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Effect of serum uric acid level on reproductive outcome in women without polycystic ovary syndrome undergoing in vitro fertilization

Leizhen Xia[1,2†], Lu Fan[1†], Jialyu Huang[1,2†], Yan Zhao[1], Lifeng Tian[1], Houyang Chen[1,2], Li Cai[3], Qiongfang Wu[1*] and Leixiang Xia[4*]

Abstract

Background Prior research showed that elevated serum uric acid (SUA) levels in women with polycystic ovary syndrome (PCOS) before in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI) treatment can lead to a lower rate of live birth and an increased risk for low birthweight. Nonetheless, it is not known whether elevated SUA results in similar reproductive outcome in women without PCOS. This study aimed to exploring the relationship between pre-pregnancy SUA levels and reproductive outcomes in non-PCOS women undergoing IVF/ICSI treatment.

Methods This single-center, retrospective study included 13,325 women without PCOS undergoing their first IVF/ICSI fresh embryo transfer cycles from January 2014 to December 2022 at a university-affiliated reproductive medicine center in China. The trends for pregnancy, obstetric and perinatal outcomes across quartiles of SUA levels were assessed. A logistic regression analysis was applied to control for baseline and cycle characteristics. Generalized addition model was used to draw spline smoothing plot.

Results There was no significant decreasing or increasing trend in the clinical pregnancy rate and live birth rate with the increase in quartiles of SUA levels. For Obstetric and perinatal outcomes following a single live birth, the percentage of hypertensive disorders in pregnancy (1.6–4.1%, P_{trend}<0.001), gestational diabetes mellitus (5.9–13.9%, P_{trend}<0.001), premature rupture of membranes (0.6–1.5%, P_{trend}=0.016), preterm birth (6.3–9.2%, P_{trend}=0.009), macrosomia (2.3–5.5%, P_{trend}<0.001), large for gestational age (10.8–14.9%, P_{trend}=0.002) all increased significantly from the lowest quartile to the highest. Logistic regression results showed that compared with those in quartile 1, the risk of maternal and infant complications mentioned above was still significantly higher in quartile 4 after adjusting for reproductive related factors. When further confounding factors were added, including body mass index (BMI), blood pressure, fasting blood glucose, and blood lipids related indicators, only gestational diabetes mellitus and macrosomia showed a significant increase.

†Leizhen Xia, Lu Fan, Jialyu Huang are co-first authors. These authors have contributed equally to this work.

*Correspondence:
Qiongfang Wu
wuqiongfang898@sina.com
Leixiang Xia
495380513@qq.com

Full list of author information is available at the end of the article

Conclusion In women without PCOS, SUA levels before IVF/ICSI treatment do not affect the probabilities of clinical pregnancy and live birth. An elevated SUA level is associated with an increased risk for hypertensive disorders in pregnancy, gestational diabetes mellitus, premature rupture of membranes, preterm birth, macrosomia, and large for gestational age. For gestational diabetes mellitus and macrosomia, the association is independent of BMI, blood pressure, blood glucose, and blood lipid.

Keywords Uric acid, In vitro fertilization, Live birth, Obstetric outcomes, Perinatal outcomes

Introduction

In recent years, there has been a rapid escalation in the prevalence of infertility. For women unable to conceive through natural processes, assisted reproductive technology (ART) represents one of the most efficacious interventions to achieve successful pregnancies. Distinct from spontaneous conception, in vitro fertilization and embryo transfer (IVF-ET) necessitate an extended treatment duration and incur substantial financial expenditure [1]. Consequently, patients conceiving via IVF-ET harbor elevated anticipations for propitious pregnancy outcomes. With unhealthy lifestyles and intricate dietary patterns, the prevalence of metabolic disorders among the infertile patients escalates annually [2]. However, the interrelation between diverse metabolic disorders and reproductive dysfunction remains ambiguous. Therefore, analyzing the clinical metabolic markers of infertile patients and implementing appropriate secondary prevention strategies is crucial for enhancing their pregnancy outcomes.

Uric acid (UA) serves as a biomarker indicative of maternal metabolic health, readily ascertainable through blood assays in clinical practice [3]. Within physiological range, serum UA (SUA) is a major contributor to antioxidant potential in vivo [4]. However, in conditions where antioxidants like ascorbic acid are diminished, SUA contributes to the pathogenesis of numerous diseases through oxidative stress within the organism [5]. Research indicates that elevated levels of SUA are recognized as markers for pathological processes implicated in female reproductive disorders [6]. During physiological pregnancies, elevated levels of SUA are deemed risk factors for pregnancy complications and adverse outcomes for both mother and infant, particularly during the first trimester [7]. SUA levels prior to 15 weeks of gestation are significantly correlated with the risk of gestational diabetes mellitus, while levels before 20 weeks are linked to pre-eclampsia [8, 9]. However, research on the adverse reproductive outcomes associated with pre-pregnancy SUA levels remains scant. A recent high-quality retrospective study suggests that elevated SUA levels may negatively influence the reproductive outcomes of women with polycystic ovary syndrome (PCOS) undergoing IVF-ET treatment [10]. It is interesting to explore whether high SUA levels in non-PCOS women also lead to adverse reproductive outcomes, and to provide more direct evidence for the relationship between SUA and ART outcomes.

Materials and methods

Study design and participants

This was a single-center retrospective cohort study. A total of 13,325 infertile women without PCOS undergoing their first IVF or intracytoplasmic sperm injection (ICSI) cycles with fresh embryo transfer were included at the Reproductive Medicine Center of Jiangxi Maternal and Child Health Hospital between January 2014 and December 2022. The inclusion criteria were as follows: (i) first IVF or ICSI treatment; (ii) embryo transfer in fresh cycles. The exclusion criteria were as follows: (i) no UA test was performed in the 3 months prior to stimulation; (ii) PCOS; (iii) sperm donation cycles; (iv) over 40 years old; (v) uterine malformations or diseases such as unicornuate uterus, bicornute uterus, uterine mediastinum, uterine fibroids, uterine adenomyosis, and endometrial polyps; (vi) chronic diseases such as obesity, diabetes, hypertension, hyperthyroidism, hypothyroidism, cardiovascular disease, liver disease, kidney related diseases, and autoimmune diseases; and (vii) lost to follow-up (Fig. 1). The study was approved by the Reproductive Medicine Ethics Committee of Jiangxi Maternal and Child Health Hospital (No. SZYX-202411), and was conducted in accordance with the Declaration of Helsinki.

In vitro fertilization procedures

Since all patients underwent fresh embryo transfer, the mild stimulation and progestin-primed ovarian stimulation protocols were excluded, as they typically required freezing of all embryos. Controlled ovarian stimulation was carried out using a gonadotropin-releasing hormone (GnRH) agonist protocol and a flexible GnRH antagonist protocol [11]. The starting dose of gonadotropin (Gn) was determined based on a comprehensive assessment of the maternal age, body mass index (BMI), ovarian reserve, and previous medical history, and subsequently adjusted according to the number and development of follicles, endometrial thickness, and serum hormone levels. When at least 2 dominant follicles were ≥18 mm in diameter, the 250 μg of recombinant human chorionic gonadotropin (hCG) (Azer, Merck Serono, Darmstadt, Germany) was injected to trigger. Oocyte retrieval was performed with transvaginal ultrasound guidance 36–38 h after the

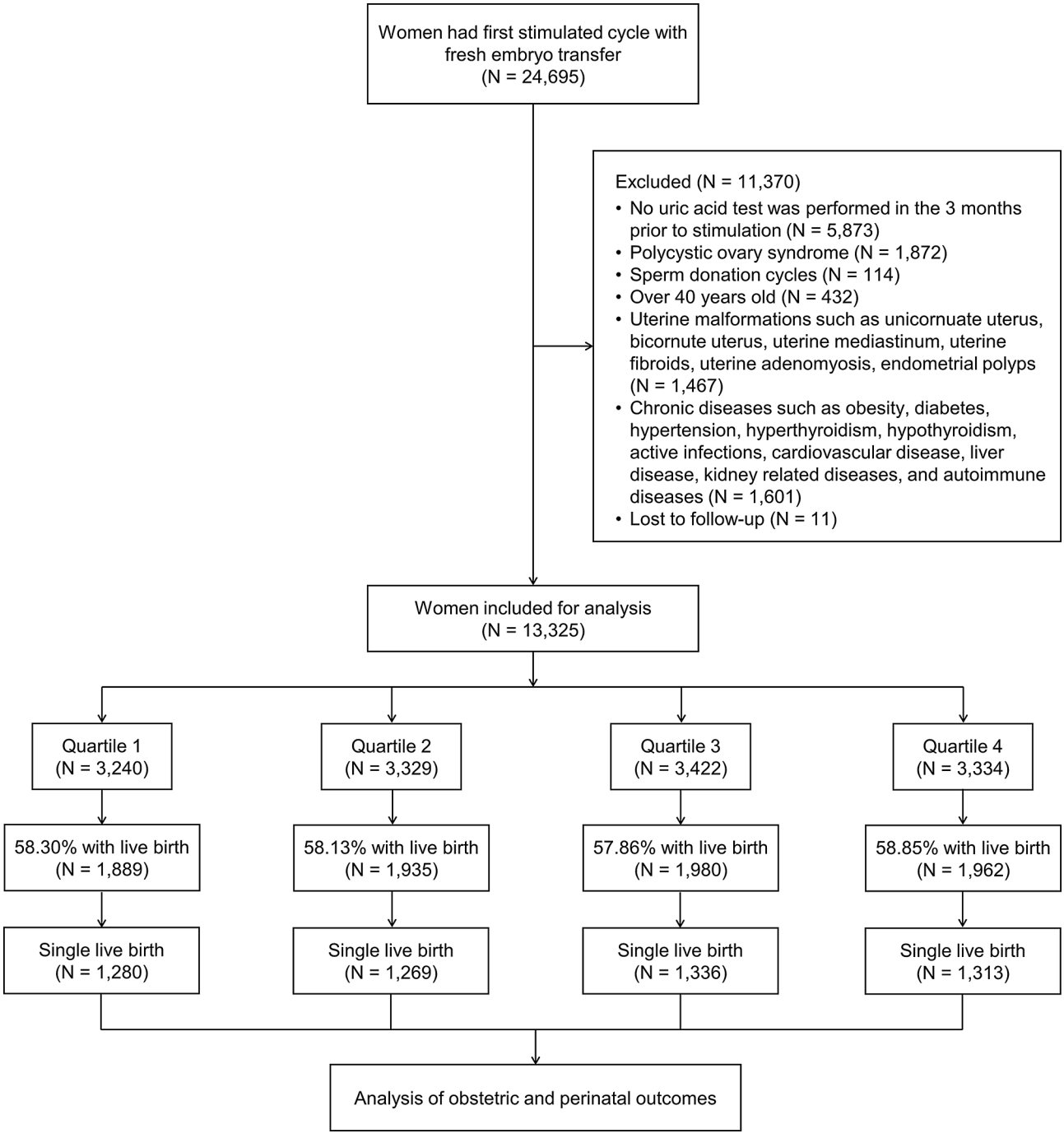

Fig. 1 Flowchart of selection for the study

trigger. Fertilization was carried out using conventional IVF and/or ICSI depending on the semen quality. Pronuclear assessment was conducted 16–18 h after fertilization. The fertilized oocytes were then cultured in G1-plus medium (Vitrolife, Sweden) until day 3 to form cleavage embryos, and based on embryo quality, a decision was made whether to continue to blastocyst culture. From the day of oocyte retrieval, luteal support was initiated. On the 3rd to 5th day of luteal support, embryologists selected one to two high-quality cleavage embryos or blastocysts for transfer.

Exposure and outcome measures

In this investigation, SUA was routinely measured for all women undergoing their first IVF/ICSI cycle using the uricase peroxidase technique on automatic analyzers with proprietary kits (AU 5800, Beckman Coulter). Blood samples were collected prior to controlled ovarian

hyperstimulation following a minimum of eight hours of overnight fasting. These parameters were quantified via a colorimetric assay (Advia2400, Siemens, IL, USA) with a detection threshold of 10 mg/dl and exhibited a coefficient of variation of 9.0%. The normative range for SUA concentrations, as assessed by the AU 5800, spans from 155 to 357 mmol/L.

Biochemical pregnancy was defined as a serum β-hCG level exceeding 5 IU/L on day 12 after cleavage-stage embryo transfer or day 10 after blastocyst transfer. Biochemical pregnancy loss was defined as the loss of hCG positivity prior to clinical pregnancy in women with a biochemical pregnancy. Clinical pregnancy was defined as the presence of one or more gestational sacs detected by transvaginal ultrasound one month after embryo transfer. The implantation rate was calculated as the number of gestational sacs divided by the number of transferred embryos. The termination of a pregnancy before 24 weeks of gestation was considered a miscarriage. Live birth was defined as a viable infant delivered after a complete gestational period of 24 weeks or more.

The obstetric and perinatal outcomes included hypertensive disorders in pregnancy (HDP), gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy, abnormal placentation, polyhydramnios, oligohydramnios, premature rupture of membranes (PROM), postpartum hemorrhage, preterm birth (PTB), very PTB, low birthweight (LBW), very LBW, macrosomia, small for gestational age (SGA), large for gestational age (LGA), and major birth defects. We defined PTB, very PTB, and postterm birth as gestational age <37, <32, and ≥ 42 weeks, respectively. LBW, very LBW and macrosomia were identified as birthweight <2500, <1500 and ≥ 4000 g, respectively. The determination of SGA and LGA was based on the birthweight reference for Chinese populations adjusted for sex and gestational age [12]. SGA was defined as birthweight lower than the 10th percentile of the referential birthweight, while LGA was defined as birthweight higher than the 90th percentile of the referential birthweight. Birth defects were categorized according to the International Classification of Diseases-10 codes Q00-Q99.

Statistics analysis

Continuous variables were tested for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. All continuous variables were found to be non-normally distributed and represented as median (interquartile range). For categorical variables, data were expressed as numbers and percentages of the total. Based on the median and interquartile range of SUA, participants were divided into four groups using the quartile method: quartile 1 (Q1: UA 69 to 245 μmol/L), quartile 2 (Q2: UA, 246 to 281 μmol/L), quartile 3 (Q3: UA, 282 to 321 μmol/L), and quartile 4 (Q4: UA, 322 to 828 μmol/L). The quartile method refers to dividing individuals into four groups based on the three nodes of the 25th (P25), 50th (P50) and 75th (P75) percentiles of SUA levels (Q1: minimum to P25; Q2: P25 to P50; Q3: P50 to P75; Q4: P75 to maximum). All baseline characteristics and clinical outcomes for each quartile were evaluated for trends across SUA quartiles by applying the Jonckheere-Terpstra test to continuous variables and the Cochran-Armitage trend tests to categorical variables, respectively. For reproductive outcomes with significant trend differences, the Bonferroni correction was applied for multiple comparisons.

Since the analysis of only complete cases (i.e., omitting patients with missing values) might decrease analytical power and yield biased results, we performed multiple imputation analysis using the fully conditional specification (FCS) method. The missing values were imputed 5 times by the FCS method of multiple imputation. A logistic regression analysis was performed to study the independent effect of SUA after controlling for potential confounders, and the crude and adjusted odds ratios (ORs) were presented with quartile 1 as the reference. Two adjusted ORs were calculated depending on the confounding factors added. In addition to BMI, blood pressure, fasting blood glucose, and blood lipids related indicators, all baseline and clinical treatment characteristics in Tables 1 and 2 were adjusted in model a; BMI, blood pressure, fasting blood glucose, and blood lipids related indicators were additionally included in model b. Besides, a sensitivity analysis was conducted to exclude women with ovulatory dysfunction, endometriosis, immune infertility and diminished ovarian reserve, focusing solely on those with tubal factor, male factor, or unexplained infertility. At last, spline smoothing plots were applied to illustrate the relationship between SUA as a continuous variable and relevant reproductive outcomes using a generalized additive model. In this study, the SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was employed for all statistical analyses. Multiple imputation was performed by the PROC MI procedure, and the PROC MIANALYZE procedure combines the results of the analyses of imputations and generates valid statistical inferences. Statistical analysis was tested on two-sided settings, with $p<0.05$ considered as statistically significant.

Results

Baseline and treatment characteristics

In total, 13,325 patients fulfilled the eligibility criteria. According to SUA quartiles, the baseline characteristics of patients without PCOS were presented in Table 1. Compared with women in the lower SUA quartiles, women in the higher quartiles tended to have higher antral follicle count, BMI, systolic pressure, diastolic

Table 1 Baseline characteristics of patients according to serum uric acid quartiles

	Quartile 1 ($n=3240$)	Quartile 2 ($n=3329$)	Quartile 3 ($n=3422$)	Quartile 4 ($n=3334$)	P_{trend}
Serum uric acid (μmol/L)	224 (205–235)	264 (255–273)	300 (291–310)	354 (335–385)	< 0.001
Age (years)	30 (27–33)	30 (27–33)	30 (27–33)	30 (27–33)	0.480
Infertility duration (years)	3 (2–5)	3 (2–5)	3 (2–5)	3 (2–5)	0.556
Nulligravida, n (%)	1228 (37.9)	1228 (36.9)	1329 (38.8)	1308 (39.2)	0.113
Nulliparity, n (%)	2058 (63.5)	2151 (64.6)	2315 (67.7)	2316 (69.5)	< 0.001
Prior preterm birth, n (%)	54 (1.7)	45 (1.4)	40 (1.2)	45 (1.4)	0.215
Prior cesarean section, n (%)	424 (13.1)	417 (12.5)	412 (12)	386 (11.6)	0.050
Infertility diseases					
Tubal factor, n (%)	2476 (76.4)	2570 (77.2)	2608 (76.2)	2507 (75.2)	0.156
Male factor, n (%)	954 (29.4)	902 (27.1)	911 (26.6)	888 (26.6)	0.011
Ovulatory dysfunction, n (%)	125 (3.9)	156 (4.7)	165 (4.8)	226 (6.8)	< 0.001
Endometriosis, n (%)	265 (8.2)	213 (6.4)	191 (5.6)	170 (5.1)	< 0.001
Diminished ovarian reserve, n (%)	266 (8.2)	262 (7.9)	241 (7.0)	250 (7.5)	0.152
Unexplained, n (%)	206 (6.4)	223 (6.7)	244 (7.1)	236 (7.1)	0.187
Antral follicle count	12 (9–15)	12 (9–16)	12 (9–16)	12 (9–17)	< 0.001
Basal FSH (mIU/mL)	6.2 (5.6–7.5)	6.1 (5.1–7.2)	6.1 (5.1–7.3)	5.9 (5.0–7.0)	< 0.001
Body mass index (kg/m2)	20.5 (19.1–22.0)	20.9 (19.5–22.8)	21.4 (19.8–23.4)	22.9 (20.8–25.2)	< 0.001
Systolic pressure (mmHG)	109 (101–118)	109 (102–118)	110 (102–120)	112 (104–120)	< 0.001
Diastolic pressure (mmHG)	65 (60–72)	66 (60–73)	66 (60–73)	68 (61–75)	< 0.001
FBG (mmol/L)	4.9 (4.6–5.2)	4.9 (4.6–5.2)	5.0 (4.6–5.3)	5.0 (4.7–5.3)	< 0.001
Blood lipids related indicators					
TG (mmol/L)	0.7 (0.6-1.0)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	1.0 (0.8–1.5)	< 0.001
TC (mmol/L)	4.1 (3.7–4.6)	4.1 (3.7–4.6)	4.2 (3.7–4.8)	4.3 (3.9–4.9)	< 0.001
HDL (mmol/L)	1.4 (1.2–1.7)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.3 (1.1–1.6)	< 0.001
LDL (mmol/L)	2.4 (2.0-2.8)	2.4 (2.0-2.9)	2.5 (2.1-3.0)	2.6 (2.1–3.1)	< 0.001
Year of treatment, n (%)					< 0.001
2014.01-2016.12	792 (24.4)	924 (27.8)	957 (28.0)	881 (26.4)	
2017.01-2019.12	1587 (49.0)	1588 (47.7)	1487 (43.5)	1321 (39.6)	
2020.01-2022.12	861 (26.6)	817 (24.5)	978 (28.6)	1132 (34.0)	

Notes: Numeric variables are reported as median (interquartile range) and categorical variables are reported as number (percentage)

Abbreviations: FSH, follicle stimulating hormone; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein

pressure, fasting blood glucose, triglycerides, total cholesterol, low-density lipoprotein, and lower basal follicle stimulating hormone and high-density lipoprotein (all $P_{trend} < 0.05$). In addition, the distribution of nulliparity, male factor, ovulatory dysfunction, and endometriosis differed significantly between quartiles. As shown in Table 2, discernible statistical variations were also observed in total gonadotropin dose, estrogen, luteinizing hormone, and progesterone level on trigger day, fertilization type, the number of embryos transferred, and the transfer of at least one good-quality embryo.

Pregnancy outcomes

Table 3 presented the different pregnancy outcomes based on the SUA quartiles. There was no significant decreasing or increasing trend in the live birth rate with the change of SUA level (Q1: 58.3%, Q2: 58.1%, Q3: 57.9%, Q4: 58.9%, $P_{trend} = 0.720$). The same trend was seen in other pregnancy outcomes, including the percentages of biochemical pregnancy, biochemical pregnancy loss, implantation, multiple pregnancy, clinical pregnancy, and miscarriage.

Obstetric and perinatal outcomes

Obstetric and perinatal outcomes following a single live birth were depicted in Table 4. Notably, the incidence of HDP (1.6–4.1%), GDM (5.9–13.9%), PROM (0.6–1.5%), PTB (6.3–9.2%), macrosomia (2.3–5.5%), LGA (10.8–14.9%) significantly increased with ascending SUA quartiles (all P_{trend} <0.005). From the results of multiple comparisons, we can also observe that the incidence of those reproductive outcomes in quartile 4 was the highest with significant difference (Fig. 2). Similarly, both birth weight and Z-score increased concomitantly with the ascending SUA quartile (all P_{trend} <0.005).

Crude and adjusted analyses

Table 5 presents the association of SUA and relevant reproductive outcomes in crude and adjusted analyses. Across all three models, with the increase of UA, the

Table 2 Clinical treatment characteristics according to serum uric acid quartiles

	Quartile 1 (*n* = 3240)	Quartile 2 (*n* = 3329)	Quartile 3 (*n* = 3422)	Quartile 4 (*n* = 3334)	P_{trend}
Ovarian stimulation protocol, n (%)					0.523
GnRH agonist	3124 (96.4)	3204 (96.3)	3311 (96.8)	3219 (96.6)	
GnRH antagonist	116 (3.6)	125 (3.8)	111 (3.2)	115 (3.5)	
Stimulation duration (days)	11 (10–12)	11 (10–12)	11 (10–12)	11 (10–12)	0.439
Total gonadotropin dose (IU)	2025.0 (1500.0-2700.0)	2025.0 (1550.0-2668.8)	2025.0 (1550.0-2662.5)	2100.0 (1650.0-2700.0)	< 0.001
E2 level on trigger day (pg/mL)	1966.5 (1394.1-2701.5)	1946.0 (1384.0-2701.0)	1909.0 (1331.0-2613.0)	1711.4 (1186.0-2411.8)	< 0.001
LH level on trigger day (mIU/mL)	1.1 (0.7–1.6)	1.0 (0.8–1.6)	1.0 (0.7–1.6)	0.9 (0.6–1.4)	< 0.001
P level on trigger day (ng/mL)	0.6 (0.4–0.9)	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.024
Endometrial thickness on trigger day (mm)	10.9 (9.3–12.7)	10.9 (9.4–12.6)	10.9 (9.3–12.6)	10.8 (9.2–12.6)	0.054
No. of oocyte retrieved	11 (8–14)	11 (8–15)	11 (8–15)	11 (8–14)	0.130
Fertilization type, n (%)					0.043
IVF	2502 (77.2)	2616 (78.6)	2753 (80.5)	2667 (80.0)	
ICSI	530 (16.4)	516 (15.5)	486 (14.2)	484 (14.5)	
IVF + ICSI	208 (6.4)	197 (5.9)	183 (5.4)	183 (5.5)	
No. of embryos transferred, n (%)					0.001
Single	866 (26.7)	838 (25.2)	845 (24.7)	773 (23.2)	
Double	2374 (73.3)	2491 (74.8)	2577 (75.3)	2561 (76.8)	
Embryo stage at transfer, n (%)					0.390
Cleavage	2799 (86.4)	2882 (86.6)	2958 (86.4)	2907 (87.2)	
Blastocyst	441 (13.6)	447 (13.4)	464 (13.6)	427 (12.8)	
Transfer at least 1 good-quality embryo, n (%)	2579 (79.6)	2667 (80.1)	2736 (80.0)	2564 (76.9)	0.009

Notes: Numeric variables are reported as median (interquartile range) and categorical variables are reported as number (percentage)

Abbreviations: GnRH, gonadotropin-releasing hormone; E2, estradiol; LH, luteinizing hormone; P, progesterone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection

Table 3 Pregnancy outcomes according to serum uric acid quartiles

	Quartile 1 (*n* = 3240)	Quartile 2 (*n* = 3329)	Quartile 3 (*n* = 3422)	Quartile 4 (*n* = 3334)	P_{trend}
Biochemical pregnancy, n (%)	2395/3240 (73.9)	2499/3329 (75.1)	2533/3422 (74.0)	2486/3334 (74.6)	0.803
Biochemical pregnancy loss rate, n/N (%)	232/2395 (9.7)	274/2499 (11.0)	245/2533 (9.7)	227/2486 (9.1)	0.260
Implantation rate, n/N (%)	2914/5614 (51.9)	3038/5820 (52.2)	3077/5999 (51.3)	3070/5895 (52.1)	0.762
Multiple pregnancy, n/N(%)	770/2163 (35.6)	840/2225 (37.8)	811/2288 (35.5)	829/2259 (36.7)	0.841
Clinical pregnancy, n (%)	2163/3240 (66.8)	2225/3329 (66.8)	2288/3422 (66.9)	2259/3334 (67.8)	0.409
Miscarriage, n/N (%)	251/2163 (11.6)	258/2225 (11.6)	277/2288 (12.1)	271/2259 (12.0)	0.581
Live birth, n (%)	1889/3240 (58.3)	1935/3329 (58.1)	1980/3422 (57.9)	1962/3334 (58.9)	0.720
Single	1280/3240 (39.5)	1269/3329 (38.1)	1336/3422 (39.0)	1313/3334 (39.4)	0.875
Multiple	609/3240 (18.8)	666/3329 (20.0)	644/3422 (18.8)	649/3334 (19.5)	0.799

Notes: Data are reported as number (percentage)

OR value for clinical pregnancy rate and live birth rate showed no significant difference, whereas the OR value for HDP, GDM, PROM, PTB, macrosomia, and LGA demonstrated an increasing trend. This trend is consistent with the results of previous trend tests. Specifically, after controlling for reproductive related confounders (model a), the risk of HDP in Q4 (OR = 1.98, 95% CI: 1.16–4.54), GDM in Q3 (OR = 1.45, 95% CI: 1.07–1.97) and Q4 (OR = 2.15, 95% CI: 1.61–2.88), PROM in Q4 (OR = 2.36, 95% CI: 1.00-5.57), PTB in Q4 (OR = 1.40, 95% CI: 1.03–1.89), macrosomia in Q3 (OR = 1.66, 95% CI: 1.04–2.64) and Q4 (OR = 2.10, 95% CI: 1.34–3.30), and LGA in Q4 (OR = 1.29, 95% CI: 1.02–1.65) were significantly higher than that in Q1. These results were similar in the unadjusted model. When BMI, blood pressure, fasting blood glucose, and blood lipids were further included in the model (model b), the increasing trend of OR values was attenuated, but the risk of GDM in Q4 (OR = 1.72, 95% CI: 1.27–2.34) and macrosomia in Q4 (OR = 1.68, 95% CI: 1.05–2.69) remained significantly higher than that in Q1. Given that SUA are strongly correlated with BMI, blood glucose, lipids, and blood pressure, it is predictable that the effect of SUA on reproductive outcomes was weakened due to their interactions.

In sensitivity analysis focusing only on women with tubal factor, male factor, or unexplained infertility, due

Table 4 Obstetric and perinatal outcomes following a single live birth according to serum uric acid quartiles

	Quartile 1 ($n=1280$)	Quartile 2 ($n=1269$)	Quartile 3 ($n=1336$)	Quartile 4 ($n=1313$)	P_{trend}
Obstetric outcomes					0.523
Hypertensive disorders in pregnancy	20 (1.6)	19 (1.5)	29 (2.2)	54 (4.1)	< 0.001
Gestational diabetes mellitus	75 (5.9)	98 (7.7)	121 (9.1)	183 (13.9)	< 0.001
Intrahepatic cholestasis of pregnancy	2 (0.2)	4 (0.3)	2 (0.2)	2 (0.2)	0.781
Abnormal placentation	25 (2.0)	35 (2.8)	30 (2.3)	28 (2.1)	0.992
Placenta previa	24 (1.9)	33 (2.6)	29 (2.2)	26 (2.0)	0.946
Placenta accreta	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	0.391
Placental abruption	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	0.697
Polyhydramnios	3 (0.2)	4 (0.3)	3 (0.2)	3 (0.2)	0.902
Oligohydramnios	1 (0.1)	2 (0.2)	0 (0.0)	2 (0.2)	1.000
Premature rupture of membranes	8 (0.6)	8 (0.6)	14 (1.1)	19 (1.5)	0.016
Postpartum hemorrhage	4 (0.3)	2 (0.2)	3 (0.2)	1 (0.1)	0.262
Perinatal outcomes					
Gender, n (%)					0.511
Male	681 (53.2)	646 (50.9)	736 (55.1)	698 (53.2)	
Female	599 (46.8)	623 (49.1)	600 (44.9)	615 (46.8)	
Gestational age (weeks)	39.1 (38.4–39.9)	39.1 (38.3–39.9)	39.1 (38.3–39.9)	39.1 (38.3–39.7)	0.158
Preterm birth, n (%)	81 (6.3)	99 (7.8)	104 (7.8)	121 (9.2)	0.009
Very preterm birth, n (%)	7 (0.6)	12 (1.0)	10 (0.8)	14 (1.1)	0.227
Postterm birth, n (%)	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0.192
Birthweight (g)	3200 (3000–3500)	3250 (3000–3500)	3250 (3000–3550)	3300 (3000–3600)	0.001
Low birthweight, n (%)	61 (4.8)	69 (5.4)	65 (4.9)	62 (4.7)	0.792
Very low birthweight, n (%)	2 (0.2)	7 (0.6)	6 (0.5)	9 (0.7)	0.082
Macrosomia, n (%)	29 (2.3)	39 (3.1)	54 (4.0)	72 (5.5)	< 0.001
Z-score	0.0 (-0.6-0.7)	0.1 (-0.5-0.7)	0.1 (-0.5-0.8)	0.2 (-0.4-0.9)	< 0.001
Small-for-gestational age, n (%)	91 (7.1)	91 (7.2)	102 (7.6)	83 (6.3)	0.549
Large-for-gestational age, n (%)	138 (10.8)	154 (12.1)	174 (13.0)	195 (14.9)	0.002
Major birth defects, n (%)	9 (0.7)	9 (0.7)	17 (1.3)	16 (1.2)	0.085

Notes: Numeric variables are reported as median (interquartile range) and categorical variables are reported as number (percentage)

to a reduced sample size, the OR value for PROM and PTB no longer show significant differences, but the overall change trend of OR value was similar (Fig. 3). To further detect any possible linear or non-linear correlation between SUA and reproductive outcomes, the SUA was analyzed as a continuous variable through spline smoothing plots in generalized additive model (Fig. 4). Those spline smoothing plots revealed that as SUA levels rose, the risk of HDP, GDM, PROM, PTB, macrosomia, and LGA demonstrated an overall increasing trend after adjusting for all potential confounding factors.

Comment

Principal findings

The outcomes of our retrospective cohort study demonstrated that elevated SUA levels may not negatively impact the rates of live birth and clinical pregnancy among non-PCOS women undergoing ART. Furthermore, elevated SUA levels are associated with an increasing risk for HDP, GDM, PROM, PTB, macrosomia, and LGA. Notably, for GDM and macrosomia, this association persists irrespective of BMI, blood pressure, glucose levels, and lipid profiles, underscoring the potential of SUA as an independent risk factor.

Interpretation of study findings and comparison with existing literature

The evidence regarding the correlation between pretreatment SUA levels and reproductive outcomes in the context of IVF/ICSI is scarce. Yang et al. identified that an elevated SUA level is associated with decreased live birth rate and an increased risk for LBW in women with PCOS [10]. This conclusion cannot be extrapolated to non-PCOS women in our investigation. Numerous studies have posited that elevated SUA levels and hyperuricemia are prevalent among PCOS women, frequently co-occurring with hyperandrogenemia [13, 14]. Moreover, certain studies have documented that increased SUA concentrations may exacerbate the metabolic disturbances characteristic of PCOS, encompassing the development of hyperandrogenemia, insulin resistance, disrupted lipid metabolism, and ensuing complications associated with PCOS [15]. This may explain why elevated SUA levels could precipitate adverse pregnancy outcomes in women with PCOS.

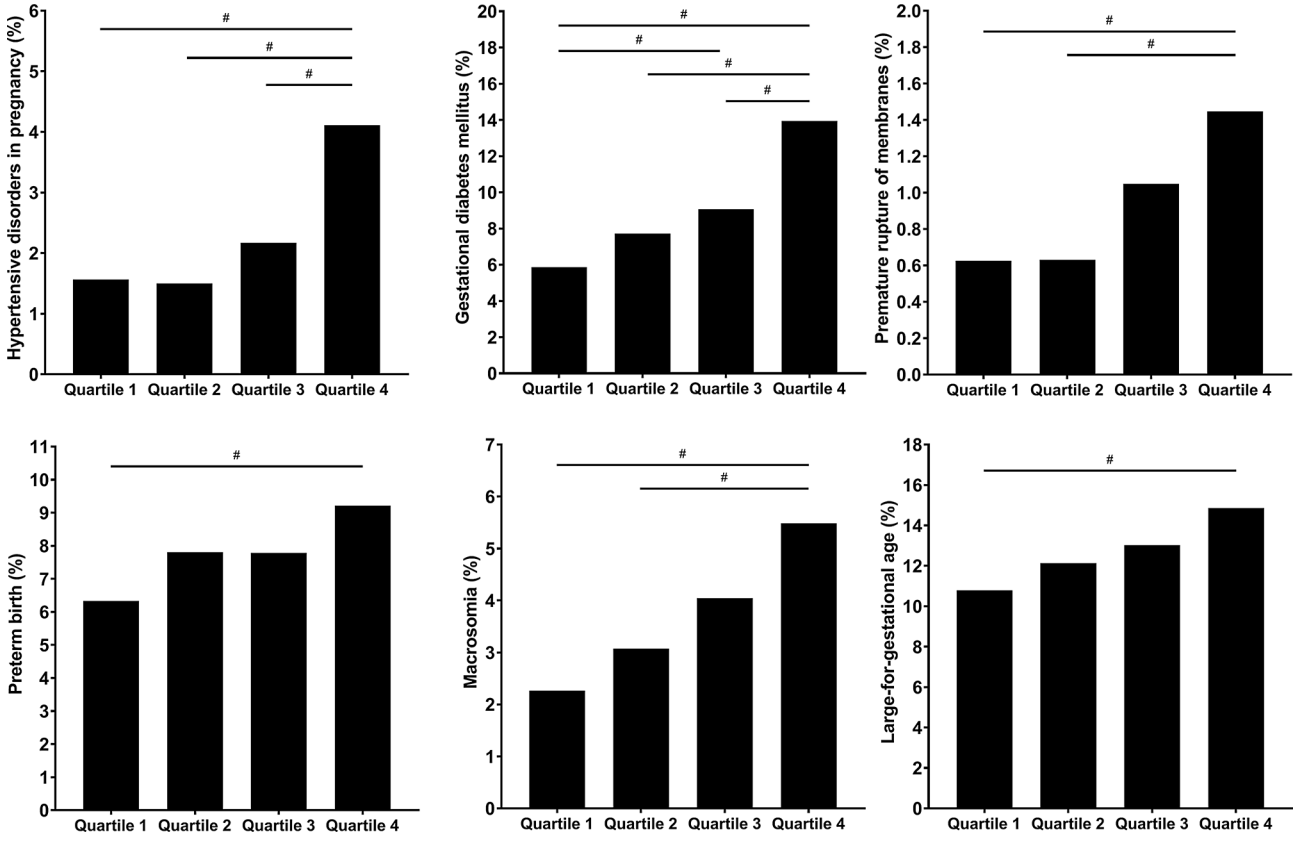

Fig. 2 Multiple comparisons between serum uric acid quartiles of reproductive outcomes

Our findings reveal that an elevated SUA level significantly increased the risk of HDP. It is well-documented that UA is intricately associated with hypertension, and a reduction in SUA concentrations aids in preserving blood pressure stability [16]. Mounting evidence indicates that SUA not only forecasts the onset of hypertension but may also play a role in its pathogenesis [17–19]. A plausible explanation for this phenomenon could be that SUA may precipitate oxidative stress, endothelial dysfunction, and smooth muscle cell proliferation [20, 21]. An alternative hypothesis could lie in the impact of SUA on the synthesis of nitric oxide and the assimilation of placental amino acids, which diminish trophoblast penetration into endothelial cell monolayers. This process could provoke placental inflammation and dysfunction, culminating in the absence of physiological transformation within spiral arteries [18, 22, 23].

Previous research has documented a significant correlation among the emergence of insulin resistance, type 2 diabetes, and SUA levels [24–26]. Consistently, we found a higher risk of GDM among women with increased SUA levels. A case-control investigation has revealed that SUA and insulin levels ascend concurrently in response to glucose stimulation, with this effect appearing more markedly in women than in men [27]. The conceivable mechanism by which UA might instigate glucose metabolism disorders could be ascribed to the induction of inflammation and oxidative stress within adipocytes [28, 29].

In addition, our study revealed that elevated SUA concentrations correlate significantly with adverse perinatal outcomes, including PROM and PTB. Wu et al. discovered that women positioned within the highest quartile of SUA levels during the third trimester of pregnancy exhibit a 48% higher risk of PROM [30]. UA may indirectly precipitate the contraction of uterine smooth muscles through the mediation of various inflammatory mediators, such as cytokines interleukin-1 receptor antagonist [31]. However, Guo et al. found that SUA has a protective function against PROM in women with GDM [32]. It is imperative to acknowledge that UA plays a different role in the context of varying diseases. A survival analysis showed that delivery occurred earlier when the SUA level was higher at 8–12 weeks of gestation. These data suggest that an elevation of SUA in early pregnancy could be involved in the later development of preeclampsia and PTB [33]. This is interesting given the recent major evidence showing that the duration of pregnancy decreased with increasing first-trimester risk for preeclampsia in patients with no preeclampsia [34].

Our research additionally observed a connection between elevated SUA and macrosomia, as well as LGA.

Table 5 Associations between serum uric acid and reproductive outcomes in crude and adjusted analyses

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P1	P2	P3
Clinical pregnancy							
Crude OR (95% CI)	Ref	1.00 (0.91–1.11)	1.01 (0.91–1.11)	1.05 (0.94–1.16)	0.947	0.929	0.391
Adjusted OR[a] (95% CI)	Ref	0.98 (0.88–1.09)	0.97 (0.87–1.08)	1.03 (0.92–1.14)	0.677	0.595	0.638
Adjusted OR[b] (95% CI)	Ref	0.97 (0.87–1.08)	0.96 (0.86–1.06)	1.00 (0.89–1.12)	0.589	0.416	0.957
Live birth							
Crude OR (95% CI)	Ref	0.99 (0.90–1.10)	0.98 (0.89–1.08)	1.02 (0.93–1.13)	0.884	0.715	0.654
Adjusted OR[a] (95% CI)	Ref	0.97 (0.88–1.08)	0.95 (0.86–1.06)	1.02 (0.92–1.13)	0.615	0.365	0.762
Adjusted OR[b] (95% CI)	Ref	0.97 (0.88–1.08)	0.95 (0.86–1.05)	1.02 (0.91–1.13)	0.617	0.350	0.759
Hypertensive disorders in pregnancy							
Crude OR (95% CI)	Ref	0.96 (0.51–1.80)	1.40 (0.79–2.48)	2.70 (1.61–4.54)	0.893	0.254	<0.001
Adjusted OR[c] (95% CI)	Ref	0.86 (0.45–1.62)	1.18 (0.66–2.11)	1.98 (1.16–3.39)	0.632	0.578	0.012
Adjusted OR[d] (95% CI)	Ref	0.87 (0.46–1.67)	1.07 (0.59–1.95)	1.53 (0.87–2.68)	0.681	0.823	0.141
Gestational diabetes mellitus							
Crude OR (95% CI)	Ref	1.35 (0.99–1.84)	1.60 (1.19–2.16)	2.60 (1.97–3.45)	0.062	0.002	< 0.001
Adjusted OR[c] (95% CI)	Ref	1.31 (0.95–1.80)	1.45 (1.07–1.97)	2.15 (1.61–2.88)	0.101	0.017	< 0.001
Adjusted OR[d] (95% CI)	Ref	1.25 (0.91–1.72)	1.34 (0.98–1.82)	1.72 (1.27–2.34)	0.172	0.069	<0.001
Premature rupture of membranes							
Crude OR (95% CI)	Ref	1.01 (0.38–2.70)	1.68 (0.70–4.03)	2.34 (1.02–5.35)	0.986	0.242	0.045
Adjusted OR[c] (95% CI)	Ref	1.14 (0.42–3.11)	1.84 (0.75–4.49)	2.36 (1.00-5.57)	0.794	0.184	0.050
Adjusted OR[d] (95% CI)	Ref	1.10 (0.40–3.01)	1.67 (0.67–4.14)	1.97 (0.81–4.78)	0.855	0.268	0.135
Preterm birth							
Crude OR (95% CI)	Ref	1.25 (0.92–1.70)	1.25 (0.92–1.69)	1.50 (1.12–2.01)	0.148	0.147	0.006
Adjusted OR[c] (95% CI)	Ref	1.20 (0.88–1.63)	1.21 (0.89–1.64)	1.40 (1.03–1.89)	0.245	0.221	0.030
Adjusted OR[d] (95% CI)	Ref	1.18 (0.87–1.61)	1.20 (0.88–1.63)	1.33 (0.97–1.82)	0.286	0.256	0.078
Macrosomia							
Crude OR (95% CI)	Ref	1.37 (0.84–2.23)	1.82 (1.15–2.87)	2.50 (1.62–3.88)	0.208	0.011	< 0.001
Adjusted OR[c] (95% CI)	Ref	1.31 (0.80–2.14)	1.66 (1.04–2.64)	2.10 (1.34–3.30)	0.286	0.033	0.001
Adjusted OR[d] (95% CI)	Ref	1.27 (0.77–2.09)	1.46 (0.91–2.34)	1.68 (1.05–2.69)	0.341	0.115	0.032
Large-for-gestational age							
Crude OR (95% CI)	Ref	1.14 (0.90–1.46)	1.24 (0.98–1.57)	1.44 (1.14–1.82)	0.284	0.077	0.002
Adjusted OR[c] (95% CI)	Ref	1.10 (0.86–1.41)	1.16 (0.91–1.48)	1.29 (1.02–1.65)	0.449	0.225	0.036
Adjusted OR[d] (95% CI)	Ref	1.05 (0.82–1.35)	1.03 (0.81–1.32)	1.01 (0.78–1.30)	0.677	0.796	0.946

Notes: OR[a] was adjusted for all baseline demographics and clinical treatment characteristics except body mass index, blood pressure, fasting blood glucose, blood lipids related indicators. OR[b] was adjusted for all baseline demographics and clinical treatment characteristics. The adjusted factors for OR[c] and OR[d] added vanishing twin pregnancies based on OR[a] and OR[b]. *P1*, *P2*, and *P3* was the *P* value of OR for quartile 2, 3, and 4 with quartile 1 as the reference

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference

This observation is particularly intriguing, given that the preponderance of research indicates an association between elevated SUA levels and SGA [30, 35, 36]. A plausible explanation for this finding could be that the high-quartile SUA levels observed in the general population diverge from those encountered in hyperuricemia. In addition, contrary to prior investigations, the UA measurements in our study pertain to the pre-pregnancy period. There are studies that support our findings. Xiong et al. found that high SUA levels increase the risk of both LGA and SGA [37]. Arslanca et al. determined that UA levels in first-trimester pregnant showed a predictive value for macrosomia with 68.1% sensitivity and 63.8% specificity at a 3.15 cut-off [38]. The reasons for this discrepancy remain unclear, a feasible explanation may be that high levels of SUA lead to a maternal insulin-resistant state, promoting glucose transfer to the fetus [39].

Clinical and research implications

It is well-established that UA exhibits a robust correlation with BMI, blood pressure, blood glucose, and blood lipid levels [40]. Upon controlling for reproductive-related factors, our findings remained consistent. However, when adjusting for confounding variables including BMI, blood pressure, fasting blood glucose, and lipid-related indicators, the observed effects were attenuated. Despite this, the association with GDM and macrosomia remained statistically significant. This implies that the association between GDM or macrosomia and SUA seems to be independent. Furthermore, empirical research demonstrates that non-pregnant women who have previously experienced GDM exhibit elevated levels of SUA, irrespective of their BMI [41, 42]. In conclusion, our research indicates that pre-pregnancy SUA levels serve as a potent predictor of pregnancy complications. Nonetheless, the

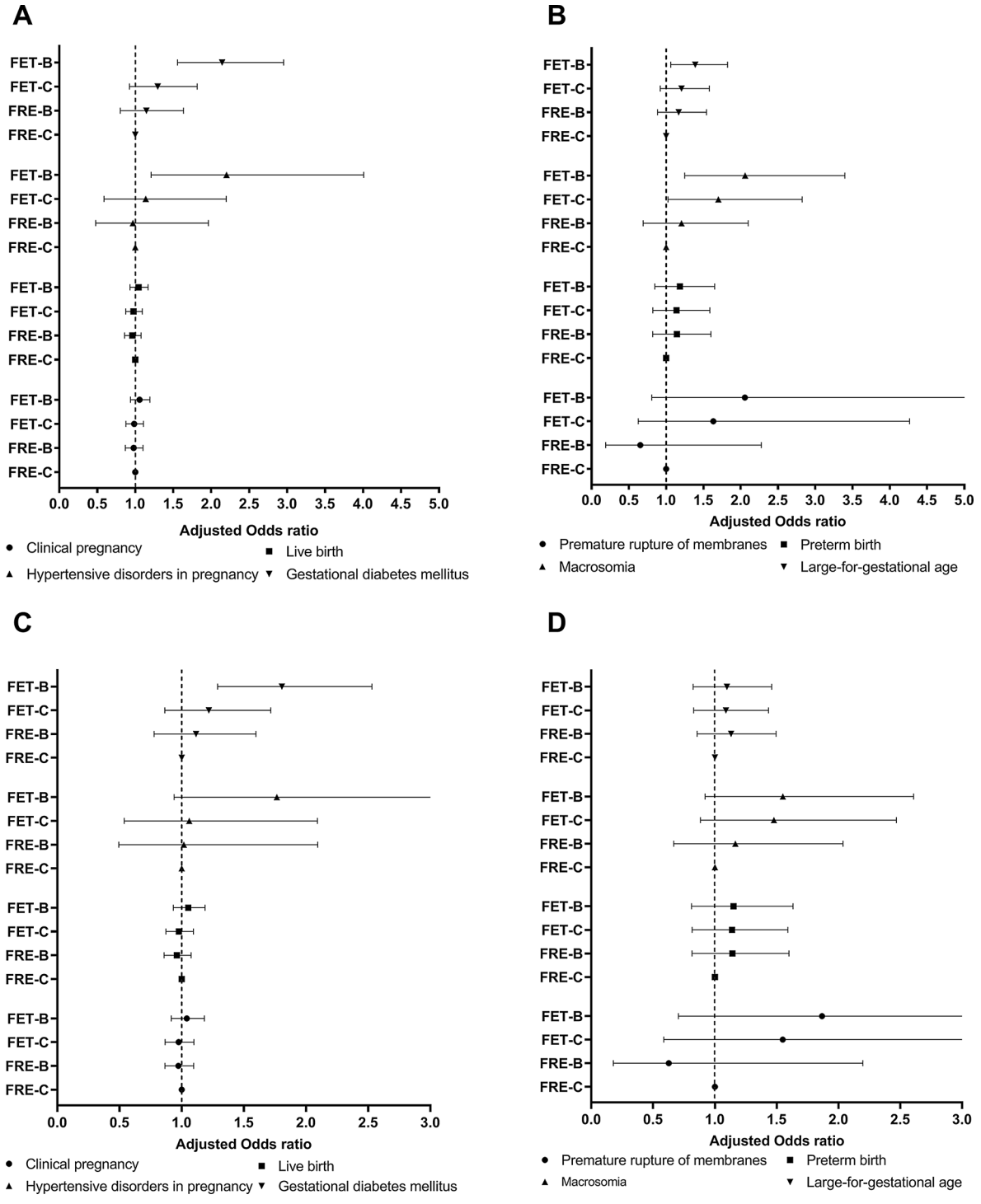

Fig. 3 Associations between serum uric acid and reproductive outcomes in women with tubal factor, male factor, or unexplained infertility. **A** and **B** was adjusted for all baseline demographics and clinical treatment characteristics except body mass index, blood pressure, fasting blood glucose, blood lipids related indicators. **C** and D was adjusted for all baseline demographics and clinical treatment characteristics. The adjusted factors for all models added vanishing twin pregnancies, except for clinical pregnancy and live birth

causal effects of elevated SUA levels on reproductive outcomes warrant additional exploration. Should causal relationships be established, vigilant observation of markers such as UA during the preconception phase could assist physicians in identifying women predisposed to adverse pregnancy outcomes.

The rising incidences of GDM and macrosomia necessitates heightened vigilance as it poses potential risks to

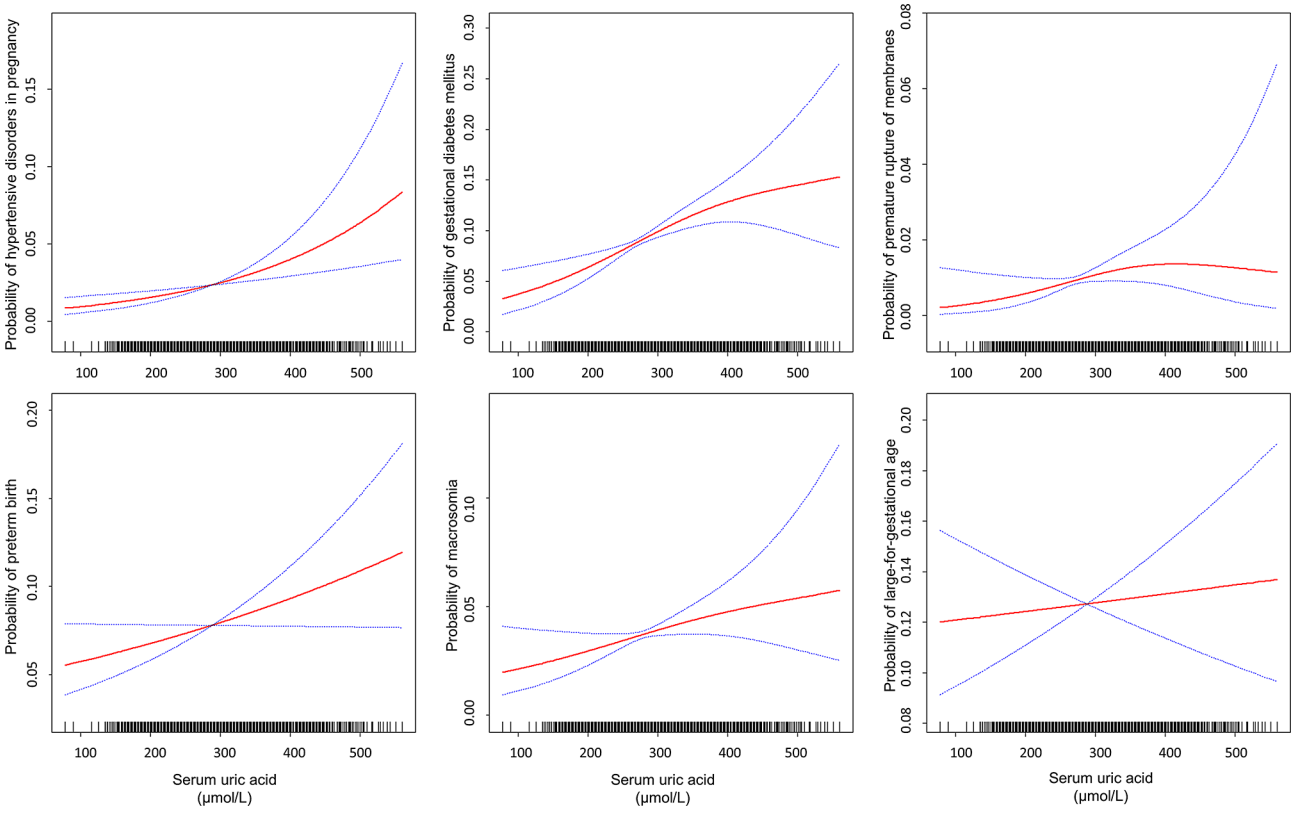

Fig. 4 Spline smoothing plots between serum uric acid and reproductive outcomes using a generalized additive model

both the mother and the baby. These risks include the heightened probability of emergency cesarean sections, a significant increase in maternal mortality rates, protracted maternal convalescence, and an elevated predisposition towards diabetes and obesity in progeny. The potential for medical interventions, including the utilization of allopurinol, to decrease SUA levels prior to pregnancy, thereby enhancing pregnancy outcomes, remains an area ripe for exploration. In the future, it will be essential to carry out a randomized controlled trial concerning allopurinol or alternative therapeutic interventions and controlled efficacy study in vivo or in vitro.

Reproduction and pregnancy are intricate processes. Emerging literature increasingly suggests that infertility has systemic effects beyond the reproductive system [43]. The impact of infertility extends to metabolic alterations and systemic transmission pathways, which in non-PCOS conditions could play a pivotal role in pregnancy outcomes. For instance, a review discusses endometriosis as a systemic disease, emphasizing its metabolic effects on liver and adipose tissue, as well as its ability to induce systemic inflammation and alter brain gene expression, leading to hyperalgesia and mood disorders [44]. Furthermore, immunometabolism, a frontier in immunological research, links metabolism with immunity, and its studies are revolutionizing the field [45]. Therefore, a multi-system approach to the study and treatment of infertility is essential, not only for a more comprehensive understanding of these conditions but also for providing more personalized care plans for patients [46].

Strengths and limitations

To date, this is the first study to investigate the correlation between SUA levels and reproductive outcomes following IVF/ICSI in women without PCOS. In this study, SUA were routinely measured to ensure the generalizability of our findings. To minimize potential interventions affecting pre-pregnancy SUA levels and to reduce the interval between SUA measurement and pregnancy, we included women who had their SUA tested within three months before ovarian stimulation and who underwent fresh embryo transfer. A primary advantage of our research is its adequate sample size, essential for the analysis of complications that manifest infrequently. Moreover, meticulous documentation of pregnancy, obstetric, and perinatal outcomes during routine follow-ups rendered our investigation more exhaustive. Lastly, the congruence between the multiple regression model and the generalized additive model enhances the robustness and credibility of our findings.

It is imperative to acknowledge certain limitations inherent in the current study. Firstly, the retrospective

cohort design introduces potential for inherent bias and residual confounding. Given the nine-year span of this retrospective analysis, improvements in IVF practices over time may also influence outcomes. Secondly, the investigation of SUA levels was confined to a single time point, precluding definitive conclusions about the causal effects between the purine-UA pathway and reproductive outcomes. Thirdly, while this study delineated trends between SUA levels and relevant reproductive outcomes, it did not establish a specific cut-off value for the prediction of individual complications. Lastly, the findings, derived from a single-center cohort, limited to fresh embryo transfer cycle. Whether the same results can be drawn for frozen embryo transfer and natural pregnancies requires further multicenter studies to ascertain their generalizability across broader populations.

Conclusion

Our study demonstrates that elevated SUA levels do not affect the probabilities of clinical pregnancy and live birth in women without PCOS undergoing IVF/ICSI. However, higher SUA levels are linked to a heightened risk of HDP, GDM, PROM, PTB, macrosomia, and LGA. Notably, for GDM and macrosomia, this association remains significant irrespective of BMI, blood pressure, blood glucose, and blood lipid levels. Further research through prospective or interventional studies is necessary to validate our findings.

Abbreviations

SUA	Serum uric acid
PCOS	Polycystic ovary syndrome
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm injection
BMI	Body mass index
ART	Assisted reproductive technology
ET	Embryo transfer
GnRH	Gonadotropin-releasing hormone
Gn	Gonadotropin
hCG	Human chorionic gonadotropin
HDP	Hypertensive disorders in pregnancy
GDM	Gestational diabetes mellitus
PROM	Premature rupture of membranes
PTB	Preterm birth
LBW	Low birthweight
SGA	Small for gestational age
LGA	Large for gestational age
FCS	Fully conditional specification
OR	Odds ratio

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Author contributions

L.Z.X., L.F. and J.H. contributed equally to the study. L.X.X. and Q.W. were responsible for the conception of study. L.Z.X., L.F. and J.H. contributed to design this study, statistical analyses, and write this manuscript. Y.Z., L.T., H.C., and L.C. revised the manuscript. All the authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Reproductive Medicine Ethics Committee of Jiangxi Maternal and Child Health Hospital (SZYX-202411). Written informed consent for participation was not required due to the retrospective nature of this study, in accordance with the national legislation and institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Reproductive Medicine Center, Jiangxi Maternal and Child Health Hospital Affiliated to Nanchang Medical College, Nanchang, China
[2]Jiangxi Key Laboratory of Reproductive Health, Nanchang, China
[3]Department of Child Health, Jiangxi Maternal and Child Health Hospital Affiliated to Nanchang Medical College, Nanchang, China
[4]Department of Acupuncture, the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Nanchang, China

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