Research Square

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Lack of Association Between Insulin Resistance and Live Birth Outcomes Among Non- PCOS Women Undergoing Their First Frozen-Thawed Single Blastocyst Transfer: A Retrospective Cohort Study

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Abstract

Purpose

To investigate whether insulin resistance is associated with live birth outcomes in non-PCOS infertile women (PCOS, polycystic ovary syndrome) undergoing their first frozen-thawed single blastocyst transfer, and to evaluate the dose-response relationship between HOMA-IR (homeostasis model assessment of insulin resistance) and live birth.

Methods

This retrospective cohort study included 349 non-PCOS infertile women who underwent their first frozen-thawed single blastocyst transfer. Patients were divided into insulin resistance group (HOMA-IR ≥ 2.71, n = 142) and non-insulin resistance group (HOMA-IR < 2.71, n = 207) based on the homeostasis model assessment of insulin resistance index. The primary outcome was live birth rate; secondary outcomes included clinical pregnancy rate and early miscarriage rate. Hierarchical multivariate logistic regression analysis was used to adjust for confounders, restricted cubic spline analysis was performed to evaluate the dose-response relationship, and ROC curve analysis was used to assess the predictive value of HOMA-IR. Sample size was estimated based on previous studies. A two-sided $P < 0.05$ was considered statistically significant, with Bonferroni correction applied for secondary outcomes. Model fit was adequate based on AIC and Hosmer-Lemeshow test.

Results

The live birth rate was 38.0% (54/142) in the IR group and 37.7% (78/207) in the non-IR group ($P = 1.000$). After adjusting for age, BMI, blastocyst quality, and endometrial thickness, IR was not an independent predictor of live birth (OR = 1.16, 95% CI: 0.71–1.92, $P = 0.549$). Restricted cubic spline analysis showed no significant dose-response relationship between HOMA-IR and live birth. ROC curve analysis showed that HOMA-IR had poor predictive value for live birth (AUC = 0.533, 95% CI: 0.469–0.598).

Conclusion

In non-PCOS patients undergoing their first FET (frozen-thawed embryo transfer) cycle, insulin resistance is not associated with live birth outcomes. This null finding suggests that the impact of IR on reproductive outcomes may be population-specific and of limited clinical significance in first-cycle patients without prior failure.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of female infertility. Insulin resistance is highly prevalent among PCOS patients, with an estimated prevalence of 50–80% [1, 2]. Numerous studies have consistently demonstrated that PCOS patients with IR undergoing frozen-thawed embryo transfer have significantly lower live birth rates and higher miscarriage rates compared to those without IR [2, 3]. Interventions targeting IR, such as metformin pretreatment, have been shown to improve reproductive outcomes in this population [4].

The biological basis for the detrimental effects of IR on reproductive outcomes is well-established. IR leads to compensatory hyperinsulinemia, which directly stimulates ovarian theca cell androgen production, disrupts follicle development, and reduces oocyte maturation rates and embryo quality [6]. Additionally, IR impairs endometrial glucose metabolism and decidualization, compromising endometrial receptivity [8, 9], and promotes microthrombosis in uterine spiral arteries, increasing miscarriage risk [10]. However, the clinical significance of these mechanistic effects may vary substantially across different patient populations, depending on their baseline metabolic and reproductive reserve [12].

The evidence regarding the impact of IR on assisted reproductive technology (ART) outcomes in non-PCOS populations remains inconclusive. Some studies in general non-PCOS populations found no significant association between IR and clinical pregnancy, live birth, or miscarriage rates [13, 14, 15, 16]. Specifically, Cai et al. [13] found that although IR was associated with endocrine-metabolic abnormalities and altered ovarian stimulation characteristics, it did not affect clinical pregnancy, live birth, or miscarriage rates in a cohort of 1,104 non-PCOS patients. Similarly, Hu et al. [14] reported that HOMA-IR was not associated with embryo quality or pregnancy outcomes in non-PCOS patients, despite its association with late miscarriage risk in a previous large-scale study. In contrast, recent studies focusing on high-risk subgroups—such as patients with recurrent implantation failure or obesity—have demonstrated that IR significantly impairs live birth outcomes [3, 7, 18]. These findings suggest that the impact of IR on reproductive outcomes may be population-specific [12], with adverse effects amplified in populations with pre-existing reproductive or metabolic vulnerabilities.

The homeostasis model assessment of insulin resistance (HOMA-IR) is the most widely used clinical surrogate for IR in large retrospective studies [20, 21, 22]. A previous large-scale study in Chinese non-PCOS infertile women established that HOMA-IR ≥ 2.71, representing the upper quartile of the HOMA-IR distribution, was significantly associated with an increased risk of late miscarriage (adjusted OR = 3.82, 95% CI: 1.59–9.17) [14]. This validated cutoff provides a robust basis for defining IR in non-PCOS Chinese populations.

However, systematic evaluations in first-cycle non-PCOS patients without prior failure remain lacking. Whether IR affects live birth outcomes in this specific population—those with no history of failed implantation who may have relatively preserved endometrial receptivity and metabolic reserve—remains an open question.

This study, based on data from 349 non-PCOS patients undergoing their first frozen-thawed single blastocyst transfer with a well-validated HOMA-IR cutoff (≥ 2.71) [14], aims to systematically evaluate the

association between IR and live birth outcomes, and to provide more refined evidence through dose-response analysis (restricted cubic spline) and predictive value assessment (ROC curve analysis), thereby filling this knowledge gap and informing population-specific clinical decision-making.

Methods

Study Design and Ethics

This was a single-center, retrospective cohort study conducted at the Reproductive Medicine Center of Huzhou Maternity & Child Health Care Hospital. The study protocol was approved by the Institutional Review Board (approval number: 2026-J-066). Due to the retrospective design, informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki.

Study Population

A total of 349 non-PCOS infertile women who underwent their first frozen-thawed single blastocyst transfer at the Reproductive Medicine Center of Huzhou Maternity & Child Health Care Hospital between June 2020 and June 2025 were included. All patients were of Chinese Han ethnicity. Data on socioeconomic status were not consistently recorded in the clinical database and could not be included in the analysis.

Inclusion criteria:

- Diagnosis of infertility, undergoing first FET cycle
- Single blastocyst transfer cycle
- Completed fasting blood glucose and fasting insulin testing prior to the procedure
- Age 20–40 years

Exclusion criteria:

- Met PCOS diagnostic criteria (Rotterdam criteria)
- Had ≥ 1 previous failed in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycle
- Known diabetes mellitus or use of medications affecting insulin sensitivity (e.g., metformin)
- Uterine cavity abnormalities (uterine fibroids, intrauterine adhesions, etc.)
- History of recurrent implantation failure

Definition of Insulin Resistance

IR was diagnosed using the homeostasis model assessment of insulin resistance index (HOMA-IR), calculated as:

HOMA-IR = [Fasting insulin (μIU/mL) × Fasting glucose (mmol/L)] / 22.5

The cutoff of ≥ 2.71 was derived from a previous large-scale study in Chinese non-PCOS infertile women (n = 3,615) [14]. In that cohort, the HOMA-IR values were ranked and the 75th percentile (upper quartile) was identified as 2.71, which was then used as the cutoff to define insulin resistance—meaning that individuals with HOMA-IR values in the top 25% of the population distribution were classified as insulin resistant. This threshold was subsequently validated by its significant association with late miscarriage (adjusted OR = 3.82, 95% CI: 1.59–9.17). Based on this previously validated criterion, HOMA-IR ≥ 2.71 was defined as insulin resistance in the present study. Patients were accordingly divided into the IR group (HOMA-IR ≥ 2.71, n = 142) and non-IR group (HOMA-IR < 2.71, n = 207). While this cutoff has been validated in a Chinese population, its generalizability to other ethnic groups requires further investigation, and the optimal threshold may vary by age, BMI, or other metabolic factors.

Outcome Measures

Primary outcome: Live birth rate, defined as the proportion of transfer cycles resulting in the delivery of at least one live newborn.

Secondary outcomes:

Clinical pregnancy rate: presence of an intrauterine gestational sac on ultrasound examination 4–6 weeks after transfer

Early miscarriage rate: spontaneous abortion before 12 weeks of gestation

Covariates:

Age, BMI, duration of infertility

Type of infertility (primary/secondary)

Blastocyst quality (good/poor quality, defined as ICM and TE both without "C" grade)

Endometrial thickness on transfer day.

Sample Size Estimation

Sample size estimation was based on a previous study reporting live birth rates of 10.34% in the IR group and 20.94% in the non-IR group among non-PCOS patients with recurrent implantation failure [3], which was the only available large-scale study reporting effect sizes for IR on live birth in a non-PCOS population at the time of study design. Using this as a conservative estimate, a sample size of at least

150 patients per group was required to achieve 80% power at a two-sided α level of 0.05. With the observed sample size (n = 349, with 142 in the IR group and 207 in the non-IR group), and assuming an overall live birth rate of approximately 38%, the study had 80% power to detect an absolute difference of approximately 13 percentage points between groups (equivalent to OR ≈ 1.7). The study was therefore adequately powered to detect moderate to large effects but may have been underpowered to detect smaller differences.

Statistical Analysis

Statistical analyses were performed using R version 4.3.2. Continuous variables with normal distribution were expressed as mean ± standard deviation and compared using independent samples t-test; non-normally distributed variables were expressed as median (interquartile range) and compared using Mann-Whitney U test. Categorical variables were expressed as counts (percentages) and compared using chi-square test. Missing data were limited to four baseline covariates: duration of infertility (2/349, 0.57%), infertility type (8/349, 2.29%), endometrial thickness (5/349, 1.43%), and blastocyst quality (5/349, 1.43%). All outcome variables (clinical pregnancy, early pregnancy loss, and live birth) had complete data for all patients. Given the extremely low missingness proportion, complete-case analysis was performed without imputation. Sensitivity analysis comparing patients with and without missing data showed no significant differences in age, BMI, or HOMA-IR (all P > 0.05).

Hierarchical multivariate logistic regression was performed with live birth as the dependent variable, building three sequential models. Hierarchical multivariate logistic regression was performed with live birth as the dependent variable, building three sequential models. Covariates were selected based on their established associations with both insulin resistance and live birth outcomes: age and BMI were included as known confounders, while blastocyst quality and endometrial thickness were added as treatment-related factors. The three models were constructed as follows:

Model	Variables included
Model 1	IR (HOMA-IR ≥ 2.71)
Model 2	Model 1 + age + BMI
Model 3	Model 2 + blastocyst quality + endometrial thickness

Results were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). A two-sided P < 0.05 was considered statistically significant. Bonferroni correction was applied for secondary outcomes (clinical pregnancy and early pregnancy loss) to control for multiple comparisons, with statistical significance set at P < 0.025. Although this approach may be conservative given the correlated nature of these outcomes, we considered it appropriate to maintain strict control of type I error in this exploratory analysis. For interaction analyses, we acknowledge that the power to detect interaction effects is typically lower than for main effects; therefore, the non-significant interaction terms should be interpreted with caution. Model fit was assessed using both the Hosmer-Lemeshow test and the Akaike

Information Criterion (AIC). Although the Hosmer-Lemeshow test showed adequate model calibration (P = 0.721), we acknowledge that this test has limited power in relatively small samples. The consistent AIC values across models further supported adequate model fit.

Restricted cubic spline (RCS) analysis with 3 knots at the 10th, 50th, and 90th percentiles was performed to evaluate the dose-response relationship between HOMA-IR as a continuous variable and live birth [23], with adjusted for age, BMI, blastocyst quality, and endometrial thickness. The reference HOMA-IR value was set at the 10th percentile.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of HOMA-IR for live birth, with the area under the curve (AUC) and 95% CI calculated using the DeLong method.

Subgroup and interaction analyses: Pre-specified interaction analyses were conducted by adding interaction terms (IR × BMI, IR × age) to Model 3 to explore whether the association between IR and live birth was modified by BMI or age. P-values for interaction were reported.

To assess the robustness of the findings, a sensitivity analysis was performed excluding patients with BMI > 28 kg/m² to evaluate whether the null association between IR and live birth was influenced by extreme obesity.

Post-hoc power analysis: Based on previously reported effect sizes [3], post-hoc power calculations were performed to assess the statistical power of this study to detect between-group differences in live birth rates.

Results

Baseline Characteristics

A total of 349 patients were included, with 142 in the IR group and 207 in the non-IR group. Baseline characteristics of the two groups are shown in Table 1. The IR group had a slightly younger mean age (30.17 ± 3.75 vs 31.57 ± 4.58 years, P = 0.002) and, as expected, a significantly higher mean BMI (24.58 ± 3.73 vs 21.53 ± 3.10 kg/m², P < 0.001), consistent with the well-established association between insulin resistance and obesity. No significant differences were observed between the two groups in duration of infertility (P = 0.996), endometrial thickness on transfer day (P = 0.654), the proportion of primary infertility (P = 0.669), or the proportion of good-quality blastocysts (P = 0.487), indicating that the two groups were comparable in these baseline characteristics. As expected, the mean HOMA-IR level was significantly higher in the IR group (4.49 ± 2.32 vs 1.71 ± 0.55, P < 0.001), confirming the validity of the grouping based on the predefined cutoff of ≥ 2.71 [14]. Missing data were limited to four baseline covariates: duration of infertility (2/349, 0.57%), infertility type (8/349, 2.29%), endometrial thickness (5/349, 1.43%), and blastocyst quality (5/349, 1.43%). No missing values were present for age, BMI, HOMA-IR, or any outcome variables.

Table 1
Baseline characteristics of IR and non-IR groups

Variable	IR group (n = 142)	Non-IR group (n = 207)	P value
Age (years)	30.17 ± 3.75	31.57 ± 4.58	0.002
BMI (kg/m^2)	24.58 ± 3.73	21.53 ± 3.10	< 0.001
Duration of infertility (years)	3.32 ± 2.53	3.33 ± 2.81	0.996
Endometrial thickness (mm)	8.75 ± 1.53	8.68 ± 1.34	0.654
HOMA-IR	4.49 ± 2.32	1.71 ± 0.55	< 0.001
Primary infertility, n (%)	70 (49.3)	96 (46.4)	0.669
Good-quality blastocyst, n (%)	81 (57.0)	127 (61.4)	0.487

Note: Data are presented as mean ± SD or n (%). IR, insulin resistance; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.

Pregnancy Outcomes

Pregnancy outcomes of the IR and non-IR groups are compared in Table 2. The clinical pregnancy rate was higher in the IR group compared with the non-IR group (55.6% vs 46.9%), although this difference did not reach statistical significance (P = 0.133; Bonferroni-adjusted threshold: P < 0.025). The early pregnancy loss rate showed a trend toward being higher in the IR group (16.2% vs 9.2%), but this difference also did not reach statistical significance (P = 0.070; Bonferroni-adjusted threshold: P < 0.025). The live birth rate was nearly identical between the two groups: 38.0% (54/142) in the IR group and 37.7% (78/207) in the non-IR group (P = 1.000), suggesting that despite a trend toward higher clinical pregnancy rates in the IR group, this did not translate into a higher live birth rate, likely due to the concurrent trend toward higher early pregnancy loss.

Table 2
Comparison of pregnancy outcomes between IR and non-IR groups

Outcome	IR group (n = 142)	Non-IR group (n = 207)	P value
Clinical pregnancy, n (%)	79 (55.6)	97 (46.9)	0.133
Early pregnancy loss, n (%)	23 (16.2)	19 (9.2)	0.070
Live birth, n (%)	54 (38.0)	78 (37.7)	1.000

Note: Data are presented as n (%). P values were calculated using Chi-square test. For secondary outcomes (clinical pregnancy and early pregnancy loss), Bonferroni correction was applied (α = 0.025).”

Dose-Response Relationship

The dose-response relationship between HOMA-IR as a continuous variable and live birth was evaluated using restricted cubic spline analysis (Fig. 1). The curve remained essentially flat across the entire HOMA-IR distribution, with no significant upward or downward trend, and the 95% confidence interval contained the null value (OR = 1) throughout the range of HOMA-IR values. These findings indicate no significant dose-response relationship between HOMA-IR and live birth, consistent with the null association observed in the binary analysis.

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis showed that IR was not significantly associated with live birth in any of the three models (Table 3). In the unadjusted Model 1, the OR for live birth in the IR group compared with the non-IR group was 1.01 (95% CI: 0.65–1.57, P = 0.948). After adjusting for age and BMI (Model 2), the OR was 1.15 (95% CI: 0.70–1.89, P = 0.577). Further adjustment for blastocyst quality and endometrial thickness (Model 3) yielded an OR of 1.16 (95% CI: 0.71–1.92, P = 0.549). The confidence interval indicates that the data are consistent with effects ranging from a 29% reduction to a 92% increase in the odds of live birth, underscoring the imprecision of the estimate. These findings remained consistent across all models, indicating that the null association between IR and live birth was robust to adjustment for potential confounders. Model fit assessment showed adequate calibration for Model 3 (Hosmer-Lemeshow test: $\chi^2 = 5.34$, df = 8, P = 0.721; AIC = 468.80).

Table 3
Multivariate logistic regression analysis of IR and live birth

Model	Adjusted OR (95% CI)	P value	AIC
Model 1 (unadjusted)	1.01 (0.65–1.57)	0.948	466.90
Model 2 (adjusted for age + BMI)	1.15 (0.70–1.89)	0.577	465.99
Model 3 (adjusted for age + BMI + blastocyst quality + endometrial thickness)	1.16 (0.71–1.92)	0.549	468.80

Note: IR, insulin resistance; OR, odds ratio; CI, confidence interval; BMI, body mass index; AIC, Akaike Information Criterion. Hosmer-Lemeshow test for Model 3: $\chi^2 = 5.34$, df = 8, P = 0.721.

Subgroup and Interaction Analyses

Pre-specified interaction analyses were performed to evaluate whether the association between IR and live birth was modified by BMI or age. No significant interaction was observed between IR and BMI (P-interaction = 0.726) or between IR and age (P-interaction = 0.576), indicating that the null association between IR and live birth was consistent across BMI and age strata.

ROC Curve Analysis

ROC curve analysis was performed to evaluate the predictive value of HOMA-IR for live birth (Fig. 2). The area under the curve (AUC) was 0.533 (95% CI: 0.469–0.598), which is close to 0.5, the value expected

for a test with no discriminatory ability. This finding further supports the null association between HOMA-IR and live birth, confirming that HOMA-IR has poor predictive value for live birth in this population.

Sensitivity Analysis

To assess the robustness of the findings, a sensitivity analysis was performed excluding patients with BMI > 28 kg/m² (n = 27 excluded, remaining n = 322). The results remained consistent with the primary analysis: IR was not significantly associated with live birth in the fully adjusted model (Model 3: OR = 1.09, 95% CI: 0.65–1.83, P = 0.748), confirming that the null association was not driven by extreme obesity.

To further test the robustness of our findings, we performed a sensitivity analysis using an alternative HOMA-IR cutoff of ≥ 2.5. The results remained consistent with the primary analysis: IR was not significantly associated with live birth in the fully adjusted model (Model 3: OR = 1.15, 95% CI: 0.71–1.87, P = 0.569), confirming that the null association was robust to the choice of HOMA-IR cutoff.

Post-hoc Power Analysis

Post-hoc power analysis revealed that the present study (349 patients, with 142 in the IR group and 207 in the non-IR group) had approximately 86% power to detect a significant difference in live birth rates between the IR and non-IR groups, based on effect sizes reported in a previous study in the RIF population (10.34% vs 20.94%) [3].

Discussion

Main Findings

This study systematically evaluated the association between insulin resistance and live birth outcomes in 349 non-PCOS patients undergoing their first frozen-thawed single blastocyst transfer. The main findings can be summarized as follows: First, there was no significant difference in live birth rates between the IR and non-IR groups (38.0% vs 37.7%, P = 1.000). Second, there was no significant dose-response relationship between HOMA-IR as a continuous variable and live birth, as demonstrated by restricted cubic spline analysis [23]. Third, multivariate regression analysis confirmed that IR was not an independent predictor of live birth across all adjusted models (Model 3: OR = 1.16, 95% CI: 0.71–1.92, P = 0.549). Fourth, ROC curve analysis confirmed that HOMA-IR had poor predictive value for live birth (AUC = 0.533, 95% CI: 0.469–0.598), further supporting the null association. These findings remained consistent across multiple analytical approaches, forming a robust chain of evidence.

Interpretation of the Null Findings

The null findings observed in this study may have several explanations. First, first-cycle patients without prior failure may possess relatively preserved "reproductive reserve," including endometrial receptivity

and embryo implantation capacity, which may be sufficient to compensate for the adverse effects of mild-to-moderate IR [8, 9]. Second, the degree of IR in our cohort was mild to moderate (mean HOMA-IR in the IR group: 4.49), and previous evidence suggests that the impact of IR on reproductive outcomes may be dose-dependent [23, 24]—only when IR is sufficiently severe, or when it coexists with other risk factors, does it produce a clinically detectable effect. A dose-response meta-analysis confirmed that each 1-unit increase in HOMA-IR is associated with a 12% increase in miscarriage risk [23], suggesting that the effect of IR may only become clinically significant at higher levels or in the presence of additional risk factors. Consistent with this, a systematic review and meta-analysis demonstrated that recurrent pregnancy loss is associated with a higher degree of insulin resistance, highlighting the importance of screening and treatment of IR in this population [27]. A systematic review on glucose metabolism and recurrent pregnancy loss further supports this threshold effect [24]. The mean HOMA-IR in the IR group was 4.49 (SD 2.32), indicating a moderate level of insulin resistance. Although we cannot exclude the possibility that more severe IR might have a different impact, the restricted cubic spline analysis did not reveal a significant association between HOMA-IR as a continuous variable and live birth across the full range of HOMA-IR values observed in this cohort (Fig. 1). This suggests that, within the range of IR severity present in our study population, IR did not significantly affect live birth outcomes. However, the relatively small number of patients with severe IR (HOMA-IR > 6) in our cohort may have limited our ability to detect a potential threshold effect. Third, while the present study had approximately 86% power to detect the effect size reported in previous studies in the RIF population, it may have been underpowered to detect the smaller effect sizes observed in this first-cycle population. However, the nearly identical live birth rates between the two groups (38.0% vs 37.7%) suggest that even if a small effect exists, its clinical significance would be marginal. A 2024 study on non-linear association between HOMA-IR and live birth in PCOS patients similarly found that the relationship may be complex and population-specific [25].

Comparison with Previous Studies and Population Heterogeneity

Our findings are consistent with studies in the general non-PCOS population [13, 14, 15, 16, 17] but contrast with studies in recurrent implantation failure (RIF) [3, 7] or overweight/obese [10, 18] populations. The most plausible explanation is population heterogeneity [12]. The impact of IR on reproductive outcomes may follow a "threshold-amplification" model: in low-baseline-risk populations (such as young first-cycle patients without prior failure), IR alone may not be sufficient to produce a detectable negative impact on pregnancy outcomes; however, in populations with additional risk factors (such as RIF-related endometrial receptivity impairment or obesity-related chronic inflammation), IR acts as a metabolic stressor that synergizes with these risk factors, amplifying the risk of adverse outcomes to a clinically detectable level. This model provides a conceptual framework for understanding why IR correction with metformin yields substantial benefit in RIF patients [3, 7] but may have limited impact in first-cycle patients. A dose-response meta-analysis of 14 studies confirmed that IR is associated with pregnancy loss in a dose-response manner [23], further supporting the biological plausibility of IR-

mediated reproductive impairment in high-risk populations. A systematic review and meta-analysis of PCOS patients undergoing IVF/ICSI also found that IR significantly impairs clinical pregnancy and live birth rates [19], highlighting the population-specific nature of IR effects.

Consistent with this, a recent Portuguese cohort study characterizing infertile couples undergoing their first IVF cycle reported that advanced female age was a key determinant of reproductive outcomes, while highlighting the variability of demographic factors across different populations [28]. These findings underscore the importance of population-specific characteristics—including ethnicity, age distribution, and healthcare setting—in influencing ART success rates, and reinforce the need for stratified approaches when interpreting metabolic risk factors such as insulin resistance.

Biological Mechanisms and Population-Specific Effects

The negative impact of IR on reproductive outcomes is mediated through well-established pathways: (1) ovarian-embryo level—IR reduces oocyte maturation rates and good-quality embryo rates through hyperinsulinemia-induced androgen excess [6, 7]; (2) endometrial receptivity level—IR impairs endometrial glucose metabolism and decidualization through PI3K/Akt pathway inhibition and GLUT4 dysregulation, with recent evidence suggesting that proteins such as smoothelin-like protein 1 may modulate insulin sensitivity in endometrial epithelial cells [8, 9]; (3) early pregnancy maintenance level—IR increases miscarriage risk through PAI-1-mediated microthrombosis [10].

In addition to these direct endocrine and metabolic pathways, emerging evidence suggests that chronic low-grade inflammation may serve as a bridging mechanism linking IR to reproductive dysfunction [16]. IR is associated with elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which may impair ovarian function, endometrial receptivity, and early placental development. Although the inflammatory axis represents an active area of ongoing research, its potential contribution to the population-specific effects of IR observed in this study cannot be excluded.

The observed pattern of higher clinical pregnancy but higher early pregnancy loss in the IR group, though not statistically significant, warrants mention. While this could reflect a genuine biological effect of IR on early pregnancy maintenance (consistent with the known association between IR and miscarriage risk), it could also be explained by chance, particularly given the limited sample size in the IR group (n = 142). The confidence intervals for these secondary outcomes were wide, and the differences did not survive Bonferroni correction. Future studies with larger sample sizes are needed to clarify whether this pattern represents a true clinical signal.

Mechanistically, the pathological intensity of these mechanisms may depend on an individual's "metabolic reserve" and "endometrial receptivity reserve." In first-cycle patients without prior failure, these reserve capacities may be sufficient to compensate for the adverse effects of mild-to-moderate IR, rendering the negative effects of IR undetectable in terms of final live birth outcomes. This explains why the effect of IR is more pronounced in RIF or obese populations (where baseline reserve is

compromised) than in low-risk populations (where reserve is preserved) [12]. The non-linear association between HOMA-IR and live birth observed in PCOS patients [25] further suggests that the IR-reproductive outcome relationship may be complex and population-specific. Moreover, a large retrospective cohort study found that elevated HOMA-IR values are significantly associated with an increased risk of unexpected poor ovarian response in non-obese women with normal ovarian reserve parameters, providing further evidence for the adverse influence of IR on ovarian response during IVF [17].

Clinical Implications and Population-Specific Strategies

Based on the above findings, this study proposes the following stratified clinical recommendations. For non-PCOS patients without additional risk factors (e.g., RIF, obesity, metabolic syndrome) undergoing their first FET: Routine HOMA-IR screening prior to the first transfer cycle may have limited clinical utility and could be deprioritized in clinical practice. Clinical resources should be preferentially allocated to the refined management of known high-risk populations. For high-risk patients with RIF or obesity: Preoperative HOMA-IR screening should be part of the standard evaluation. Peng et al. [3] have demonstrated that for IR-positive RIF patients, metformin pretreatment can improve live birth rates from 10.34% to 33.51%. A study further confirmed that metformin significantly improves pregnancy outcomes in RIF patients with IR [7]. A systematic review and meta-analysis also supports metformin pretreatment for IR patients undergoing IVF/ICSI [4]. This substantial benefit suggests that correcting IR in high-risk populations has clear and important clinical significance.

Furthermore, our findings suggest that population-wide metabolic screening strategies may not be cost-effective. A stratified screening approach—targeting high-risk subgroups rather than the general first-cycle population—may offer better clinical utility and resource allocation. Recent consensus guidelines [5] also emphasize the importance of risk-stratified management, which aligns with our proposed approach. Based on our findings, we propose the following screening algorithm for clinical practice: For non-PCOS patients without additional risk factors (no RIF, no obesity [BMI < 28 kg/m²], no metabolic syndrome) undergoing their first FET cycle, routine HOMA-IR screening prior to the first transfer is not recommended. The absence of association between IR and live birth in this population suggests that routine screening would offer limited clinical utility and may lead to unnecessary patient anxiety and healthcare costs. For patients with one or more of the following risk factors—RIF, obesity (BMI ≥ 28 kg/m²), or metabolic syndrome—preoperative HOMA-IR screening is recommended as part of the standard evaluation. If HOMA-IR ≥ 2.71, metformin pretreatment may be considered, based on evidence demonstrating improved live birth rates in IR-positive high-risk populations [3, 7].

Our findings suggest that current guidelines recommending universal metabolic screening prior to FET may need to be stratified by patient risk status. Future guidelines should consider distinguishing between first-cycle low-risk patients and high-risk populations such as those with RIF or obesity.

Strengths

This study has several strengths. First, it is the first study specifically focusing on non-PCOS patients undergoing their first FET cycle with a sample size of 349 patients, providing the largest dataset in this specific population to date. Second, the use of a well-validated HOMA-IR cutoff (≥ 2.71) from a large Chinese cohort [14] ensures the applicability of our findings to the local population. Third, the comprehensive statistical approach—including hierarchical regression to reveal the stepwise influence of confounders, RCS analysis to verify the absence of a dose-response relationship [23], and ROC curve analysis to confirm the lack of predictive value—provided robust and multifaceted evidence. Fourth, the transparent reporting of null findings with clear clinical interpretation contributes to counterbalancing publication bias in reproductive medicine.

Limitations

This study has several limitations. First, the single-center retrospective design cannot completely exclude selection and information biases. Although our study included consecutive patients meeting the inclusion criteria, the retrospective design cannot exclude the possibility that patients who underwent HOMA-IR testing may differ from those who did not. Multi-center prospective studies with diverse patient populations are needed for further validation. Second, the study population consisted exclusively of Chinese Han women, and cautious generalization to other ethnic populations is warranted. Third, HOMA-IR was calculated from a single fasting blood sample obtained prior to the FET cycle, which may not fully reflect an individual's true insulin sensitivity over time. However, single-timepoint HOMA-IR measurement is the standard approach in large retrospective cohort studies due to its practicality and established correlation with the gold-standard clamp technique. Fourth, despite adjusting for major clinical confounders including age, BMI, blastocyst quality, and endometrial thickness, we cannot exclude the possibility of residual confounding from unmeasured factors such as lifestyle (diet, exercise, smoking), other metabolic parameters (lipid profile, blood pressure), detailed infertility etiology, and specific treatment protocols. These variables were not consistently recorded in our clinical database, and the available data were insufficient to allow reliable adjustment in the multivariate models. However, the consistency of our findings across multiple analytical approaches—including unadjusted, partially adjusted, and fully adjusted models, as well as sensitivity analysis—suggests that residual confounding is unlikely to fully explain the null association. Furthermore, our single-center design with standardized clinical protocols may have reduced variability in treatment protocols and laboratory conditions. Fifth, the study did not include a metformin intervention arm, so we could not assess whether correcting IR with metformin would alter outcomes in this population—though this question has been addressed in RIF populations [3, 7] and systematic reviews [4]. Sixth, the sample size estimation was based on effect sizes reported in a high-risk RIF population, which may not be directly applicable to first-cycle patients. Although the study had adequate power to detect moderate to large effects (≥ 13 percentage points difference), it may be underpowered to detect smaller but potentially clinically meaningful differences. The relatively wide confidence interval (OR = 1.16, 95% CI: 0.71–1.92) suggests that modest effects cannot be excluded. Future large-scale prospective studies are needed to confirm these findings. Seventh, although the proportion of missing data was low (< 2.5% for all variables) and all outcome variables had complete data, the sparse missingness pattern precluded formal testing of the MCAR

assumption. However, complete-case analysis with such low missingness is unlikely to introduce substantial bias, and the consistent results from sensitivity analyses support the robustness of our findings.

Conclusion

In this cohort of non-PCOS patients undergoing their first FET cycle, insulin resistance was not significantly associated with live birth outcomes. These findings suggest that the impact of IR on reproductive outcomes may be population-specific, with limited clinical significance in first-cycle patients without prior failure. In contrast, IR remains clinically relevant in high-risk populations such as those with RIF or obesity. Routine HOMA-IR screening prior to the first FET cycle may be of limited clinical utility in this specific population, and metabolic screening strategies should be implemented in a risk-stratified manner.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of Huzhou Maternity & Child Health Care Hospital between June 2020 and June 2025. The study protocol was approved by the Institutional Review Board (Approval No: 2026-J-066). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study and the use of anonymized data.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

TFW and YJZ contributed to conceptualization, data curation, formal analysis, methodology, and writing the original draft. LJP and YL contributed to writing, review, and editing. SY and MYZ supervised the study. All authors read and approved the final manuscript.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Figures

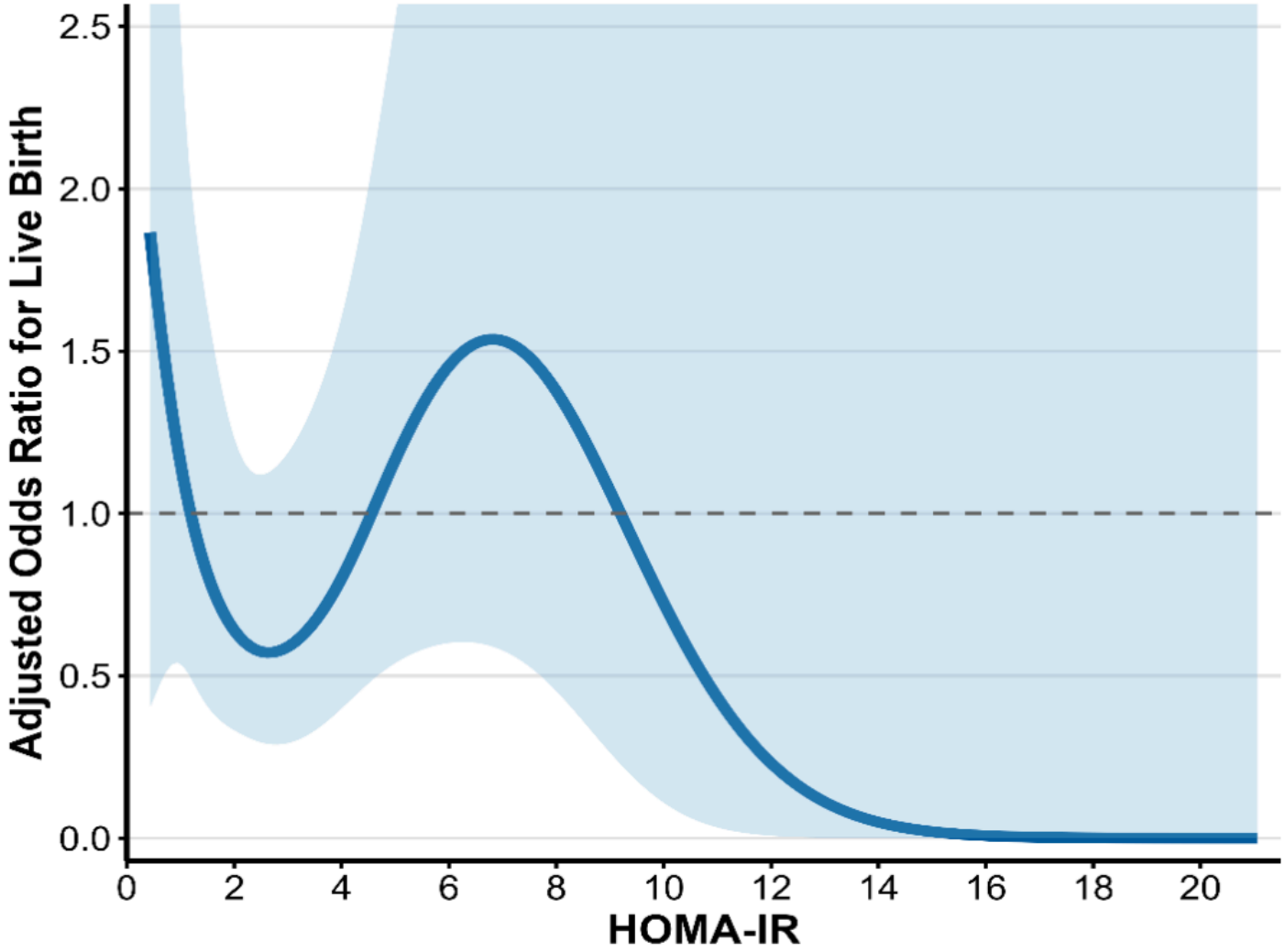


Figure 1

Dose-response relationship between HOMA-IR and live birth using restricted cubic spline analysis. The solid blue line represents the adjusted odds ratio for live birth across the range of HOMA-IR values, with the reference set at the 10th percentile. The shaded blue area represents the 95% confidence interval. The horizontal dashed line at OR = 1 indicates the null value. The model was adjusted for age, BMI, blastocyst quality, and endometrial thickness. The curve remained essentially flat across the entire HOMA-IR distribution, indicating no significant dose-response relationship between HOMA-IR and live birth. P-overall and P-nonlinear values are shown in the figure.

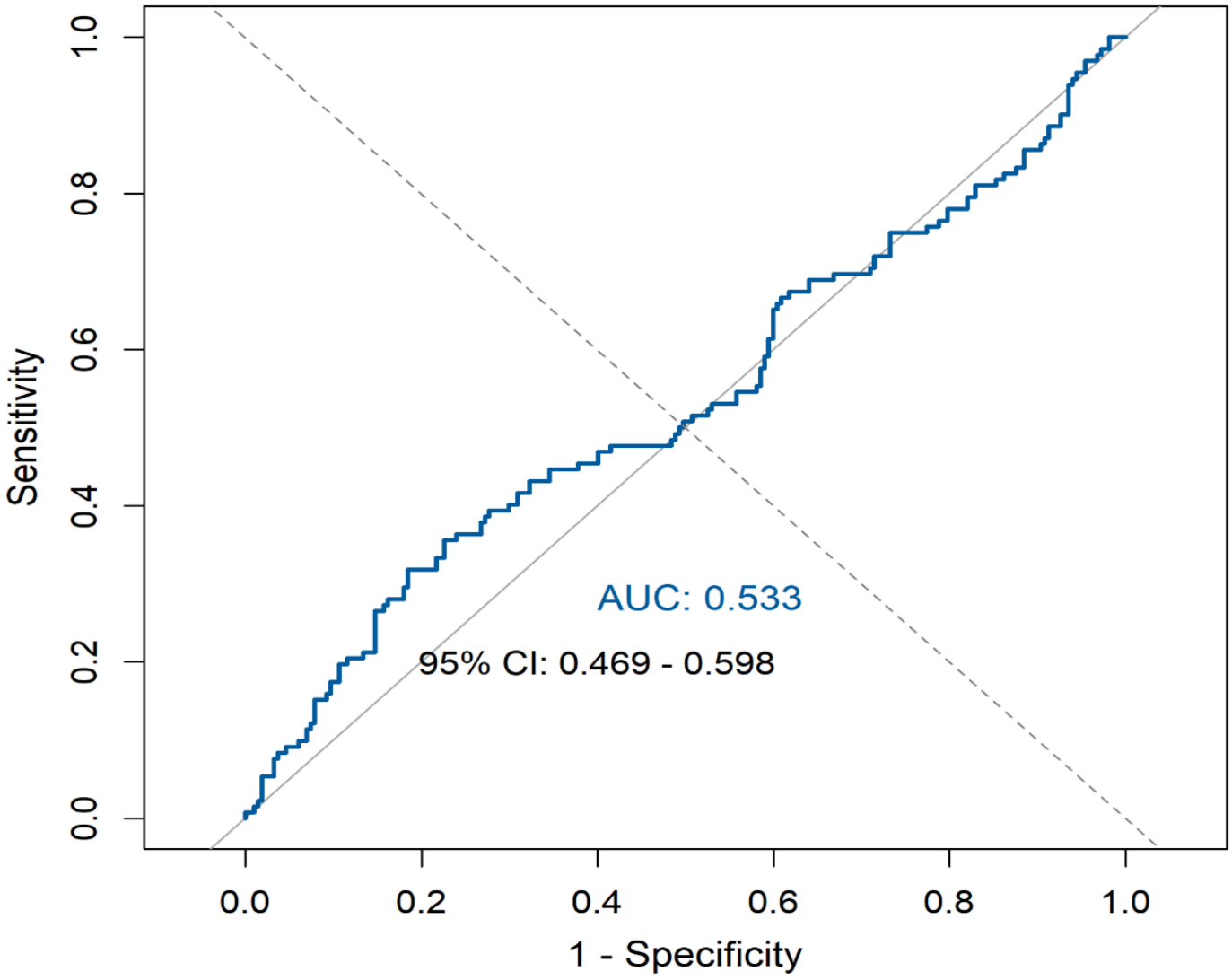


Figure 2

Receiver operating characteristic (ROC) curve of HOMA-IR for predicting live birth in non-PCOS patients undergoing their first frozen-thawed single blastocyst transfer. The blue curve represents the ROC curve. The area under the curve (AUC) was 0.533 (95% CI: 0.469-0.598). The diagonal dashed line represents the reference line of AUC = 0.5, corresponding to a test with no discriminatory ability. The AUC close to 0.5 indicates that HOMA-IR has poor predictive value for live birth in this population.