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Association of HOMA-IR with unexpected poor ovarian response in non-obese women in poseidon 1: a retrospective cohort study

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Abstract

Background Insulin resistance (IR) is related with adverse outcomes of in vitro fertilization (IVF) in women with obesity, but little is known about the relationship between IR and unexpected poor ovarian response (uPOR) in non-obese subjects with sufficient ovarian parameters (classified as POSEIDON group 1). This research aims to explore the association between the homeostasis model assessment of insulin resistance (HOMA-IR) and uPOR in non-obese women with normal biomarkers of ovarian reserve.

Methods The retrospective cohort study was conducted at a fertility center. The main inclusion criteria were age < 35 years, body mass index (BMI) < 28 kg/m^2, normal ovarian reserve (anti-Mullerian hormone ≥ 1.2 ng/ml, antral follicle count ≥ 5). Women undergoing the first oocyte retrieval cycle were included consecutively between 2018 until 2023. Patients who have ≤ 9 oocytes retrieved were defined as uPOR. The multivariable logistic model and subgroup analysis were conducted after adjusting confounders.

Results A total of 6977 cycles were included. The adjusted odds ratio was 1.25 (95% confidence interval [CI], 1.12–1.39) for the increment of Ln HOMA-IR which was taken as a continuous variable. Meanwhile, as a sensitivity analysis, elevated tertile of HOMA-IR exhibited an increase in risk of uPOR for the third tertile (≥ 2.75) when compared with the first tertile (< 1.75) with OR of 1.33 (95%CI, 1.15–1.54). In the subgroup analysis, the positive association remained consistent.

Conclusion Elevated HOMA-IR values is significantly associated with increased risk of uPOR in non-obese women classified as POSEIDON group 1. Our study provided evidence for the adverse influence of IR on the ovarian response during IVF and shed light on the importance of IR measurement at the time of pre-stimulation among non-obese women.

Keywords Insulin resistance, Unexpected ovarian poor response, HOMA-IR, ART, POSEIDON

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Background

Insulin resistance (IR) is a metabolic disorder associated with obesity, hypertension, cardiovascular disease, type 2 diabetes and polycystic ovary syndrome (PCOS), which is a multifaceted global health issue [1–3]. Various studies have shown that individuals with normal body weight can also become IR [4–6]. It has been reported the prevalence of IR is 44.8% among young adults aged 18 to 44 years and nearly half of them with IR are nonobese [7].

In the setting of assisted reproductive technology (ART), poor ovarian response (POR) remains one of the most difficult problems [8]. The POSEIDON classification identifies the unexpected poor ovarian response (uPOR), those patients who, despite having good ovarian reserve markers, obtained a lower oocyte number: between 4 and 9 oocytes retrieved or even fewer than 4 oocytes retrieved [9, 10]. The incidence of uPOR varies between 10 and 40% [11–13]. Although studies in expected POR are emerging and risk factors have been well studied, there are very few researches have been done on uPOR and its etiology remains unsolved. Some factors were blamed for this phenomenon, including polymorphisms of gonadotropins (Gn) and their receptors, dietary habits, environmental contaminants and oxidative stress [14–16].

The relationship of IR with ovarian response is still controversial. As previous studies reported, hyperinsulinemia promoted early folliculogenesis which could result in hyper-response to controlled ovarian stimulation (COS) [17, 18]. In contrast, some researchers showed that IR was associated with the decreased percentage of mature eggs and poor embryo quality in non-PCOS women [19]. In addition, elevated dietary glycaemic load as well as carbohydrate intake has been found significantly associated with uPOR [15]. Our previous studies also demonstrated the negative association between ovarian sensitivity index and homeostasis model assessment of insulin resistance (HOMA-IR) in women undergoing COS [20].

Previous studies have focused on the adverse effect of IR on ART outcome in obese women. It is noteworthy that IR can also occur in infertile women without obesity [2]. As an index of IR, HOMA-IR is broadly used in clinical research [21–23]. In clinical practice, explaining why a poor response is obtained in a young patient with normal ovarian reserve and body weight can be challenging. Most clinicians and patients would like to have information before the first stimulation [8]. Therefore, in this retrospective cohort study, we aimed to investigate the association between HOMA-IR and uPOR in non-obese women aged < 35 years with adequate ovarian reserve undergoing their first ART cycle.

Methods

Study design and patient population

This study was a retrospective cohort analysis. Non-obese women with adequate ovarian reserve (AMH ≥ 1.2 ng/ml, AFC ≥ 5) who received their first complete oocyte pickup cycles between Jan 2018 and Oct 2023 were consecutively included in the analysis at reproductive medical center of Henan Provincial People's Hospital, China. BMI of ≥ 28 kg/m^2 was defined as obesity according to Working Group on Obesity in China [24]. Diagnosis of PCOS was based on the Rotterdam criteria [25].

We included individuals under 35 years with body mass index (BMI) of < 28 kg/m^2 who underwent standard Gonadotropin releasing hormone (GnRH) agonist protocols in the first in vitro fertilization (IVF) cycle with complete data on ovarian reserve and insulin resistance, including anti-mullerian hormone (AMH), antral follicle count (AFC), fasting plasma glucose (FPG), fasting serum insulin (FINS). The exclusion criteria were as follows: preimplantation genetic testing (PGT) and oocyte freezing cycles, women with diabetes mellitus, malignant diseases, congenital adrenal hyperplasia and history of ovariectomy. Moreover, cycles of canceling oocyte retrieval were also excluded.

Laboratory assays and indicator calculation

Serum basal follicle-stimulating hormone (BFSH), luteinizing hormone (LH), estradiol, total testosterone and progesterone concentrations were measured during the menstrual cycle from day 2 to 4. Serum AMH levels were measured by chemiluminescent immunoassay on any day of the menstrual cycle and the detection limit of the test was ≤ 0.06 ng/ml. Fasted blood samples were collected to measure insulin and glucose. The inter-assay laboratory coefficient of variation (CV) of FPG testing was lower than 3.5%, which was detected by ADVIA2400ChemistrySystem (ADVIA 2400, SIEMENS, Germany). FINS concentration was determined by the electro-chemiluminescence immunoassay method (CV < 3.2%) on the full-automatic chemiluminescence immunoassay analyzer (Cobas8000 e602; Roche Diagnostics GmbH, Mannheim, Germany) in the laboratory of the Department of Reproductive Endocrinology at Henan Provincial People's Hospital. Our laboratory is checked for qualification by the External Quality Assessment of Clinical Laboratory Center annually (Ministry of Health of the People's Republic of China, Beijing, China).

HOMA-IR was assessed by formula as follows: HOMA-IR = FPG (mmol/L) x FINS (μU/ml) / 22.5 [21]. BMI was calculated according to the formula, weight (kg) / height (m)^2.

Controlled ovarian stimulation

The COS protocols consisted of short-acting and long-acting GnRH agonist down regulation protocols. These dose step-up regimens were individualized according to women's age, BMI and ovarian reserve. In short-acting GnRH agonist down regulation protocol, subcutaneously injected 0.1 mg triptorelin was scheduled for patients from the 6th-8th day after ovulation to the 14th-16th day after ovulation until sufficient downregulation of the pituitary was achieved. After that, exogenous Gn and 0.05 mg triptorelin was administered simultaneously until the day of human chorionic gonadotropin (HCG) triggering. In the long-acting GnRH agonist down regulation protocol, patients received a single dose of triptorelin acetate (Diphereline; 3.75 mg) on day 2–4 of the menstrual cycle. If downregulation of the pituitary was satisfactory after 30–35 days, exogenous Gn was injected to initiate the cycle. The HCG was administered when at least two follicles had reached a mean diameter of 17–18 mm and the serum estradiol levels were consistent with the ultrasound findings. Ultrasound-guided follicular aspiration was performed at 35–37 h after the administration of the HCG injection. On day 3, all the embryos were assessed for blastomere number, regularity and presence of cytoplasmic fragmentation. Viable embryos meant day 3 embryos that reached more than four cells scored as 2 or 3 [26].

Outcome measures

Patients who have ≤9 oocytes retrieved were defined as uPOR. The objective was to evaluate the association of HOMA-IR with uPOR in young non-obese women with adequate ovarian reserve. In addition, the association between HOMA-IR and uPOR were further explored in subgroup analysis.

Statistical analysis

Patients were divided into three groups according to the tertiles of HOMA-IR. The Kolmogorov-Smirnov statistic was performed to test continuous variables for normality. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD). Continuous variables with skewed distribution were presented median with interquartile range (IQR). Categorical variables were expressed as frequency (percentage). Between-group statistical comparisons of mean values were done using ANOVA tests and for median values the Kruskal-Wallis test was used. Between-group comparisons of categorical variables were performed using Pearson Chi-square tests or Fisher's Exact Test.

The data distribution of HOMA-IR was strongly skewed. Thus, we performed log e transformation (Ln HOMA-IR) before analysis. We first examined the association of Ln HOMA-IR as a continuous variable with uPOR, and then we evaluated the relationship when HOMA-IR was treated as variables categorized as tertiles. In addition, linear trend tests were performed by entering the median value of each HOMA-IR category as a continuous variable in the models.

Univariate logistic regression models were applied to evaluate the association of uPOR with baseline characteristics. In the multivariable logistic regression models, age, BMI, AMH, BFSH, initial Gn dose, AFC, and PCOS-status were adjusted to estimate the association between HOMA-IR and uPOR. Unadjusted and adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated.

Subgroup analysis was conducted according to age (≤30 and >30 years), BMI (<24 and ≥24 kg/m^2), AMH tertiles, AFC (≤16 and >16), BFSH tertiles, Initial Gn dose (<150 and ≥150 IU) and PCOS diagnosis. Next, we used Log likelihood ratio test to obtain a *P*-value for interaction effect in each subgroup. Statistical analysis was undertaken by using software packages R (http://www.R-project.org, The R Foundation) and Empower (R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Data from non-obese young women with adequate ovarian reserve undergoing their first oocyte retrieval cycles were analyzed. A total of 10,238 medical records between Jan 2018 and Oct 2023 were screened and 6977 cycles were finally included in the analysis (Fig. 1).

Patient characteristics were presented in Table 1. Subjects with higher HOMA-IR tended to be younger and had higher levels of BMI, AMH, AFC, FINS, FPG, initial Gn dose, total Gn dose and duration of Gn used. Individuals in the higher tertile were more likely to PCOS. The BFSH levels and the number of retrieved oocytes, metaphase II (MII) oocytes, 2PN and viable day-3 embryos were prone to be decreased in the higher tertile. Moreover, the incidence of uPOR significantly increased across HOMA-IR tertiles (Table 1).

As determined by univariate analysis, age > 30 years (OR = 1.22, 95%CI, 1.10–1.35, *P* = 0.0001), BMI ≥ 24 kg/m^2 (OR = 1.47, 95%CI, 1.32–1.63, *P* < 0.0001), BFSH > 6.77 mIU/ml (OR = 2.04, 95%CI, 1.80–2.31, *P* < 0.0001) and initial Gn dosage ≥ 150 IU (OR = 1.56, 95%CI, 1.41–1.73, *P* < 0.0001) were positively associated with the risk of uPOR, whereas AMH ≥ 5.00 ng/ml (OR = 0.31, 95%CI, 0.27–0.35, *P* < 0.0001), AFC > 16 (OR = 0.48, 95%CI, 0.43–0.53, *P* < 0.0001) and PCOS (OR = 0.73, 95%CI, 0.64–0.84, *P* < 0.0001) were negatively associated with the risk of uPOR (Table 2).

Table 3 showed the univariate and multivariable logistic regression models assessing the association of HOMA-IR

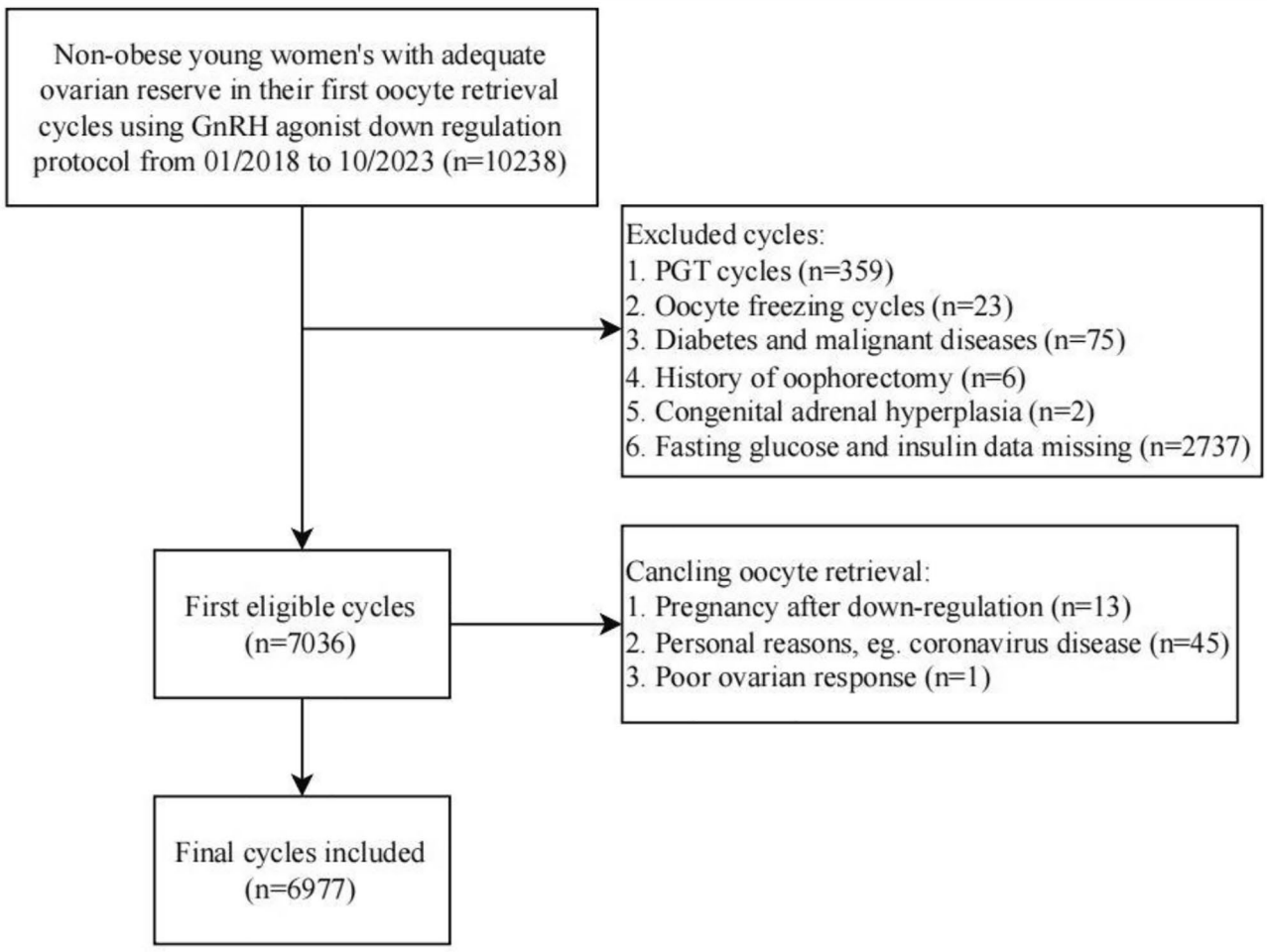

Fig. 1 Flowchart of data collection process

with uPOR. In the unadjusted model, the ORs of uPOR significantly augmented when the HOMA-IR increased or the tertiles of HOMA-IR graded. There was a 23% increase in the risk of uPOR for per unit increase in Ln HOMA-IR (OR=1.23, 95%CI, 1.12–1.34, $P<0.0001$). The OR for tertile 3 was significantly higher than the OR for tertile 1 (OR=1.32, 95%CI, 1.17–1.50, $P<0.0001$). In the full-adjustment model for confounders, including age, BMI, AMH, BFSH, initial Gn dose, AFC, and PCOS, the positive association between HOMA-IR and uPOR was still found. In model 2, Ln HOMA-IR as a continuous variable was associated with a 25% increased risk of uPOR (OR=1.25, 95%CI, 1.12–1.39, $P<0.0001$). Meanwhile, elevated tertile of HOMA-IR exhibited an increase in risk of uPOR for the third tertile (vs. the first tertile) with OR of 1.33 (95%CI, 1.15–1.54, $P=0.0001$). Additionally, the risk of uPOR increased with the elevation of HOMA-IR tertiles ($P$for trend=0.0002) (Table 3).

Figure 2 revealed a highly consistent relationship between HOMA-IR and uPOR in each subgroup, higher levels of HOMA-IR resulted in a significant increase in uPOR risk, with ORs ranging from 1.17 to 1.45. In addition, no evidence of interaction effect was found among all subgroup, including age ($P$for interaction=0.2693), BMI ($P$for interaction=0.6431), AMH ($P$for interaction=0.5814), AFC ($P$for interaction=0.8605), BFSH ($P$for interaction=0.8778), initial Gn dose ($P$for interaction=0.1886), and PCOS ($P$for interaction=0.2760) (Fig. 2).

Discussion

We found that the rise in HOMA-IR values in non-obese young women with seemingly sufficient ovarian reserve parameters was related to the increased risk of uPOR after adjusting potential confounders. Additionally, the significant correlation remained consistent in subgroup analysis. Few studies have been previously performed on the relationship between IR and uPOR in non-obese population. To our knowledge, only one study depicted a positive association between glycaemic load and uPOR on infertile women with normal BMI [15]. Our findings

Table 1 Demographic parameters and cycle outcomes of patients stratified by HOMA-IR tertiles

Variables	HOMA-IR tertiles			*P* value
	T1 (< 1.75) *n* = 2326	T2 (1.75–2.75) *n* = 2325	T3 (≥ 2.75) *n* = 2326	
Age (y)	29.78 ± 2.96	29.34 ± 3.17	28.92 ± 3.37	< 0.001
Primary Infertility (%)	41.87 (974/2326)	44.17 (1027/2325)	41.75 (971/2326)	0.170
PCOS (%)	10.58 (246/2326)	13.89 (323/2325)	23.82 (554/2326)	< 0.001
BMI (kg/m^2)	21.04 ± 2.31	22.23 ± 2.44	23.87 ± 2.43	< 0.001
AMH (ng/ml)	3.59 (2.45–5.60)	3.76 (2.48–5.60)	4.09 (2.70–6.36)	< 0.001
BFSH (mIU/ml)	6.53 ± 1.73	6.30 ± 1.64	5.99 ± 1.49	< 0.001
AFC	15.16 ± 5.29	15.50 ± 5.52	17.28 ± 5.85	< 0.001
FPG (mmol/l)	4.66 ± 0.43	4.86 ± 0.44	5.08 ± 0.48	< 0.001
FINS (μU/ml)	6.26 (5.06–7.35)	10.22 (9.15–11.32)	16.59 (14.25–20.83)	< 0.001
HOMA-IR	1.31 (1.04–1.54)	2.19 (1.97–2.43)	3.69 (3.13–4.70)	< 0.001
Initial Gn Dose (IU)	138.15 ± 38.72	141.96 ± 40.13	143.73 ± 35.10	< 0.001
Total Gn Dose (IU)	2026.41 ± 751.64	2078.84 ± 808.99	2259.15 ± 970.58	< 0.001
Duration of Gn (d)	11.30 ± 2.03	11.28 ± 2.25	11.74 ± 2.81	0.006
No. of Oocytes	12 (9–16)	12 (8–16)	11 (8–16)	< 0.001
Metaphase II Oocytes	11 (7–14)	10 (7–14)	10 (6–14)	< 0.001
2-Pronuclei Embryos	7 (5–11)	7 (5–10)	7 (4–10)	< 0.001
Viable day-3 Embryos	6 (4–9)	6 (4–9)	5 (3–8)	< 0.001
uPOR (%)	30.40 (707/2326)	35.10 (816/2325)	36.63 (852/2326)	< 0.001

*Mean values with standard deviation, median values with interquartile range

Table 2 The unadjusted association between baseline characteristics and uPOR

Variables	*N*	Crude OR (95% CI)	*P* value
Age (y)			
≤ 30	4103	Reference	
> 30	2874	1.22 (1.10 to 1.35)	0.0001
BMI (kg/m^2)			
< 24	4928	Reference	
≥ 24	2049	1.47 (1.32 to 1.63)	< 0.0001
AMH tertiles (ng/ml)			
T1 (< 2.94)	2321	Reference	
T2 (2.94–5.00)	2327	0.43 (0.38 to 0.48)	< 0.0001
T3 (≥ 5.00)	2329	0.31 (0.27 to 0.35)	< 0.0001
AFC			
≤ 16	3980	Reference	
> 16	2997	0.48 (0.43 to 0.53)	< 0.0001
BFSH tertiles (mIU/ml)			
T1 (< 5.55)	2314	Reference	
T2 (5.55–6.77)	2335	1.28 (1.13 to 1.46)	0.0001
T3 (> 6.77)	2328	2.04 (1.80 to 2.31)	< 0.0001
Initial Gn dose (IU)			
< 150	3952	Reference	
≥ 150	3024	1.56 (1.41 to 1.73)	< 0.0001
PCOS Diagnosis			
Non PCOS	5854	Reference	
PCOS	1123	0.73 (0.64 to 0.84)	< 0.0001

*The model used univariate logistic regression analysis

may establish a role of IR in poor ovarian response in POSEIDON group 1 without obesity.

Early recognition of uPOR in the ART attempt has always been difficult in non-obese young women with adequate parameters of ovarian reserve which would be considered as having normal ovarian function [27]. Similarly to our results, previous research suggested age, BMI, AMH and AFC were risk factors for uPOR [8]. Based on our findings, HOMA-IR value could be considered as risk factor of uPOR which should be brought to the forefront, except for the general conditions such as BMI and ovarian reserve markers.

HOMA-IR is a measurement frequently used to assess insulin sensitivity and has high sensitivity and specificity for measuring IR [28]. Direct, dynamic methods for measuring IR are accurate but inconvenient for clinical practice in large populations [29]. Many studies selected HOMA-IR of 2.5 as an indicator of IR based on the original study by Matthews et al. [21]. Similarly, our results indicated that those who had HOMA-IR of tertile 2 (HOMA-IR 1.75–2.75) and tertile 3 (HOMA-IR ≥ 2.75) had significant increases in risks of uPOR. Thus, we suggested that IR may be positively associated with the risk of uPOR.

The exact etiology of uPOR is not fully understood. We suggest IR may play an important role in the impairment of folliculogenesis. However, the precise mechanism behind these findings were not actively explored in the current study and could therefore only be postulated. When IR is existed, it has been reported that there is decreased follicle activity, increased oxidative stress

Table 3 Risk association between HOMA-IR and uPOR

Variable	Crude Model		Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Ln HOMA-IR	1.23 (1.12, 1.34)	< 0.0001	1.24 (1.11, 1.37)	< 0.0001	1.25 (1.12, 1.39)	< 0.0001
HOMA-IR tertile						
T1 (< 1.75)	Reference (1.0)		Reference (1.0)		Reference (1.0)	
T2 (1.75–2.75)	1.24 (1.10, 1.40)	0.0006	1.22 (1.07, 1.39)	0.0027	1.20 (1.05, 1.37)	0.0062
T3 (≥ 2.75)	1.32 (1.17, 1.50)	< 0.0001	1.32 (1.14, 1.52)	0.0001	1.33 (1.15, 1.54)	0.0001
P for trend		< 0.0001		0.0003		0.0002

*Crude model adjusted for none; Model 1 adjusted for: age, BMI, AMH, and BFSH; Model 2 adjusted for: age, BMI, AMH, BFSH, initial Gn dose, AFC, and PCOS. The model 1 and model 2 used multivariable logistic regression analysis

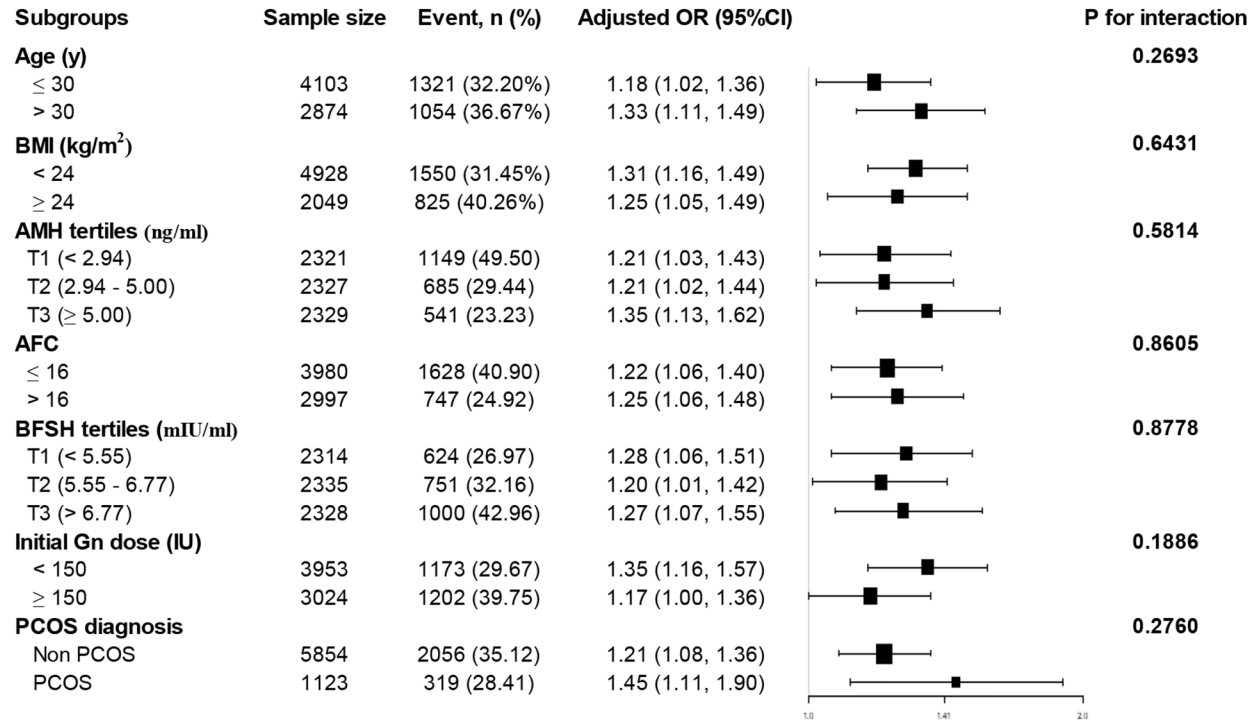

Fig. 2 Risk association between HOMA-IR as a continuous variable and uPOR in subgroup of age, BMI, AMH, AFC, BFSH, initial Gn dose and PCOS-status. The multivariable regression model adjusted, if not stratified, for age, BMI, AMH, BFSH, initial Gn dose, AFC, and PCOS

and ovarian dysfunction [30, 31]. In lean infertile women without PCOS, IR was reported to be associated with the decreased percentage of mature eggs and poor embryo quality [19]. Genetic variation of FSH receptors was described to influence the degree of ovarian response to stimulation [14]. However, various studies performed on this subject show contradictory results and a difference in response for specific FSH receptor subtypes may be very small, and not likely to be the basis for the wide variation in the number of oocytes retrieved in response to COS [32, 33].

In the clinic, doctors pay more attention to the treatment of insulin resistance in obese patients. However, previous study has suggested that normal-weight individuals with insulin resistance are not rare [34]. Our results showed that patients with insulin resistance may need higher doses of gonadotropins and longer time for COS. The identification of risk factors such as high HOMA-IR values, offering valuable insights for clinical decision-making. It may help in counseling those patients regarding the risk of uPOR in their first IVF cycles, considering the time, financial, and emotional commitments in the future. It is well known that advanced maternal age and obesity may impair the ovarian response to stimulation during IVF treatment [35, 36]. Our results showed that, even in subjects without obesity, the positive association between HOMA-IR and uPOR was still exist. Thus, our results provide evidence for the role of insulin resistance on ovarian response. Therefore, doctors may pay more attention to the diagnosis and treatment of IR in non-obese patients, for example, metformin administration and lifestyle intervention, to improve IVF outcome.

Currently, there is a lack of consensus on the definition of poor ovarian response [37]. Previous research showed the cumulative livebirth rate (CLBR) per initiated cycle was poorer in the group of patients with ≤9 oocytes when compared to patients with 10 or more oocytes [38]. According to the data from our center, for young women with normal ovarian reserve, retrieving 10~12 oocytes might result in optimized pregnancy outcomes in a fresh cycle with low OHSS risk and would not compromise cumulative outcomes [39]. Based on these data it would seem reasonable to define poor ovarian response as retrieval of ≤9 oocytes following conventional stimulation for young women with adequate ovarian reserve in our study.

Certain limitations exist in this study. The findings should be interpreted with caution because of its retrospective nature. The concern about sensitivity and accuracy of HOMA-IR to assess IR compared with the gold standard technique for measuring IR which we did not perform. However, due to convenience and cost-saving, HOMA-IR is considered appropriate for the large-scale study [40]. Additionally, lack of information on interventions for the patients with increased HOMA-IR levels during IVF treatment may have influenced the effect estimates of HOMA-IR on uPOR. But it is noteworthy that the potential resulting from interventions would bias towards to null and thus result in an underestimation of the association between HOMA-IR and uPOR. As an observational study, we cannot conclude that insulin resistance is the cause of uPOR. Moreover, the Chinese ethnicity of our participants may limit generalization of the findings to different ethnic groups and patient diagnosis, age, and COS protocols may vary from study to study. To prove the credibility of these results, randomized controlled trials are required to be conducted to establish cause and effect.

In conclusion, the results mainly showed that elevated HOMA-IR values were associated with increased risk of uPOR in non-obese women classified as POSEIDON group 1. Future research is needed to validate our results and investigate the mechanistic links between IR and ovarian response.

Abbreviations

POR	Poor ovarian response
PCOS	Polycystic ovary syndrome
IR	Insulin resistance
ART	Assisted reproductive technology
UPOR	Unexpected poor ovarian response
HOMA-IR	Homeostasis model assessment of insulin resistance
COS	Controlled ovarian stimulation
GnRH	Gonadotropin releasing hormone
IVF	In vitro fertilization
AMH	Anti-mullerian hormone
AFC	Antral follicle count
FPG	Fasting plasma glucose
FINS	Fasting serum insulin
PGT	Preimplantation genetic testing
HCG	Human chorionic gonadotropin
Gn	Gonadotropin
BFSH	Basal follicle-stimulating hormone
LH	Luteinizing hormone

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Author contributions
Y.L conceived the study and wrote the manuscript; SD Z and CL Z participated in data curation.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due to privacy policy of hospital but are available from the corresponding author on resonable request.

Declarations

Attestation statements
Data regarding any of the subjects in the study has not been previously published unless specified.

Ethics approval
Ethics approval for the study was obtained from the Ethics Committee of the Henan Provincial People's Hospital (No. 2022139).

Consent for publication
The authors consent for publication of this article.

Conflict of interest
The authors have none to declare.

Consent to participate
Patient consents were not required as this study was based on data obtained from databases in which patients cannot be identified.

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