International Journal of Women's Health

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ORIGINAL RESEARCH

Association Between Triglyceride Glucose Index and Infertility in Reproductive-Aged Women: A Cross-Sectional Study

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Purpose: In recent years, female infertility has become a research hotspot in the field of health management, and its cause may be related to insulin resistance (IR). We used a novel and practical IR indicator, the TyG index to explore its association with infertility.

Patients and Methods: We calculated the TyG index using data from adult women who participated in the National Health and Nutrition Examination Survey (NHANES) from 2013 to 2018. Then, we used multivariate logistic regression, smooth curve fitting, and subgroup analysis to examine the association between the TyG index and infertility in women.

Results: Logistic regression models showed a positive correlation between the TyG index and infertility, which remained significant even after adjusting for all confounders (OR=1.51,95% CI:1.14–2.00, p=0.005). This association was consistent in all subgroups (age, education level, marital status, BMI, smoking, alcohol consumption, hypertension, diabetes, pelvic inflammatory disease/PID treatment, and menstrual regularity in the past 12 months) (p>0.05 for all interactions). However, the diagnostic power of the TyG index for infertility was limited (AUC=0.56, 95% CI: 0.52–0.61).

Conclusion: The TyG index is positively correlated with infertility, but its diagnostic value is limited. Further research is needed on the TyG index as an early predictor of infertility.

Keywords: cross-sectional study, NHANES, infertility, insulin resistance, triglyceride glucose index, TyG

Introduction

Infertility is the inability to conceive after more than 12 months of routine, unprotected sexual activity without the use of contraception.[1,2] In the United States, approximately 7% to 15.5% of women of childbearing age suffer from infertility.[3] The World Health Organization (WHO) has classified infertility as a major public health problem worldwide, affecting about 186 million people, including 15% of women of childbearing age.[4–6] In recent years, infertility has seriously threatened the progress of human civilization, and the US Centers for Disease Control and Prevention has proposed prioritizing the diagnosis and treatment of infertility.[7]

Epidemiological studies have shown that infertility is a fertility disorder caused by a variety of etiologies. Previous studies have shown that alcohol consumption, smoking, education level, and past medical history are associated with female infertility.[8–10] Metabolic abnormalities (such as metabolic syndrome; and obesity) are also prevalent in patients with infertility.[11,12] Studies have shown that insulin resistance (IR) is significantly associated with polycystic ovary syndrome (PCOS) and is a common cause of female infertility.[13] Currently, the "gold standard" for IR is glucose clamps. The steady-state model assessment (HOMA-IR) and quantitative insulin sensitivity check (QUIC) are alternatives to glucose clamp methods for assessing insulin and glucose levels to determine IR,[14,15] but they are expensive and difficult to perform in most underdeveloped regions, limiting the applicability of these indicators. Several recent studies have shown that the triglyceride-glucose (TyG) index, calculated using fasting triglyceride (TG) and glucose levels, is a simple

Received: 30 January 2024
Accepted: 11 May 2024
Published: 27 May 2024

and reproducible marker for measuring insulin resistance (IR).[16,17] Given that the TyG index is an important indicator of insulin resistance, we hypothesize that it is associated with infertility.

A recent cross-sectional study explored the relationship between different insulin resistance substitutes and infertility in women of childbearing age.[18] However, our study aims to explore a potential association between a single TyG index and female infertility using a nationally representative sample of women of childbearing age from the National Health and Nutrition Examination Survey (NHANES). This may provide a new perspective in the field of female reproductive health management.

Material and Methods

Data Source

Data for this study are from the National Health and Nutrition Survey (NHANES), a national program that assesses nutrition and health in the United States, published by the National Center for Health Statistics (NCHS). The survey was conducted using a complex multi-stage probabilistic design to produce a nationally representative sample of non-institutionalized Americans. Participants conducted a family interview to collect data on their health, socioeconomic status, and other factors. A mobile examination facility served as the setting for physical and laboratory examinations.

Study procedures are reviewed and standardized annually by the National Center for Health Statistics (NCHS) Ethics Review Committee (NCHS IRB/ERB Protocol #2011-17). All participants provided informed consent before data collection. For more detailed information, please refer to http://www.cdc.gov/nchs/nhanes/index.htm. As the data in the NHANES database are publicly available, the approval statement and informed consent requirements are waived for this study. This cross-sectional study followed the criteria for enhanced epidemiological observational reporting.[19]

Study Population

Infertility-related health problems were only included in the NHANES cycle from 2013 to 2018. Therefore, we used this time period as our data. In our analysis, we included participants with comprehensive information on infertility and TyG index. Initially, a total of 29,400 participants were included. After excluding male participants (n=14,452), participants lacking data on TyG index (n=10,433), fertility information (n=2120), and participants older than 45 years or younger than 18 years (n=839), our final analysis included 1556 eligible participants (Figure 1).

Triglyceride Glucose Index

Serum levels were measured for participants who were examined in the morning session only. The distribution of serum triglycerides should be estimated only for participants aged 12 and above who fasted for at least 8.5 hours, but less than 24 hours. Fasting total triglyceride concentration was determined using an automated biochemistry analyzer. The TyG index was calculated using the formula: Ln[fasting triglycerides (mg/dL)×fasting plasma glucose (mg /dL)/2].[20]

Infertility

Self-reported infertility data were obtained from the NHANES Reproductive Health Questionnaire (RHQ). The presence of infertility was assessed based on the following question: "Have you ever tried to conceive for at least a year without becoming pregnant?" Women who answered "yes" were considered infertile, while those who answered "no" were considered to be childbearing.

Covariables

Based on the available literature,[21–23] this study included a variety of covariates that may affect the relationship between the TyG index and the risk of developing infertility. Variables considered included age, Race, education level, marital status, poverty income ratio (PIR), body mass index (BMI), hypertension, diabetes, smoking status, alcohol consumption, regular menstrual periods in the past 12 months (yes/no), previous treatment for pelvic infection/pelvic inflammatory disease (yes/no), previous use of birth control pills (yes/no), total cholesterol (TC), fasting triglycerides(TG), fasting

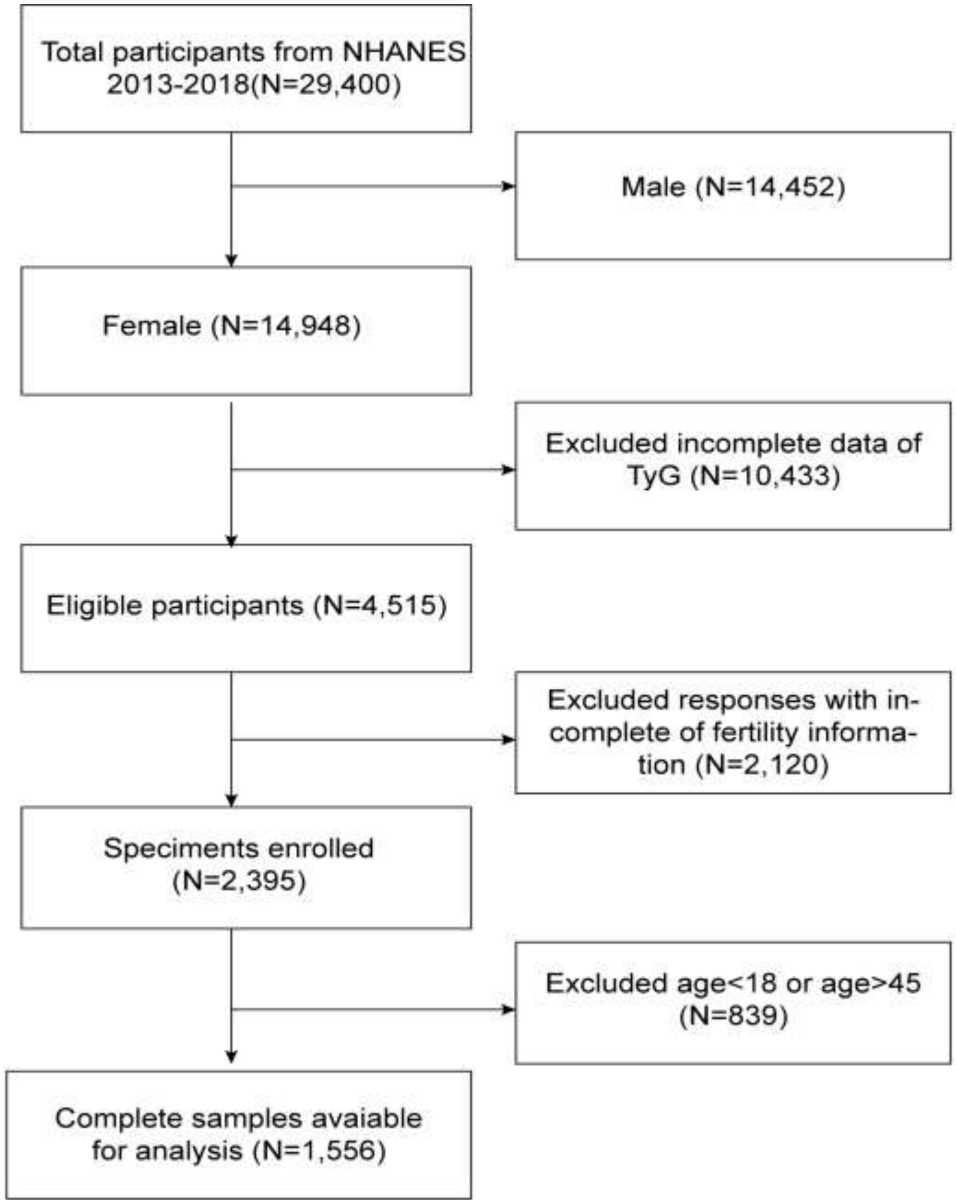

Figure 1 Flow chart of the inclusion and exclusion of study participants.

plasma glucose(FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glycosylated hemoglobin (HbA1c).

Statistical Analysis

All statistical analyses for this study were performed in accordance with Centers for Disease Control and Prevention (CDC) guidelines. Dividing the 2-year weights for each cycle by 2, we arrive at the new sample weights for the combined survey periods.

In descriptive analysis, the two comparison groups identified based on infertility status were assessed using either a weighted Student-*t*-test (for continuous variables) or a weighted chi-square test (for categorical data). Categorical parameters were expressed as proportions, while continuous variables were summarized as means and standard deviations. A multivariate logistic regression model using the NHANES complex sampling design (sampling weights) was used to investigate the association between TyG index and infertility expressing the relationship with OR values and 95%

confidence intervals (95% CI). In the analysis we developed three models, Model I crude model without any adjustment, minimum adjusted (Model II) adjusted age and race and fully adjusted model (Model III) adjusted for all covariate we further assessed the differences in the risk of infertility between the different TyG index tertile groups using lowest tertile group as reference one. Subgroup analysis was used to study the relationship between TyG index and infertility in age, education level, marital status, BMI, smoking, alcohol consumption, hypertension, diabetes mellitus, regular menstruation in the past 12 months, and pelvic inflammatory disease/PID treatment. The interaction test and stratified analysis was used to study whether the relationship between TyG index and infertility was consistent among each subgroup. The method of smooth curve fitting was used to explore the nonlinear relationship between the TyG index and infertility. To determine the diagnostic validity of the TyG index for infertility, the receiver operating characteristic (ROC) curve was used, and the area under the ROC curve (AUC) was calculated to quantify its screening value. All analyses were performed using Empower software and R version 4.3.2. A p-value of <0.05 was considered significant.

Results

Baseline Characteristics

A total of 1556 participants aged 18 to 45 years were included, of whom 169 were infertility patients. The characteristics of the study participants according to their infertility status are shown in Table 1. Self-reported infertility was more prevalent in women who were older, married/cohabiting, had a higher BMI, smoked, drank alcohol, had high blood pressure and diabetes, had received pelvic inflammatory disease/PID treatment, and had irregular menstrual periods. In addition, self-reported infertility was also more prevalent among women with a higher TyG index, averaging 8.34±0.63.

Association Between TyG Index and Infertility

The relationship between the TyG index and infertility is shown in Table 2. Our findings suggest that a higher TyG index is associated with a higher risk of infertility. Both the crude model and the minimum/fully adjusted model showed a positive correlation between the TyG index and infertility. In the fully adjusted model, participants had a 51% increased risk of infertility for each unit increase in the TyG index (OR=1.51, 95% CI:1.14–2.00). This association remained statistically significant after converting the TyG index from a continuous variable to a categorical variable (tertiles). Individuals in the highest TyG index had a 72% increased risk of infertility compared to participants in the lowest TyG

Table 1 Baseline Characteristics of Participants

Characteristic	Total	Control	Infertility	*P*-value
	N=1556	N=1387	N=169	
Age, (years)	31.40 ± 8.07	30.92 ± 8.03	34.88 ± 7.51	<0.001
Poverty income ratio (PIR)	2.56 ± 1.64	2.55 ± 1.64	2.69 ± 1.66	0.294
Fasting Glucose (mg/dl)	98.33 ± 22.05	97.77 ± 20.09	102.40 ± 32.63	0.007
Total Cholesterol (mg/dl)	179.37 ± 35.88	179.25 ± 35.73	180.25 ± 36.97	0.718
HDL Cholesterol (mg/dl)	57.76 ± 15.97	58.27 ± 15.99	54.04 ± 15.35	<0.001
LDL cholesterol (mg/dl)	103.47 ± 30.50	103.04 ± 30.37	106.65 ± 31.27	0.123
Triglyceride (mg/dl)	91.30 ± 62.01	90.21 ± 59.94	99.22 ± 74.88	0.061
HbA1c (%)	5.34 ± 0.67	5.31 ± 0.63	5.51 ± 0.94	<0.001
TyG	8.22 ± 0.63	8.21 ± 0.63	8.34 ± 0.63	0.005
Race, (%)				0.486
Mexican American	11.93	12.26	9.56	
Other Hispanic	7.89	8.03	6.93	
Non-Hispanic white	55.90	55.07	61.89	
Non-Hispanic black	13.16	13.26	12.41	
Other Races	11.12	11.38	9.21	

(*Continued*)

Table 1 (Continued).

Characteristic	Total N=1556	Control N=1387	Infertility N=169	*P*-value
Education level (%)				0.253
Less than high school	12.04	11.82	13.57	
High school	20.72	21.38	16.27	
Above high school	67.23	66.80	70.17	
Marital status				<0.001
Married or living with partner	60.48	57.47	80.92	
Living alone	39.52	42.53	19.08	
BMI (kg/m^2)				<0.001
<25	36.57	38.18	24.95	
≥25	63.43	61.82	75.05	
Smoking status (%)				0.027
Yes	31.61	30.64	38.59	
No	68.39	69.36	61.41	
Alcohol drinking status (%)				0.007
Yes	7.70	6.92	12.80	
No	92.30	93.08	87.20	
Hypertension (%)				<0.001
Yes	14.10	12.55	25.35	
No	85.90	87.45	74.65	
Diabetes (%)				<0.001
Yes	4.78	3.91	11.03	
No	95.22	96.09	88.97	
Had regular periods in past 12 months (%)				<0.001
Yes	89.33	90.33	82.14	
No	10.67	9.67	17.86	
Ever treated for a pelvic infection/PID (%)				0.003
Yes	4.25	3.69	8.28	
No	95.75	96.31	91.72	
Ever taken birth control pills (%)				0.140
Yes	73.18	72.56	77.65	
No	26.82	27.44	22.35	

Table 2 Associations Between TyG Index and the Risk of Infertility

TyG Index	Infertility [OR (95% CI)]
Crude model (model 1)	
Continuous	1.41 (1.12, 1.79)
Categories	
Quartile 1	Reference
Quartile 2	1.51 (0.99, 2.29)
Quartile 3	1.65 (1.10, 2.49)
Minimally adjusted model (model 2)	
Continuous	1.45 (1.14, 1.85)
Categories	
Quartile 1	Reference
Quartile 2	1.52 (1.00, 2.32)
Quartile 3	1.72 (1.13, 2.63)

(*Continued*)

Table 2 (Continued).

TyG Index	Infertility [OR (95% CI)]
Fully adjusted model (model 3)	
Continuous	1.51 (1.14, 2.00)
Categories	
Quartile 1	Reference
Quartile 2	1.78 (1.12, 2.83)
Quartile 3	1.72 (1.05, 2.84)

Notes: In sensitivity analysis, the TyG index was converted from a continuous variable to a categorical variable (tertiles). Model 1, No covariates were adjusted; Model 2, Adjusted for age and race; Model 3, Adjusted for age, ratio of family income to poverty, race, education level, marital status, smoked at least 100 cigarettes, had at least 12 alcohol drinks/1 year, ever treated for a pelvic infection/PID, ever taken birth control pills, had regular periods in past 12 months.
Abbreviations: 95% CI, 95% Confidence Interval; OR, Odds Ratio.

index (OR=1.72,95% CI:1.05–2.84) (Table 2). Additionally, we further investigated the relationship between the TyG index and the risk of infertility using smooth curve fitting, which showed a positive nonlinear relationship (Figure 2).

Subgroup Analyses

We conducted subgroup analyses to assess the stability of the relationship between TyG index and infertility across various factors. We found that in participants aged ≥35 years, each unit increase in TyG index was associated with an 81% higher likelihood of infertility (OR:1.81,95% CI:1.10–2.99). As shown in Table 3, factors such as age, education level, marital status, BMI, smoking, alcohol consumption, hypertension, diabetes, pelvic inflammatory disease/PID treatment, and menstrual regularity in the past 12 months did not significantly affect the positive correlation between TyG and infertility (all $p>0.05$).

Diagnostic Efficacy of TyG Index for Infertility

The diagnostic validity of the TyG index was analyzed using the receiver operating characteristic (ROC) curve (Figure 3). The cut-off value for the diagnosis of infertility was 7.725 (AUC=0.56, 95% CI:0.52–0.61, sensitivity=89%, specificity=24.2%). AUC values above 0.5 are considered to have diagnostic utility.

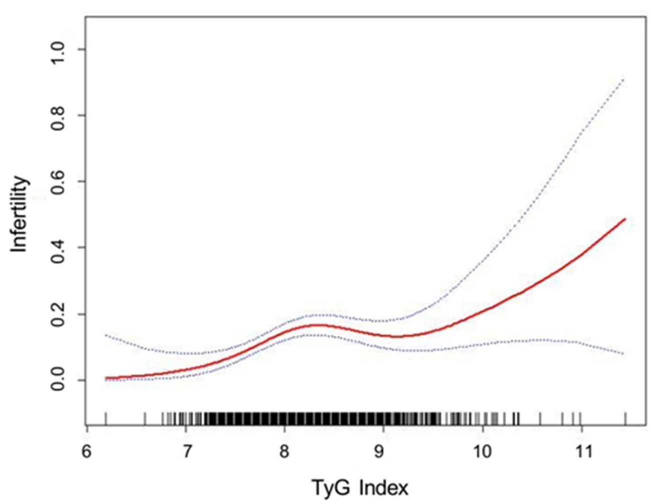

Figure 2 Smoothing curve fitting of TyG index and infertility.

Table 3 Subgroups Analyses of the effect of TyG Index on Infertility

Subgroup	Infertility [OR (95% CI)]	*P* for Interaction
Age		0.056
<35	0.96 (0.62, 1.47)	
≥35	1.81 (1.10, 2.99)	
Marital status		0.843
Married or living with partner	1.04 (0.74, 1.46)	
Living alone	1.11 (0.65, 1.90)	
Education level		0.633
Less than high school	1.19 (0.56, 2.53)	
High school	1.08 (0.51, 2.28)	
Above high school	0.98 (0.68, 1.41)	
BMI		0.837
<25	1.17 (0.57, 2.40)	
≥25	1.08 (0.78, 1.49)	
Smoking status		0.820
Yes	1.27 (0.77, 2.10)	
No	1.18 (0.78, 1.77)	
Alcohol drinking status		0.765
Yes	0.98 (0.32, 3.04)	
No	1.18 (0.84, 1.65)	
Diabetes		0.333
Yes	1.75 (0.68, 4.54)	
No	1.07 (0.78, 1.48)	
Hypertension		0.210
Yes	0.79 (0.46, 1.36)	
No	1.19 (0.84, 1.68)	
Had regular periods in past 12 months		0.113
Yes	1.14(0.82,1.59)	
No	3.07(0.91,10.39)	
Ever treated for a pelvic infection/PID		0.110
Yes	3.04(0.85,10.88)	
No	1.09(0.79,1.51)	

Discussion

The study, which evaluated the relationship between TyG index and infertility through the NHANES database, showed that TyG index levels were significantly higher in the infertility group than in the non-infertility group. Smooth curve fitting was used to demonstrate a positive linear relationship between TyG index and infertility. Importantly, there was still a statistically significant correlation between TyG index and infertility after adjusting for multiple confounders in the fully adjusted model, suggesting that TyG index may be used as a simple indicator to assess infertility in the future. However, the diagnostic validity of the TyG index for infertility is limited, and further research is needed to fully explore its potential as an early risk predictor of infertility.

The TyG index, consisting of triglycerides and fasting blood glucose, has been shown to be a good predictor of insulin resistance. Infertility and insulin resistance (IR) have been found to be closely related (IR),[13] with a significantly increased risk of infertility in young adults and non-diabetic individuals as insulin resistance increases.[24,25] In addition, PCOS affects 5% to 15% of women of childbearing age worldwide and is a major cause of infertility. Its occurrence is associated with insulin resistance and glucose tolerance disorders.[26] In this setting, IR is generally considered to be the primary pathophysiological mechanism leading to infertility in PCOS.[27,28] At the same time, IR also has a negative impact on assisted reproductive technology (ART). Song et al[29] conducted a retrospective study of 329 women undergoing IVF, and the results showed a significant reduction in clinical pregnancy rates in participants with higher HOMA-IR and BMI. Another prospective cohort study from China found that the proportion of eggs and embryo quality decreased in infertility patients without PCOS.[30]

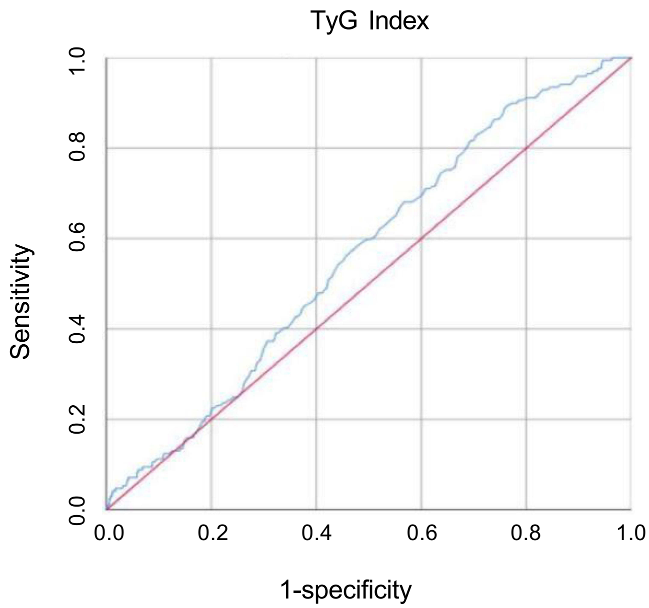

Figure 3 ROC curve of the TyG index used to diagnose infertility.

In our study, an elevated TyG index was observed to be associated with a higher prevalence of infertility in participants over 35 years of age. In Integral Chinese, most women aged 36 years or older had a reduced number of oocytes and an increased risk of infertility.[31] In the current study, we confirmed through interaction tests that age had no significant effect on the outcome of the correlation. We believe a plausible explanation for this is that an increase in the TyG index may be associated with a greater degree of insulin resistance (IR), a higher prevalence of IR-related comorbidities, and ultimately an increased risk of infertility due to the increase in comorbidities.

The details of the mechanism that explains the relationship between the TyG index and infertility still need to be further explored, and there are several possible explanations. First, insulin resistance (IR) may affect oocyte quality by decreasing mitochondrial function. Studies have shown that mitochondrial dysfunction can disrupt the insulin signaling pathway and impair glucose metabolism.[32] Secondly, IR has a regulatory effect on oocyte energy metabolism. Glucose transporter (GLUT4) is key to intracellular energy supply, and the decrease in GLUT4 expression in PCOS patients with IR affects the uptake and utilization of glucose by ovarian granulosa cells. This ultimately reduces oocyte quality and affecting reproductive function.[33] Additionally, hyperandrogenism is thought to play an important role in PCOS leading to infertility. Systemic hyperandrogenism perpetuates abnormal glucose/insulin metabolism, decreases hepatic sex hormone-binding globulin production, alters hypothalamic-pituitary-ovarian (HPO) signaling, and dysregulates growth factor activity (IGF1, GDF9, activin, albumin, etc.), all of which exacerbate the sensitive feedback system of the reproductive cycle.[34,35] Studies have also found improved fertility in women with hyperandrogenic PCOS treated with androgen blockers such as fluticasone.[36] Finally, in addition to affecting oocyte quality, IR also affects endometrial tolerance through multiple pathways, including chronic inflammation. This, in turn, affects female fertility.[37–39]

A recent cross-sectional study found that the TyG-BMI index had a higher predictive power than the TyG index in assessing infertility in women of childbearing age.[18] However, our findings suggest that the TyG index has limited ability to diagnose infertility (AUC=0.56), which is similar to our findings. This may be because the TyG-BMI index contains not only markers of insulin resistance, but also BMI indicators to measure obesity. The combination of the two will inevitably improve the predictive power. However, our study only explored the association of a single index with infertility in women of childbearing age. In the future, it is necessary to further explore the joint index to evaluate its potential for prediction.

The advantage of our study is the use of a complex multi-stage probabilistic sampling design, which increases the reliability and representativeness of our research. Our study also had limitations. First of all, due to the cross-sectional design of the analysis, we were unable to determine the causal relationship between TyG index and infertility. In addition, due to limitations in the NHANES database, the definition of female infertility outcome variables is based on self-report and, while a useful measure, may be less accurate in some cases. For example, women who are planning to become pregnant for less than a year but have already sought medical attention may be included, as well as other definitions of infertility (ie, medical records or time spent pregnant) that may influence the probability of developing infertility.[40,41] Further research needs to consider the implications of different definitions. Finally, while we adjust for some confounders, it is not possible to completely rule out the influence of other possible confounders. This study confirms the association between the TyG index and infertility, despite these limitations.

Conclusion

Current research shows that the TyG index of adult women in the United States is positively correlated with infertility. However, the TyG index has limited diagnostic validity for infertility. Further research is needed to fully explore the potential of the TyG index as a predictor of infertility.

Data Sharing Statement

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes.

Acknowledgments

The authors express their gratitude towards the participants and staff of the NHANES database for their noteworthy contributions.

Funding

This study was supported by the Wuxi Taihu Lake Talent Plan, Supports for Leading Talents in Medical and Health Profession (Mading academician, 4532001THMD), and grant from the Fund of Wuxi Health Commission(M202214).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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