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ORIGINAL RESEARCH

Serum Uric Acid and Intrauterine Insemination Outcomes in Non-Polycystic Ovary Syndrome Women: A Retrospective Study

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Purpose: To investigate the association between serum uric acid (SUA) levels and reproductive outcomes in non-polycystic ovary syndrome (PCOS) women undergoing intrauterine insemination (IUI) treatment.

Patients and Methods: This retrospective study examined 2448 IUI cycles at a large reproductive health center from 2015 to 2024. They were categorized into four groups according to SUA quartiles. Differences in pregnancy and obstetric outcomes of women without PCOS were compared among these groups. Logistic regression analysis was applied to obtain the odds ratio (OR) and 95% confidence interval (CI) for outcomes with or without adjusting for confounding variables.

Results: There was no significant difference in the biochemical pregnancy rate from the lowest SUA quartile (Q1: 18.81%) to the highest (Q4: 17.81%) (adjusted OR 0.80, 95% CI: 0.58–1.09, P=0.455). Similarly, both the unadjusted and adjusted models indicated that SUA level had no significant effect on most reproductive outcomes including clinical pregnancy rate, miscarriage rate, and live birth rate (P>0.05). Notably, mean birth weight in Q3 (3376.93 ± 64.63 g) was the highest among the four groups (P=0.021). Consistent with this result, the low birth weight rate in Q3 was significantly lower than in Q1 in Model 3 (adjusted OR 0.21, 95% CI: 0.05–0.94, P=0.041) after adjusting for factors such as age, body mass index, menstrual cycle, and systolic blood pressure.

Conclusion: We conclude that pre-pregnancy SUA does not impair reproductive outcomes in women without PCOS undergoing IUI treatment. Fetal growth and subsequent birth weight would appear to benefit from an appropriate maternal SUA level. However, the precise efficacy and mechanism of action need to be further investigated.

Keywords: uric acid, intrauterine insemination, infertility, sex hormones, pregnancy rate, reproductive outcomes

Introduction

Uric acid (UA) is the end metabolite of both exogenous and endogenous purines and has dual biological effects on human physiology.[1] It acts as a powerful antioxidant at normal levels, protecting cells from oxidative damage.[2] However, it becomes a pro-oxidant at high concentrations, accelerating a chain reaction of free radicals and the formation of UA crystals, participating in the occurrence of diseases.[3] In addition to gout, high levels of serum UA (SUA) have also been confirmed as risk factors for hypertension,[4] type 2 diabetes,[5] obesity,[6] and metabolic syndrome.[7] However, we still know little about the relationship between SUA levels and infertility.

In recent years, oxidative stress (OS) and inflammation have been considered key factors in female infertility.[8–10] OS is not only associated with oocyte aging, low fertilization rate and delayed embryonic development, but also involved in various pathological conditions such as recurrent pregnancy loss, preeclampsia, preterm labor, intrauterine growth retardation, and even fetal death.[11] Although inflammation is necessary for successful reproduction, abnormal activation

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of inflammatory processes can disrupt normal ovarian follicle dynamics and lead to devastating effects on pregnancy outcomes.[12] Notably, SUA level is a significant biomarker for OS and inflammation in the body.[13,14] Thus, some researchers have speculated that UA might be implicated in diverse pathological processes mediated by OS and act as a pro-inflammatory factor contributing to systemic inflammation, thereby adversely affecting female reproductive function and fecundity.[15,16]

Compared with in-vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), intrauterine insemination (IUI) is less invasive, less expensive and more patient-friendly, and thus has been widely used in the treatment of infertile couples in specific cases.[17] Moreover, there are significant differences between IUI and IVF/ICSI in terms of the degree of hormonal stimulation and the location of fertilization.[18] Previous studies have investigated the relationship between pre-pregnancy SUA levels and reproductive outcomes among women with polycystic ovary syndrome (PCOS) undergoing IVF or ICSI cycles and demonstrated that elevated SUA level is associated with a decreased live birth rate and an increased incidence of gestational diabetes mellitus, gestational hypertension and low birth weight (LBW).[19,20] The risk of hypertensive disorders in pregnancy, gestational diabetes mellitus, premature rupture of membranes, preterm birth, macrosomia, and large for gestational age increased as SUA levels rose in non-PCOS women after adjusting for all potential confounding factors.[21] Nonetheless, it is not known whether elevated SUA would lead to similar outcomes of IUI cycles. Among women undergoing IUI, the percentage of PCOS cases is significantly lower than that of participants who did not suffer from PCOS.[22] Thus, in this retrospective cohort study, we identified and examined correlations between pre-pregnancy SUA levels and reproductive outcomes in infertile women without PCOS undergoing IUI treatment, hoping to provide information and references for improving female pregnancy health and addressing infertility challenges.

Materials and Methods

Study Design and Population

This study was a retrospective analysis of a total of 2448 IUI cycles in 1437 infertile couples who attended the Affiliated Hospital of Jining Medical University between January 2015 and December 2024. To be eligible for enrolling in this study, the participants had to fulfill all of the following criteria: (1) women aged 20 to 40 years old; (2) couples failing to conceive for more than 12 months; (3) a minimum of 10 million motile sperm per milliliter (mL) after ejaculating; (4) at least one patent fallopian tube. The exclusion criteria were as follows: (1) PCOS diagnosed based on the Rotterdam criteria; (2) chronic diseases such as diabetes, hypertension, cardiovascular disease, and autoimmune disorders; (3) using donated sperm to conceive; (4) uterine malformations such as unicornuate uterus, bicornuate uterus, and septate uterus; (5) endocrine abnormalities (hyperprolactinemia, hyperthyroidism, hypothyroidism, hypogonadotropic hypogonadism); (6) female body mass index (BMI) ≥30 kg/m^2 because women with BMI ≥30 kg/m^2 were advised to reduce weight before the treatment. Based on the SUA quartiles, participants were divided into four groups: quartile 1 (Q1: 0–25 percentile, ≤212 μmol/L), quartile 2 (Q2: 25–50 percentile, 213–250 μmol/L), quartile 3 (Q3: 50–75 percentile, 251–293 μmol/L), and quartile 4 (Q4: 75–100 percentile, ≥294 μmol/L). Figure 1 shows the flowchart of the study.

Ethics Approval and Consent to Participate

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Affiliated Hospital of Jining Medical University (approval number: 2025–06-C008). Informed written consent was waived because retrospective data collection and analysis were based on electronic medical records without any intervention in clinical treatment.

Laboratory Measurements

Trained nurses measured weight and height according to standard procedures. BMI was calculated as the weight in kilograms divided by the height squared in meters. Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured after 5 min of quiet rest using an Omron HBP-1300 electronic sphygmomanometer. Participants provided venous blood samples after a minimum of 8 h of fasting. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2),

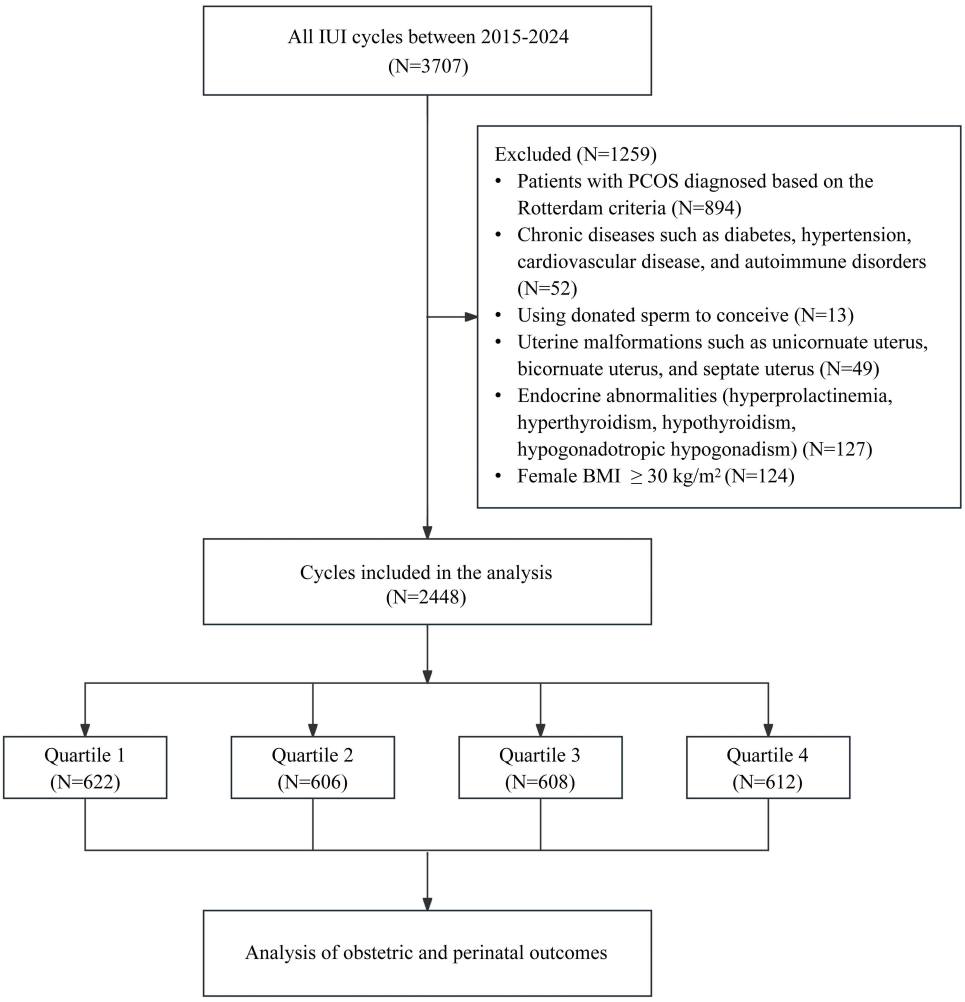

Figure 1 Flow chart of the study.
Abbreviations: *IUI*, intrauterine insemination; *BMI*, body mass index; *PCOS*, polycystic ovary syndrome.

prolactin (PRL), testosterone (T), progesterone (P), anti-Müllerian hormone (AMH) and thyroid-stimulating hormone (TSH) were quantified using the UniCel Dxi 800 Access Immunoassay System (Beckman Coulter Inc., Fullerton, CA, USA). Fasting blood glucose (FBG) level was determined using a glucometer. Antral follicle count (AFC) and endometrial thickness were evaluated by transvaginal ultrasonography. SUA levels were measured by the uricase method using commercial kits from Meikang Biotechnology Co., Ltd. (Ningbo, Zhejiang, China). The normative range for SUA levels at the study center was 155–357 μmol/L.

Semen Preparation

After 3 to 7 days of sexual abstinence, semen samples were taken by masturbation into sterile containers on the day of IUI. An initial evaluation of semen was performed after 30 min of liquefaction at 37°C, and 1 to 2 mL of ejaculate were prepared for insemination with two-layer density gradient centrifugation. In accordance with World Health Organization guidelines, the volume of semen, sperm concentration, and other laboratory indicators were recorded before and after the process. After analysis, the ultimate sample was suspended in 0.5 mL culture medium and incubated at room temperature until insemination.

Ovarian Stimulation and IUI Procedure

The natural cycle protocol was administered to females with normal ovulation. For women with ovulation disorders, irregular menstruation, or unexplained infertility, ovarian stimulation was carried out as previously described by us.[23] Briefly, patients were given letrozole (LE), clomiphene citrate (CC), human menopausal gonadotropin (HMG), or FSH before the operation. The monitoring of follicular development and endometrial thickness was performed starting from day 10 of the menstrual cycle. When the leading follicle reached 18 mm in diameter or serum LH was positive, recombinant human chorionic gonadotropin (hCG) (5000–10000 IU) was administered intramuscularly to trigger ovulation. The patients were placed in the bladder lithotomy position during the operation. After vaginal and cervical secretions were rinsed with physiological saline, 0.3–0.5 mL of semen suspension was infused into the uterine cavity slowly and the patients then rested in the supine position for 15 min.

Pregnancy Outcome Evaluation and Follow-Up Visit

All patients were required to have a serum hCG test 14 days after the insemination to identify whether biochemical pregnancy occurred. In women with positive hCG results, transvaginal sonography was performed at 7 weeks' gestation to confirm clinical pregnancy by detecting the presence of an intrauterine gestational sac with or without fetal heart activity. Pregnant women were followed up via phone interviews till the end of pregnancy (by abortion or delivery). Miscarriage was defined as a pregnancy that ended spontaneously before the fetus reached 28 weeks' gestation or the fetal weight was less than 1000 g. Ectopic pregnancy referred to the presence of at least a gestational sac outside of the uterine cavity. Live birth was considered as the delivery of an infant exhibiting signs of life, such as heartbeat, breathing, voluntary muscle contraction and umbilical cord pulsation at 28 weeks' gestation or later. LBW infant was regarded as a newborn with a birth weight below 2500 g.

Statistical Analysis

All obtained data were statistically analyzed by a standard statistical package (SPSS 27.0, Chicago, IL). Categorical variables were expressed as number (percentage) and compared between groups using the Chi-square test or Fisher exact test. Continuous variables were presented as mean ± standard error (SE) and evaluated with the Kruskal–Wallis test. Median values were used to replace missing values for continuous variables, and modes were used to replace missing categorical variables. A logistic regression analysis was conducted to estimate the crude and adjusted odds ratio (OR) with 95% confidence interval (CI) for IUI outcomes according to the SUA quartiles. Three models were constructed: Model 1 had no adjusted variables; Model 2 adjusted for age and BMI; Model 3 further adjusted for education, age at menarche, menstrual cycle, type of infertility, basal FSH, basal E2, basal PRL, basal T, TSH, AFC, FBG, DBP, SBP, smoking in men, progressive motile sperm, normal sperm morphology, and treatment protocol based on Model 2. Probability values less than 0.05 were regarded as statistically significant.

Results

Baseline Characteristics of Study Participants

We analyzed 2448 IUI cycles in 1437 couples during the study period. The baseline characteristics of the subjects according to SUA quartiles were summarized in Table 1. No differences were observed in endometrial thickness, duration of infertility, indication for IUI, and number of IUI cycles among the four groups ($P>0.05$). The data of basal

Table 1 Baseline Characteristics of Patients According to SUA Quartiles

Variable	Quartile 1 (n=622)	Quartile 2 (n=606)	Quartile 3 (n=608)	Quartile 4 (n=612)	*P* value
SUA (μmol/L), mean ± SE	183.69 ± 0.90	231.33 ± 0.44	270.50 ± 0.50	336.74 ± 1.49	
Female					
Age (years), mean ± SE	32.28 ± 0.16	32.12 ± 0.17	31.39 ± 0.17	30.87 ± 0.17	<0.001
BMI (kg/m^2), mean ± SE	21.48 ± 0.10	21.62 ± 0.10	22.46 ± 0.11	23.58 ± 0.12	<0.001

(*Continued*)

Table 1 (Continued).

Variable	Quartile 1 (n=622)	Quartile 2 (n=606)	Quartile 3 (n=608)	Quartile 4 (n=612)	*P* value
Education, % (n/N)					<0.001
Less than high school	34.89% (217/622)	28.88% (175/606)	20.72% (126/608)	23.86% (146/612)	
High school	13.02% (81/622)	12.05% (73/606)	16.78% (102/608)	14.54% (89/612)	
More than high school	52.09% (324/622)	59.08% (358/606)	62.50% (380/608)	61.60% (377/612)	
Smoking, % (n/N)					1.000
Yes	0.16% (1/622)	0.00% (0/606)	0.00% (0/608)	0.00% (0/612)	
No	99.84% (621/622)	100.00% (606/606)	100.00% (608/608)	100.00% (612/612)	
Age at menarche (years), mean ± SE	13.90 ± 0.48	13.86 ± 0.44	13.63 ± 0.44	13.74 ± 0.04	<0.001
Menstrual cycle (days), mean ± SE	30.28 ± 0.31	30.91 ± 0.64	30.95 ± 0.33	31.67 ± 0.35	<0.001
Endometrial thickness (mm), mean ± SE	6.11 ± 0.08	6.20 ± 0.08	6.21 ± 0.09	6.10 ± 0.09	0.393
Duration of infertility (years), mean ± SE	2.47 ± 0.07	2.45 ± 0.08	2.43 ± 0.07	2.42 ± 0.07	0.520
Type of infertility, % (n/N)					<0.001
Primary	36.50% (227/622)	43.56% (264/606)	52.80% (321/608)	55.39% (339/612)	
Secondary	63.50% (395/622)	56.44% (342/606)	47.20% (287/608)	44.61% (273/612)	
Indication for IUI, % (n/N)					0.105
Female factor	13.18% (82/622)	10.56% (64/606)	13.82% (84/608)	12.09% (74/612)	
Male factor	33.12% (206/622)	32.51% (197/606)	32.07% (195/608)	34.31% (210/612)	
Both factor	8.04% (50/622)	4.95% (30/606)	8.22% (50/608)	5.56% (34/612)	
Unexplained	45.66% (284/622)	51.98% (315/606)	45.89% (279/608)	48.04% (294/612)	
Number of IUI cycles (n), mean ± SE	1.70 ± 0.05	1.62 ± 0.04	1.66 ± 0.04	1.59 ± 0.04	0.554
Basal FSH (mIU/mL), mean ± SE	8.23 ± 0.12	8.56 ± 0.17	8.06 ± 0.16	7.52 ± 0.10	<0.001
Basal LH (mIU/mL), mean ± SE	7.13 ± 0.35	7.65 ± 0.42	8.23 ± 0.46	8.24 ± 0.47	0.141
Basal E2 (pg/mL), mean ± SE	75.26 ± 5.10	80.00 ± 5.84	69.67 ± 3.76	65.58 ± 3.68	0.034
Basal PRL (ng/mL), mean ± SE	16.51 ± 0.86	14.83 ± 0.29	15.65 ± 0.30	15.98 ± 0.33	0.024
Basal T (ng/mL), mean ± SE	0.52 ± 0.07	0.60 ± 0.09	0.47 ± 0.01	0.57 ± 0.05	<0.001
Basal P (ng/mL), mean ± SE	0.70 ± 0.04	0.68 ± 0.05	0.69 ± 0.04	0.73 ± 0.05	0.269
AMH (ng/mL), mean ± SE	3.61 ± 0.11	3.76 ± 0.11	4.00 ± 0.12	3.82 ± 0.11	0.095
TSH (mIU/L), mean ± SE	2.04 ± 0.04	2.19 ± 0.05	2.21 ± 0.04	2.36 ± 0.05	<0.001
AFC (n), mean ± SE	13.70 ± 0.28	14.36 ± 0.31	14.82 ± 0.30	15.31 ± 0.30	<0.001
FBG (mmol/L), mean ± SE	4.91 ± 0.02	4.95 ± 0.02	5.01 ± 0.03	5.05 ± 0.02	<0.001
DBP (mmHg), mean ± SE	72.81 ± 0.29	72.69 ± 0.29	72.48 ± 0.33	74.28 ± 0.30	0.009
SBP (mmHg), mean ± SE	113.97 ± 0.37	114.61 ± 0.39	114.02 ± 0.45	115.71 ± 0.40	0.040
Male					
Age (years), mean ± SE	32.77 ± 0.18	32.08 ± 0.18	31.89 ± 0.18	31.48 ± 0.17	<0.001
BMI (kg/m^2), mean ± SE	25.55 ± 0.15	25.52 ± 0.17	26.25 ± 0.16	25.81 ± 0.18	0.016
Smoking, % (n/N)					0.008
Yes	11.41% (71/622)	13.04% (79/606)	16.61% (101/608)	10.46% (64/612)	
No	88.59% (551/622)	86.96% (527/606)	83.39% (507/608)	89.54% (548/612)	
Raw semen					
Semen volume (mL), mean ± SE	2.75 ± 0.02	2.75 ± 0.03	2.77 ± 0.03	2.80 ± 0.02	0.151
Semen concentration (×10^6 per mL), mean ± SE	33.36 ± 0.49	33.70 ± 0.49	33.94 ± 0.51	34.99 ± 0.54	0.422
Total motility (%), mean ± SE	56.95 ± 0.44	56.27 ± 0.45	55.81 ± 0.43	55.89 ± 0.46	0.154
Progressive motile sperm (%), mean ± SE	33.78 ± 0.34	33.80 ± 0.36	32.76 ± 0.35	33.03 ± 0.34	0.033
Normal sperm morphology (%), mean ± SE	4.20 ± 0.07	4.18 ± 0.10	4.08 ± 0.07	4.02 ± 0.07	0.057
Prepared semen					
Semen volume (mL), mean ± SE	0.40 ± 0.00	0.40 ± 0.00	0.40 ± 0.00	0.40 ± 0.00	0.566
Semen concentration (×10^6 per mL), mean ± SE	63.40 ± 0.92	63.79 ± 0.98	62.81 ± 0.95	64.50 ± 0.94	0.620
Total motility (%), mean ± SE	81.64 ± 0.34	80.64 ± 0.39	81.14 ± 0.36	80.29 ± 0.39	0.061
Progressive motile sperm (%), mean ± SE	67.88 ± 0.35	66.77 ± 0.39	66.85 ± 0.36	66.51 ± 0.37	0.059
Normal sperm morphology (%), mean ± SE	7.78 ± 0.18	7.66 ± 0.21	7.31 ± 0.15	7.19 ± 0.14	0.003

Notes: Continuous variables are expressed as mean ± SE and categorical data as percentages. *P*<0.05 was considered statistically significant.

Abbreviations: *SUA*, serum uric acid; *BMI*, body mass index; *IUI*, intrauterine insemination; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *E2*, estradiol; *PRL*, prolactin; *T*, testosterone; *P*, progesterone; *AMH*, anti-Müllerian hormone; *TSH*, thyroid-stimulating hormone; *AFC*, antral follicle count; *FBG*, fasting blood glucose; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure; *SE*, standard error.

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LH, basal P and AMH were also similar. Notably, with the increase of SUA, mean values of BMI, menstrual cycle length, AFC, and FBG level were significantly increased, while couples' age and secondary infertility rate were decreased (all $P<0.001$). Compared with Q1, women in Q4 had lower levels of hormones including basal FSH (7.52 ± 0.10 vs 8.23 ± 0.12 mIU/mL, $P<0.001$), E2 (65.58 ± 3.68 vs 75.26 ± 5.10 pg/mL, $P=0.034$), and PRL (15.98 ± 0.33 vs 16.51 ± 0.86 ng/mL, $P=0.024$), but higher values of DBP (74.28 ± 0.30 vs 72.81 ± 0.29 mmHg, $P=0.009$) and SBP (115.71 ± 0.40 vs 113.97 ± 0.37 mmHg, $P=0.040$). In addition, there was no significant difference regarding semen parameters of male partners across the groups except for the percentages of progressive motile sperm in raw semen and normal sperm morphology in prepared semen.

Ovarian Stimulation Protocols

The present study included 1398 natural cycles and 1050 ovarian stimulation cycles (Table 2). Interestingly, the proportion of natural cycles significantly decreased with ascending SUA quartiles ($P<0.001$). Stimulated protocols were divided according to the medication types: LE+HMG, FSH/HMG, CC+HMG, LE, and CC. The results indicated that there was no substantial difference between these cycles ($P=0.805$).

Pregnancy and Obstetric Outcomes

Table 3 presented the percentages of different reproductive outcomes according to SUA quartiles. There was no clear increasing or decreasing trend in the biochemical pregnancy rate with the fluctuation of SUA level (Q1: 18.81%, Q2: 18.65%, Q3: 18.26%, Q4: 17.81%, $P=0.970$). Similar results were also obtained in other pregnancy and obstetric outcomes such as clinical pregnancy, pregnancy type, miscarriage, ectopic pregnancy and live birth rate. The birth

Table 2 Stimulation Protocol for the Study Population

Variable	Quartile 1 (n=622)	Quartile 2 (n=606)	Quartile 3 (n=608)	Quartile 4 (n=612)	*P* value
Treatment protocol					<0.001
Natural cycle, % (n/N)	61.58% (383/622)	63.86% (387/606)	57.73% (351/608)	45.26% (277/612)	
Ovarian stimulation cycle, % (n/N)	38.42% (239/622)	36.14% (219/606)	42.27% (257/608)	54.74% (335/612)	
Ovarian stimulation protocol					0.805
LE + HMG, % (n/N)	39.75% (95/239)	37.44% (82/219)	43.19% (111/257)	38.81% (130/335)	
FSH/HMG, % (n/N)	23.43% (56/239)	26.94% (59/219)	21.40% (55/257)	25.37% (85/335)	
CC + HMG, % (n/N)	21.34% (51/239)	19.63% (43/219)	17.90% (46/257)	22.09% (74/335)	
LE, % (n/N)	12.13% (29/239)	10.50% (23/219)	12.84% (33/257)	10.75% (36/335)	
CC, % (n/N)	3.35% (8/239)	5.48% (12/219)	4.67% (12/257)	2.99% (10/335)	

Notes: The data are presented as percentages. $P<0.05$ was considered statistically significant.
Abbreviations: *HMG*, human menopausal gonadotropin; *LE*, letrozole; *CC*, clomiphene citrate; *FSH*, follicle-stimulating hormone.

Table 3 Pregnancy and Obstetric Outcomes According to SUA Quartiles

IUI Outcomes	Quartile 1 (n=622)	Quartile 2 (n=606)	Quartile 3 (n=608)	Quartile 4 (n=612)	*P* value
Biochemical pregnancy rate, % (n/N)	18.81% (117/622)	18.65% (113/606)	18.26% (111/608)	17.81% (109/612)	0.970
Clinical pregnancy rate, % (n/N)	17.36% (108/622)	15.51% (94/606)	15.63% (95/608)	16.01% (98/612)	0.803
Ectopic pregnancy rate, % (n/N)	0.00% (0/108)	2.13% (2/94)	5.26% (5/95)	2.04% (2/98)	0.079
Miscarriage rate, % (n/N)	16.67% (18/108)	14.89% (14/94)	18.95% (18/95)	19.39% (19/98)	0.831
Live birth rate, % (n/N)	83.33% (90/108)	82.98% (78/94)	75.79% (72/95)	78.57% (77/98)	0.483
Pregnancy type, % (n/N)					0.114
Single	74.07% (80/108)	79.79% (75/94)	72.63% (69/95)	69.39% (68/98)	
Multiple	9.26% (10/108)	3.19% (3/94)	3.16% (3/95)	9.18% (9/98)	
Birth weight (g), mean ± SE	3132.00 ± 65.57	3223.95 ± 54.21	3376.93 ± 64.63	3149.19 ± 58.56	0.021
LBW rate, % (n/N)	13.00% (13/100)	7.41% (6/81)	4.00% (3/75)	11.63% (10/86)	0.173

Notes: Continuous variables are expressed as mean ± SE and categorical data as percentages. $P<0.05$ was considered statistically significant.
Abbreviations: *SUA*, serum uric acid; *IUI*, intrauterine insemination; *LBW*, low birth weight; *SE*, standard error.

Table 4 Logistic Regression Analysis to Measure the OR and 95% CI for Reproductive Outcomes According to Quartiles of SUA

IUI Outcomes	OR (95% CI)				*P* value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Biochemical pregnancy					
Model 1	Ref	0.99 (0.74–1.32)	0.96 (0.72–1.29)	0.94 (0.70–1.25)	0.970
Model 2	Ref	0.98 (0.74–1.31)	0.90 (0.68–1.21)	0.81 (0.60–1.10)	0.538
Model 3	Ref	1.00 (0.75–1.34)	0.92 (0.68–1.24)	0.80 (0.58–1.09)	0.455
Clinical pregnancy					
Model 1	Ref	0.87 (0.65–1.18)	0.88 (0.65–1.19)	0.91 (0.67–1.22)	0.804
Model 2	Ref	0.87 (0.64–1.18)	0.81 (0.60–1.11)	0.77 (0.56–1.05)	0.388
Model 3	Ref	0.89 (0.65–1.21)	0.82 (0.60–1.12)	0.73 (0.53–1.02)	0.298
Miscarriage					
Model 1	Ref	0.88 (0.41–1.87)	1.17 (0.57–2.40)	1.20 (0.59–2.45)	0.832
Model 2	Ref	0.90 (0.42–1.96)	1.34 (0.62–2.89)	1.31 (0.59–2.88)	0.732
Model 3	Ref	0.92 (0.40–2.11)	1.33 (0.58–3.03)	1.57 (0.65–3.75)	0.627
Live birth					
Model 1	Ref	0.98 (0.47–2.04)	0.63 (0.31–1.25)	0.73 (0.36–1.48)	0.487
Model 2	Ref	0.94 (0.44–1.99)	0.53 (0.26–1.11)	0.66 (0.31–1.41)	0.315
Model 3	Ref	0.93 (0.41–2.07)	0.52 (0.23–1.15)	0.54 (0.23–1.26)	0.272
LBW					
Model 1	Ref	0.54 (0.19–1.48)	0.28 (0.08–1.02)	0.88 (0.37–2.12)	0.202
Model 2	Ref	0.54 (0.19–1.49)	0.30 (0.08–1.12)	0.98 (0.38–2.54)	0.204
Model 3	Ref	0.38 (0.12–1.21)	0.21 (0.05–0.94)	0.73 (0.24–2.22)	0.135

Notes: *P*<0.05 was considered statistically significant. Model 1: unadjusted model; Model 2: adjusted for age and BMI; Model 3: adjusted for the variables in Model 2 plus education, age at menarche, menstrual cycle, type of infertility, basal FSH, basal E2, basal PRL, basal T, TSH, AFC, FBG, DBP, SBP, smoking in men, progressive motile sperm, normal sperm morphology, and treatment protocol.

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; *SUA*, serum uric acid; *IUI*, intrauterine insemination; *Ref*, reference; *LBW*, low birth weight.

weight in Q3 (3376.93 ± 64.63 g) was higher than other groups (Q1: 3132.00 ± 65.57 g, Q2: 3223.95 ± 54.21 g, Q4: 3149.19 ± 58.56 g, *P*=0.021), but the prevalence of LBW did not show much difference among all groups (*P*>0.05).

Logistic Regression Analysis of Reproductive Outcomes in Women According to the SUA Quartiles

To confirm the reliability of the results, we used logistic regression to calculate the OR for reproductive outcomes based on the different SUA quartiles (Table 4). The results showed that there were still no significant differences in the rates of biochemical pregnancy, clinical pregnancy, miscarriage, and live birth among the groups in all adjusted models (*P*>0.05). However, with further adjustment for more confounding factors such as basal E2, basal PRL, basal T, TSH, menstrual cycle, and type of infertility in Model 3, the risk of LBW in Q3 was significantly lower than that in Q1 (adjusted OR 0.21, 95% CI: 0.05–0.94, *P*=0.041).

Discussion

Due to improved living standards and altered dietary patterns, SUA levels and the prevalence of hyperuricemia in the general population have been growing across both developed and developing countries over the past decades.[24,25] Thus, the potential effects of abnormal UA metabolism on human reproduction attracted widespread attention. Our retrospective analysis indicated that elevated SUA in women without PCOS did not negatively affect most of the pregnancy and delivery outcomes such as clinical pregnancy and live birth following IUI cycles, and these results remained the same after adjusting for potential confounders. However, maternal SUA level seemed to be associated with birth weight.

These insights could inform the clinicians' treatment decision-making process and provide new avenues for improving female reproductive health and preventing infertility.

Previous studies have analyzed the changes in SUA levels in adult samples with a wide age range and yielded controversial results. Mikkelsen et al reported that in American women there was a slight rise in SUA values beyond puberty, but the curve quickly fell until menopause.[26] Similar results were also obtained in a study with a sample size of 30349 Japanese women.[27] The above findings were consistent with our result that the higher quartiles of SUA levels were correlated with lower ages among Chinese women aged 20–40 years. However, Zitt et al found that the mean SUA levels stayed fairly constant until the age of 50 in a large population-based Austrian cohort.[28] These inconsistent age-related patterns of SUA levels among different populations might be attributed to the influences of genetic and environmental factors on SUA levels in individuals. Genome-wide association studies conducted in American, Indian, European, Chinese and Japanese populations have identified significant correlations between UA levels and single nucleotide polymorphisms of ABCG2 and SLC2A9 genes.[29–33] Moreover, the descriptive data of ethnically similar cohorts of indigenous and migrant Japanese showed SUA levels were significantly lower in the indigenous Japanese population than in the Japanese-American individuals living in California and Hawaii.[34] To further investigate the relationship between SUA levels in non-PCOS women and IUI outcomes, we excluded this confounding factor in subsequent adjustments.

In addition to causing OS mentioned in the introduction, UA has also been proposed to be able to alter the follicular microenvironment and result in a decreased blood supply to follicles.[35] Mumford et al found a higher level of SUA was associated with increased odds of sporadic anovulation, even among young women with regular menstrual cycles.[36] Moreover, the pro-inflammatory cytokine interleukin-1β produced in response to inflammation induced by elevated UA may inhibit endometrial metaplasia, affect embryo implantation, and thereby lead to infertility.[37] Currently, multiple studies have investigated the effects and mechanisms of UA on pregnancy and obstetric outcomes. As a small molecule UA can freely pass into the fetal circulation and inhibit endothelial cell proliferation in both the mother and fetus.[38] High levels of SUA induce a pro-contractile phenotype in vascular smooth muscle cells via activating activator protein-1, nuclear factor-κB and mitogen-activated protein kinase pathways and downstream expression of C-reactive protein, monocyte chemoattractant protein-1, and thromboxane A2, which may impair endometrial blood flow and fetal circulation and ultimately lead to pregnancy loss.[12] In addition, UA has been reported to have inhibitory effects on the ability of first trimester trophoblast cells to invade and integrate into the monolayer of uterine microvascular endothelial cells, thus becoming a potential pathogenic factor in the developing placenta.[39] However, fortunately in our study, the rates of biochemical pregnancy, clinical pregnancy, miscarriage, and live birth showed no significant correlation with SUA levels.

Results from previous studies on the relationship between SUA levels in non-PCOS women undergoing IVF treatment and neonatal birth weight remain controversial. Yan et al found that SUA showed no significant effect on the birth weight of infants after frozen embryo transfer.[35] However, Xia et al reported that the mean birth weight gradually increased in fresh embryo transfer cycles with increasing SUA although LBW rate was comparable among groups.[21] In our study, the mean value of birth weight in Q3 was the highest when compared with the other quartiles. Moreover, the LBW rate in this group was significantly lower than in Q1 after adjusting for confounding variables. Establishing and maintaining the optimal balance between reactive oxygen species production and endogenous antioxidant defense is essential to provide the appropriate intrauterine environment for fetal development. Both the increase of reactive oxygen species and the lack of antioxidant availability and activity could increase the senescence of syncytiotrophoblast and impair fetal vascular development in the villous tree, eventually leading to intrauterine growth restriction and LBW.[40] Thus, this U-shaped relationship between SUA levels and birth weight in our study might be due to the dual action of UA as both an antioxidant and a prooxidant. In human plasma, approximately half of the antioxidant capacity comes from UA.[41] It can prevent lipid and protein peroxidation, tetrahydrobiopterin inactivation and peroxynitrite-induced protein nitrosylation.[42] Furthermore, physiological levels of UA have also been shown to regulate vascular redox state by modulating the activity of superoxide dismutase in vivo.[43]

Our study is the first to explore the association of SUA levels with reproductive outcomes following IUI in women without PCOS. There were several notable strengths of this research. First, the inclusion and exclusion criteria were strict, which eliminated the bias in the effect of other variables on pregnancy outcomes. Second, the sample size of our

study was relatively large compared to other similar studies. Third, we used logistic regression analysis to adjust for potential confounding factors and yielded stable results across various adjustment models. Meanwhile, several limitations of our study should also be considered. Although the sample size was large, it was only a single-center study and the findings reported here should be confirmed in future multicenter studies. Also, despite attempts to control for confounding factors, there might still be some unmeasured variables such as lifestyle patterns and environmental factors that could influence the outcomes. Moreover, the study's retrospective nature prevented us from dynamically measuring changes in SUA levels over time. Future research should explore the mechanism of action of SUA during pregnancy to improve obstetric and perinatal outcomes.

Conclusion

In conclusion, our study did not find any significant correlation of pre-pregnancy SUA levels with most pregnancy outcomes in women without PCOS, which means that strictly controlling and regulating SUA levels of these patients before undergoing IUI procedures may not be necessary. However, the strong positive relationship between BMI and SUA levels indicates that it is still an essential need to change lifestyle including diet and physical activity in hyperuricemic patients, especially for those who are overweight or obese. Notably, an appropriate maternal pre-pregnancy SUA level exerted beneficial effects on birth weight, whereas high SUA level might compromise fetal growth by disrupting placental angiogenesis and leading to reduced blood flow and nutrient delivery to the fetus. These results not only help to improve the risk awareness of pregnant women but also can be used to identify and prevent adverse fetal outcomes in pregnant women with hyperuricemia as soon as possible. In the future, large-scale multicenter prospective studies are needed to ensure broader generalizability of our findings and explore the potential physiological mechanisms involved in greater depth.

Abbreviations

SUA, serum uric acid; IUI, intrauterine insemination; PCOS, polycystic ovary syndrome; OR, odds ratio; CI, confidence interval; UA, uric acid; OS, oxidative stress; IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection; LBW, low birth weight; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; PRL, prolactin; T, testosterone; P, progesterone; AMH, anti-Müllerian hormone; TSH, thyroid-stimulating hormone; FBG, fasting blood glucose; AFC, antral follicle count; LE, letrozole; CC, clomiphene citrate; HMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; SE, standard error.

Data Sharing Statement

All the data used during the study are openly available from the Mendeley data repository at https://data.mendeley.com/drafts/pjdw6swf28.

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the Affiliated Hospital of Jining Medical University (approval number: 2025-06-C008) and was conducted in accordance with the Declaration of Helsinki. Informed written consent was waived because retrospective data collection and analysis were based on electronic medical records without any intervention in clinical treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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