricted expansion. As a result, ectopic lipid accumulation in the skeletal muscle and liver develops, which is critical for establishing insulin resistance. [2]. It has also been linked to oxidative stress, which may raise the production of reactive oxygen species (ROS) by raising the activity of nicotinamide adenine dinucleotide phosphate oxidase and lowering the bioavailability of nitric oxide [10–12]. This suggests that obesity may enhance endoplasmic reticulum stress and, as a result, IR. It's commonly recognized that losing weight and exercising decrease insulin resistance and prevent obesity and the consequent metabolic syndrome [13]. We propose that HOMA-IR is a crucial and revolutionary marker and target in metabolic disorders that has the potential to impact reproductive capacity based on the data currently available [3,14,15]. This study aims to explore the effects of obesity and insulin resistance on ICSI outcomes.

METHODS

Study design and setting

This prospective comparative study was done on 90 infertile females who were undergoing ICSI at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Baghdad, Iraq, during the period from September 2021 until May 2023.

Inclusion criteria

Women ranging in age from 18 to 40 years with primary or secondary infertility and various causes of infertility (tubal blockage, unexplained infertility, and mild cases of male factor), a GnRH antagonist was used for pituitary down regulation, and women who accepted to participate in the study with different causes of infertility were included.

Exclusion criteria

Patients with hyperprolactinemia, poor reserve, PCOS, pelvic inflammatory disease, hypertension, diabetes, chronic disease, azoospermia male partner, and patients rejected to participate were excluded from the research.

Evaluation and outcome measurements

Complete obstetrical, gynecological, surgical, and medical histories of infertile couples were obtained. A comprehensive physical examination of the infertile ladies was performed, including a gynecological and general checkup. BMI is calculated by measuring the female's height and weight (BMI = weight (kg) / [height (m)]^2) [7]. This equation was used to calculate the sample size (N = p (1-p) z^2/me^2), where P is the prevalence rate of the infertile female (12%) according to a preceding study [16]. Z = 1.96, Me = 0.05. The sample size was 163. Seventy-three of the 163 infertile patients who were not qualified for the study were excluded (six empty follicles, twenty frozen embryos, six poor responses, three abnormal embryos, and three atretic embryos) and 35 were excluded. The remaining 90 infertile patients were categorized according to body mass index (BMI) classification into three groups based on the National Institute of Health (NIH) and the World Health Organization (WHO) [17]. On day two of the spontaneous menstrual cycle, the baseline hormonal analysis and basal transvaginal ultrasound were done. A flexible gonadotropin-releasing hormone (GnRH) antagonist regimen for controlled ovarian hyperstimulation was used for all participants. The program included subcutaneous recombinant follicular stimulating hormone (r-FSH) (Gonal-F®, Merk-Serono, Switzerland), initiated on the 2nd day of the menstrual cycle. The gonadotropin starting dosage was

determined according to the woman's age, BMI, ovarian reserve marker (antral follicular count, anti-mullerian hormone), and previous response to ovarian stimulation in the IVF cycle. A transvaginal ultrasound was conducted on day 5 of stimulation, and further ultrasound examinations were performed as suggested every two to three days. A daily subcutaneous injection of 0.25 mg of cetrorelix acetate (Cetrotide®, Merck Serono, Geneva, Switzerland) was administered as soon as the leading follicles achieved a diameter of 13–14 mm. until the trigger day. Follicular growth was monitored by trans-vaginal ultrasonography and E2 levels until the trigger day. When 2-3 leading follicles reach an average diameter of 17–18 mm, final oocyte maturation is accomplished by giving subcutaneous recombinant human chorionic gonadotropin. (r-hCG) 500 µg (Ovitrelle® Merk-Serono, Switzerland). The same embryologist evaluated the embryo morphology, and the grading system followed the Istanbul consensus workshop on embryo assessment. The grading system was done based on the number of blastomeres, blastomere symmetry (equal = score 1, different = 2), and the percentage of fragmentation (≤10% = score 0; 11–20% = score 1; 21 30% = score 2; >30% = score 3). Under ultrasound guidance with a soft catheter, the cleavage stage (day 3) of fresh embryo transfer was done [18]. Luteal support was initiated on the oocyte pickup day with vaginal progesterone every day (Cyclogest®400mg; Actavis, UK) and 250mg progesterone injection depot twice a week. Serum B-hCG levels were measured 14 days after embryo transfer [19].

Sample collection and biochemical analysis

On the day of oocyte pickup, venous blood samples were drawn from the antecubital veins of all females precipitated in the study for the analysis of fasting glucose and fasting insulin levels. These 3.0 ml of blood samples were put into a serum-separating tube (gel and clot activator) with a disposable syringe. They were left to clot for 10 to 15 minutes at room temperature, and then they were centrifuged at 3000 rpm for 20 minutes. The serum was extracted and kept at -20°C in an Eppendorf tube. The enzyme-linked immune assay (ELISA) technique used in the current study for the measurement of insulin levels using a detection kit (YL Biotech Co., Ltd., Shanghai, China) and a microplate reader capable of calculating absorbance at 450 nm (Huma reader HS, Human, USA) was utilized in this research. The GOD-PAP enzymatic colorimetric test technique with the glucose liquicolor kit was used to measure fasting glucose levels. Fasting glucose levels were measured using a semi-automatic microprocessor-controlled photometer (Humalyzer Primus, Human, USA). Insulin resistance was estimated by using the homeostatic model assessment of IR (HOMA-IR) = [fasting glucose (mg/dl) × Fasting insulin (mIU/L)] /405. The normal value in adults was < 2.

Ethical consideration

Ethical approval The study was carried out in conformity with the moral standards set forth in the Declaration of Helsinki. Before a sample was taken, it was done with the patient's informed consent. A local Ethics Committee on Human Research from the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, approved the research protocol (code 0701 PF-2021S5).

Statistical Analysis

The gathered information was coded, compiled, and statistically examined by Statistical Package for Social Sciences (SPSS) version 28.0 and Microsoft Excel 2019. Number and percentage were used to express categorical variables, while quantitative variables that are normally distributed were expressed as mean and standard deviation. Analysis of variance ANOVA (comparison of more than two groups), independent sample *t*-test (comparison of two groups), and Chi-square (comparison of percentages and non-continuous variables) were used to compare the groups, and Pearson's correlation coefficient (*r*) was used as an indicator of the degree of relationship between variables. The receiver operating characteristic (ROC) curve was used to determine the cut-off value, sensitivity, and specificity. and the results were considered statistically significant when the *p*-value was less than 0.05.

RESULTS

Ninety infertile females who enrolled in this study were divided into three groups according to their body mass index ranking: Group 1: Twenty-seven normal-weighted females. Group 2: thirty-five over weighted females. Group 3: Twenty-eight obese females.

Table 1: Demographic characteristics of infertile women according to Body Mass Index

Characteristic	BMI (19.9-24.9) Normal (*n* = 27)	BMI (25-29.9) Over weight (*n* = 35)	BMI (≥ 30) Obese (*n* = 28)	*p*-value
Age (years)	29.96±530	32.34±4.96	31.50±6.33	0.24
BMI (kg/m^2)	23.02±0.89	26.97±1.29	32.05±1.46	< 0.001
Waist/Hip ratio	0.78±0.04	0.83±0.04	0.88±0.04	<0.001
Causes of infertility				
Male *n*(%)	10(11.11)	14(15.56)	10(11.11)	0.85
Unexplained *n*(%)	13(14.44)	18(20)	15 (16.67%)	
Female (Tubal) *n*(%)	4(4.44)	3(3.33)	3 (3.33 %)	

Values are expressed as mean±SD, frequency and percentage. *n*: number of cases.

Table 1 shows the main demographic information of the studied patients. The statistical study revealed no substantial differences (p>0.05) among the groups. Table 2 illustrates no significant differences between the groups regarding basal AMH, FSH, LH, E2 and E_2 levels on the day of rhCG with p>0.05. However, there was a significant difference (p=0.01) regarding the dose of gonadotrophins. The highest doses of gonadotrophins received were found in obese females.

Table 2: Serum hormonal levels of infertile women according to BMI

Hormone	BMI (19.9-24.9) Normal (n = 27)	BMI (25-29.9) Over weight (n = 35)	BMI (≥ 30) Obese (n = 28)	p-value
Basal AMH (pg/ml)	2.96±1.59	3.03±1.82	3.23±1.68	0.83
Basal FSH (mIU/ml)	5.18±1.85	5.22±2.26	4.93±2.05	0.85
Basal LH (mIU/ml)	5.60±1.29	5.34±1.46	5.34±2.16	0.79
Basal E_2 (pg/ml)	35.78±8.86	37.16±7.69	35.51±8.23	0.69
E_2 level of hCG (pg/ml)	1317.0 ±468.07	1426.36±533.94	1248.70±417.40	0.34
Total gonadotropin dose (IU)	1416.67±170.69	1510.71±296.75	1684.82±423.03	0.01

Values are expressed as mean±SD. *n*: number of cases.

In Table 3, there are big differences between the three groups of patients regarding the number of oocytes, MII oocytes, oocyte maturation rate, and grade I embryos. There is more grade I embryos in the normal weight group. However, there were no significant differences regarding fertilized oocytes, MI oocytes, germinal vesicles, grade II or grade III embryos (p>0.05).

Table 3: Oocyte and embryo characteristics of infertile women according to BMI

Characteristic	Total (n =90)	BMI (19.9-24.9) Normal (n =27)	BMI (25--29.9) Over weight (n =35)	BMI (≥ 30) Obese (n =28)	p-value
Number of oocyte	12.39±3.35	14.37±4.26	11.94±2.80	11.04±1.88	<0.001
MII	7.02±2.23	8.81±2.43	8.81±2.43	5.61±1.17	0.002
MI	2.59±1.75	2.63±2.04	2.63±1.78	2.50±1.45	0.95
Germinal vesicle	1.11±0.69	0.96±0.58	1.09±0.81	1.29±0.60	0.22
Maturity index	58.11±14.68	65.34±15.89	57.27±11.85	52.18±14.17	0.003
Grade I	2.49±1.41	3.04 ±1.56	2.51±1.17	1.93±1.36	0.01
Grade II	1.39±0.92	1.15±0.90	1.31±0.86	1.71±0.93	0.6
Grade III	0.77±0.60	0.63±0.49	0.77±0.64	0.89±0.62	0.26

Values are expressed as mean±SD. *n*: number of cases; MI: metaphase I (immature) oocytes; MII: metaphase II (mature) oocytes; PN: pro-nuclei.

Table 4 showed that obese females had higher fasting glucose, fasting insulin, and HOMA-IR than normal and overweight females, with significant differences (p=0.006, p=0.001, and p<0.001, respectively).

Table 4: Fasting sugar, fasting insulin and HOMA-IR of infertile women according to Body Mass Index

Characteristic	BMI (19.9-24.9) Normal (n = 27)	BMI (25-29.9) Over weight (n = 35)	BMI (≥ 30) Obese (n = 28)	p-value
Fasting glucose (mg/dl)	95.3±9.73	97.6±11.29	103.9 ±9.14	0.006
Fasting insulin (mIU/L.)	4.28±1.20	5.33±1.45	6.48 ± 1.77	0.001
HOMA-IR	1.02±0.34	1.30±0.43	1.68 ± 0.55	<0.001

Data were expressed as mean±SD; n: number of cases.

Table 5 demonstrated significant differences between groups regarding pregnancy rate (p=0.02). with the lowest pregnancy rate among obese females.

Table 5: Biochemical pregnancy outcome in infertile women enrolled in this study

Pregnancy outcome	Total n = 90	BMI (19.9-24.9) Normal (n = 27)	BMI 25--29.9 Over weight n = 35	BMI ≥ 30 Obese n = 28	p-value
Positive	26(28.88)	12(13.33)	11(12.22)	3(3.33)	0.02
Negative	46(71(12)	15(16.67)	24(26.67)	25(25.78)	

Values are expressed as frequency and percentage.

Table 6 illustrates significantly lower BMI, waist/hip ratio, and HOMA-IR in pregnant females when compared with non-pregnant lades (p=0.002, p=0.027, and p=0.001, respectively). Table 7 demonstrated a significant negative correlation between metaphase II oocytes, maturation rate, grade 1 embryos and pregnancy outcome with fasting insulin, HOMA-IR (p<0.05).

Table 6: Comparison of BMI, and HOMA-IR levels between pregnant and-non pregnant females

Parameter	Non-Pregnant (n = 64)	Pregnant (n = 26)	p-value
BMI (kg/m^2)	28.14±3.76	25.45±3.08	0.002
Waist/Hip ratio	86.04±7.31	91.55±9.69	0.027
HOMA-IR	1.46 ± 0.54	1.02±0.24	< 0.001

Values are presented as mean±SD.

Table 7: Correlations between fasting insulin, HOMA-IR with ICSI outcome

Parameters		Fasting insulin	HOMA-IR
Metaphase II oocytes	*r*	-0.330	-0.316
	p	0.002	0.002
Metaphase I oocytes	*r*	0.246	0.276
	p	0.091	0.08
Maturation rate	*r*	-0.478	-0.543
	p	<0.001	<0.001
Fertilization Rate	*r*	-0.157	-0.172
	p	0.141	0.106
Grade 1 embryos	*r*	-0.418	-0.402
	p	<0.001	<0.001
Grade 2 embryos	*r*	0.145	0.165
	p	0.172	0.121
pregnancy	*r*	-0.317	-0.351
	p	0.002	<0.001

r: Pearson's correlation coefficient.

The receiver-operative characteristic (ROC) curve has been used to calculate insulin and HOMA-IR cut-off values to predict a positive pregnancy with acceptable sensitivity, specificity and accuracy. The result is demonstrated in Figures 1 and 2 and Table 8.

Table 8: Characteristics of ROC curve analysis

Characteristic	Serum insulin	HOMA-IR
Cut off value	≤ 4.64	≤ 1.1
AUC	0.70	0.71
95% CI	0.59-0.79	0.61-0.8
p-value	0.001	0.001
Sensitivity (%)	67	69
Specificity (%)	76	71
Accuracy (%)	70.0	71.8

AUC: area under the curve; CI: confidence interval.

Regarding serum insulin, the cutoff value was ≤ 4.64 and the area under curve (AUC) was more than 0.7, making it a good predictor of positive pregnancy success with an accuracy level of 70%, a sensitivity level of 67%, and a specificity level of 76%**.** Regarding HOMA-IR, the cutoff value was ≤ 1.1 and the area under curve (AUC) was more than 0.71, making it a good predictor of positive pregnancy success with an accuracy level of 71.8 %, a sensitivity level of 69%, and a specificity level of 71 %.

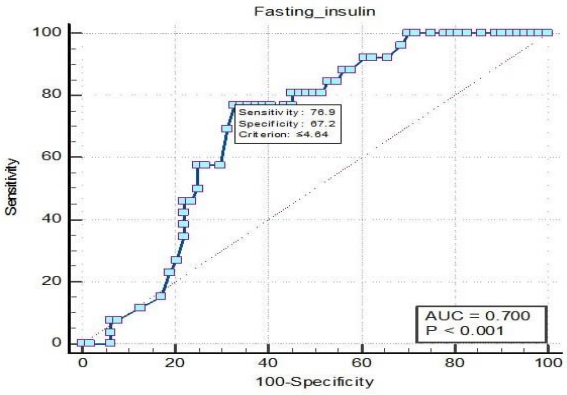

Figure 1: Receiver operator characteristic (ROC) curve analysis of serum insulin levels cutoff value that can predict positive pregnancy success.

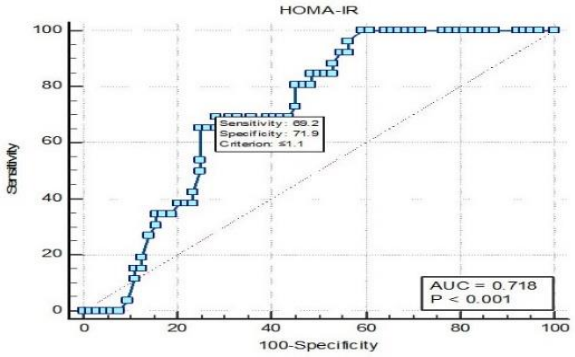

Figure 2: Receiver operator characteristic (ROC) curve analysis of HOMA-IR cutoff value that can predict positive pregnancy success.

DISCUSSION

As reproductive medicine continues to evolve with ongoing improvements in the success rates of assisted reproductive technologies [20], Several physiological queries, such as: Does BMI affect fertility and ICSI outcomes? With an increased body mass index (BMI), women are more likely to experience ovulatory disorders, irregular menstrual periods, and hypothalamic-pituitary-ovarian axis disturbance, all of which contribute to higher infertility rates [21]. In this study, there were 30% normal-weighted females (Group 1), 39% overweight females (Group 2), and 31% obese females (Group 3). Therefore, the study shows that 70 % of infertile women who participated were either overweight or obese. The two possible explanations for the finding are that being overweight or obese is common in our community, as shown by multiple Iraqi studies [4,22,23]. The second possibility is a link between high BMI (overweight and obesity) and female infertility [21,24]**.** Obese women may face fertility issues in assisted reproductive programs as their weight can affect the quality of oocytes, reduce the preimplantation rate, and impair the receptivity of the uterus [23]. The results showed no significant differences in demographic characteristics (age and cause of infertility) or serum hormonal levels among the three studied groups. The lack of significant differences in these parameters confirms the statistical matching among the groups. Any differences in ICSI results can be attributable to causes other than these parameters. The total gonadotropin dose was significantly different among groups. The need for higher doses of gonadotrophins in obese and overweight females can be attributed to a variety of factors. Firstly, it may be related to altered pharmacodynamic characteristics of drugs and a larger distribution volume in overweight and obese patients. Actually, changes in absorption, metabolism, bioavailability and clearance of gonadotrophins had been reported in these women [25]. The second factor is that obesity is linked to a relative gonadotrophin resistance that is unrelated to insulin resistance [26,27]. This finding agrees with a previous study, which

identified that obese women required a larger dose of gonadotropin for stimulation and had a lower probability of pregnancy after ICSI [28–31]. The current study discovered that women of normal weight had considerably greater mean total oocyte yield, mean metaphase II (MII) oocyte count, and maturity index than overweight and obese women. The drop in mean total oocyte production and mean MII oocytes is consistent with previous research [23,32]. The decrease in mean total oocyte count and mean mature oocytes may be related to oocyte injury mediated by effects of impaired maternal endocrinology systemic and metabolism, like elevations in insulin, glucose, or free fatty acids, as well as modifications in adipokines that result in a chronic low-grade inflammatory state and cellular damage [33]. According to a study conducted by Broughton and Moley (2017), obesity can lead to endoplasmic reticulum stress, abnormal meiotic spindle formation, and abnormal mitochondrial dynamics [5]. Oocyte growth requires bidirectional contact with surrounding cells, and several studies have been carried out to evaluate the impact of obesity on these ovarian cells. Increased lipid accumulation, endoplasmic reticulum stress, apoptosis, and mitochondrial dysfunction were seen in the granulosa and cumulus cells of rodents fed a high-fat diet. As a result, aberrant granulosa cell activity decreases the number of mature oocytes by compromising the oocyte's quality and developmental potential [33,34]. Obesity has been linked to oxidative stress, as previously stated, and directly increases reactive oxygen species (ROS) generation through increased NADPH oxidase activity and decreased nitric oxide bioavailability [15,33]. As a result, reactive oxygen species (ROS) may cause endoplasmic reticulum stress, apoptosis, and mitochondrial malfunction in granulosa and cumulus cells. As a result, the function of granulosa cells is disrupted, and oocyte quality decreases. There was a significant difference in the percentage of embryo grades I (GI), with a relatively higher percentage in the normal weight group. These findings support previous research showing that obese women are more likely to produce poor-quality embryos [23,26,29]. The observations can be interpreted as follows: Excess free fatty acids in obese or overweight females have a lipotoxic influence on the egg and its organelles, resulting in a detrimental effect on the future embryo [5]. According to many studies, obesity in women and animal models leads to aberrant mitochondrial distribution and elevated ROS levels in the oocyte. During oocyte and embryonic development, mitochondria, a primary source of energy in oocytes for various metabolic and cellular processes, are necessary for controlling cellular calcium homeostasis, apoptosis, and mitosis. Moreover, mitochondrial malfunction in obese women's oocytes is linked to a variety of meiotic errors, including increased spindle and chromosomal abnormalities, elevated ROS production, and finally impaired control of molecular and cellular processes [3,12]. All of these factors may have a deleterious impact on oocyte quality and embryonic development. Human oocytes from overweight and obese people have lower glucose consumption and higher endogenous triglyceride levels that greatly impact the oocyte competence and their capacity of development to the blastocyst stage [35]. These modifications in the glucose and lipid metabolism are also observed in blastocysts from overweight and obese people, and this would be one of the causes that impact the proportion of high-quality blastocysts [35,36]. Herrero *et al.* found similar results were seen in overweight or obese women whose embryos were less likely to reach the blastocyst stage; those that did grow into blastocysts exhibited faster preimplantation development with fewer trophectoderm cells [37]. Another probable reason for the significant difference in embryo quality is that obese female patients may have inherited genomic instability, especially telomere attrition, which is caused by higher oocyte oxidative stress. Inefficient telomere reconstruction in the cleavage stage embryo is likely to produce anaphase lag, mosaicism, and copy number variations, resulting in delayed and worse embryonic development [38]. It is critical to point out that the effect of overweight and obesity on oocyte competence and embryo development would begin post-fertilization rather than after day 3 of the cleavage stage, as reported by Comstock *et al*. [36]. These findings are in line with other research that suggests obesity may provide a risk for adverse ICSI outcomes, such as unsuccessful fertilization, pregnancy, increased miscarriage, and cycle cancellation [39,40,30]. In this study, obese females had the greatest homeostatic model assessment of insulin resistance (HOMA-IR), whereas normal-weight females had the lowest, and the difference was significant. In accordance with the present findings, Yang *et al*. (2022) discovered that mean HOMA-IR increased with increasing mean BMI in 3,615 women undergoing ICSI cycles [14]. The current study's findings are similarly consistent with those of Abdul Kareem *et al*. (2020) [41]. Insulin resistance is characterized physiologically as a decreased response in insulin-targeting tissues to high physiological insulin levels. In obesity, it has been demonstrated that the tyrosine kinase activity of insulin receptor tyrosine kinase and insulin receptor substrate 1, tyrosine phosphorylation, were decreased in insulin-resistant skeletal muscle [2]. Furthermore, it has been discovered that the reduced fat storage capacity of the adipose tissue in obesity causes ectopic fat deposition and contributes to the development of insulin resistance [6]. Obesity is also known to increase endoplasmic reticulum stress, which has been proposed as the etiology of insulin resistance [11]. Finally, it has been proposed that persistent systemic inflammation caused by obesity is responsible for obesity-induced insulin resistance [10]. This study found that pregnant females had considerably lower HOMA-IR levels than non-pregnant females. There was also a negative correlation discovered between fasting insulin, HOMA-IR, and

pregnancy outcome. previous reports established increased serum fasting insulin and HOMA-IR effects on pregnancy outcomes [42,43]. Hyperinsulinemia is thought to disturb the intrafollicular milieu during folliculogenesis, slowing fertilization and reducing embryonic development potential. Furthermore, disruption of insulin signaling in the uterus may affect gene expression and glucose consumption, as well as have an influence on the decidualization process, endometrial receptivity, and implantation, resulting in a reduced pregnancy rate [3]. As a result, it is reasonable to expect that increased pregnancy chances will be related to a lower BMI and lower insulin resistance. Song and colleagues (2022) examined the value of HOMA-IR in ICSI cycles and discovered that the pregnancy rate was significantly lower in non-PCOS women with HOMA-IR levels higher than 3.15 (OR, 0.018, 95% CI, 0.004-0.081; p0.05) [42]. These findings are supported by the current study. Furthermore, this study found that pregnant women had a considerably higher waist-to-hip ratio than non-pregnant women, which is consistent with prior research [44,45]. To explain these findings, more visceral fat, in contrast to subcutaneous fat, may be the primary source of the lower pregnancy rate in obese women with a higher waist circumference. Higher visceral fat levels can promote inflammation and metabolic dysfunction, which manifest as insulin resistance and oxidative stress [45]. These complications are linked to poor-quality oocytes and embryos, as well as decreased endometrial receptivity and, as a result, a lower pregnancy rate. The current study's findings demonstrated significant differences in pregnancy rates based on body mass index ranking across groups (p= 0.02). Obese females had the lowest pregnancy rate (3.33%). Furthermore, when the patients enrolled in this study were compared based on pregnancy outcome, pregnant females had a considerably lower BMI. Obesity has a significant impact on fertility, which is typically accompanied by metabolic and endocrine abnormalities. Obese females are more likely to have reproductive issues such as embryonic development difficulties, infertility, and malformed offspring. Obesity in women is a complicated, multifactorial disorder. as it has a range of mechanisms through which it influences the development of numerous reproductive problems, among which insulin resistance, hyperinsulinemia, inflammation and lipotoxicity are the foremost mechanisms. Still, the accurate mechanism behind their association remains indistinct. This finding supports previous data suggesting that obesity negatively impacts conception and pregnancy rates [15]. In the current study, serum insulin and HOMA-IR were better predictors of positive pregnancy outcomes in infertile women enrolled in the study in terms of the area under the curve of the ROC curve analysis, which was more than 0.7, which means good test quality. In this study, serum insulin and HOMA-IR have been determined to have two cutoff values of ≤ 4.64 (ng/ml) and ≤ 1.1, respectively. were better predictors of positive pregnancy outcomes in infertile women enrolled in the current study with acceptable levels of sensitivities, specificities and accuracies. To the best of our knowledge, no other published work has addressed the topic of employing HOMA-IR in predicting pregnancy success in Iraqi infertile women undergoing ICSI; as such, this study views this point as an original point. Prior studies have relied on conventional variables such as hormonal levels in serum and follicular fluid, in addition to oocyte characteristics, embryo grading, and endometrial thickness, as predictors of pregnancy outcome in women undergoing ICSI; however, the authors are aware of the small sample size due to different factors. One is that cultural beliefs limit the response rate. Second, a probability of sampling bias is not uncommon because there is no documented data related to the size of the required population.

Conclusion

Resistance to insulin negatively impacts the outcomes of ICSI for infertile women. Moreover, infertile women who are obese may have an increased susceptibility to insulin resistance; thus, reducing HOMA-IR and BMI will have a beneficial effect on ICSI outcomes.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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